CAFFEINE AS A SUBSTANCE FOR BETTER PERFORMANCE

A systematic collection of published scientific literature on “caffeine and exercise in sports” 2000-2015

Åke Andrén-Sandberg
CONTENT

SUMMARY

INTRODUCTION
Proposed effects of caffeine
  Improvements in mood, cognition and perception
Proposed underlying physiological ways of action
Ergogenic claims

HISTORY OF ANTI-DOPING WITH REGARD TO CAFFEINE
Caffeine levels before and after the removal of caffeine from the doping list

DOCUMENTED USE OF CAFFEINE BY ATHLETES
UK
Spain
Canada
Belgium
Use as a flavor for consuming behavior
Emergency medicine residents' use

PHARMACOLOGY OF CAFFEINE
Absorption, blood levels and half-life
  Absorption of caffeine
Pharmacokinetics
Urinary caffeine levels
Environmental influences on blood levels
Pharmacokinetic interactions between dietary caffeine and medications
Urinary concentration of caffeine after ad libitum caffeinated carbohydrate solution

Individual sensitivity
  Exercise and obesity

PHYSIOLOGICAL MODE OF ACTION OF CAFFEINE
Methylxanthines
Activation of 5’AMP-activated protein kinase (AMPK)
Effect on adenosine receptors
  Experimental
Acceleration of fat metabolism
  Delay fatigue through CNS mechanisms by blocking adenosine receptors
Mobilization of intracellular calcium
Adrenaline-induced effects
A peripheral as opposed to a central neural mechanism of caffeine
  Effects of neural recovery
Inhibiton of the phosphodiesterase
Effect on lipolysis
  Mobilization of fat
  Duration of coffee- and exercise-induced changes in the fatty acid profile
Increased post-exercise muscle glycogen accumulation (neoglycogenesis)
Hypoalgesia
Effects on muscles
No effects on endothelial function
METABOLISM OF CAFFEINE
Fate in the liver
Factors influencing serum caffeine concentrations
  Dependence on time of the day of caffeine's effects
  Time for abstention from drunken caffeine

DOSING OF CAFFEINE
Sources of caffeine
  Roasting
  Powder or capsules
  In preparations against common cold
  Phenolic compounds such as chlorogenic acids
  Caffeinated "energy shots"
  Caffeinated beverages
  Caffeinated chewing gum
  Caffeine gel
  Time-release caffeine containing supplement
  Guarana
  Mouth rinsing
  Aerosol form
  Coffee, tea and cola drinks
  Caffeinated versus decaffeinated coffee
  Caffeine versus anhydrous caffeine
  Turkish coffee

Bioavailability of coffee
Effect versus dosage
  Dosage versus endurance cycle time
  Users versus non-users
  Duration of effect
  Optimum time to exercise after caffeine ingestion
  Divided doses or bolus?

Lethal dosage
Low doses of caffeine
  Are low doses of caffeine ergogenic during endurance exercise?
  Small doses of caffeine late in prolonged exercise
  Low caffeine doses ingested before endurance exercise
  Running
  Stop-and-Go individual and team sports
  Low caffeine doses and high-intensity exercise in anaerobic sports
  Low caffeine doses and vigilance, alertness, mood and cognitive function
  Gastrointestinal function
  Reducing the dose of caffeine and ephedrine preserving the ergogenic effect

Mouth-rinse
  Carbohydrate and caffeine mouth rinses
  Carbohydrate mouth rinse and caffeine improves high-intensity interval running
  Caffeine and maltodextrin mouth rinsing
  Prior coffee consumption impact on subsequent effect of anhydrous caffeine

EFFECTS ON EXERCISE OF CAFFEINE
Overviews
  Meta-analysis of the effects of caffeine ingestion on exercise testing

Confounding factors
  Coffee polyphenol caffeic acid
  Coffee versus caffeine
Effect of caffeine on repeated exercise in team-sport like tests
   Effects of caffeine on sprint
   Effect on caffeine on repeated anaerobe performance
   Dose effects of caffeine on acute hormonal responses to resistance exercise
   A meta-analysis
Effect of caffeine on endurance
   Effect of caffeine intake on endurance performance and metabolism
   Effects of caffeine on short-endurance performance after limitation of sleep
   Pre-exercise caffeine ingestion on endurance performance
   Repeated caffeine ingestion on repeated exhaustive exercise endurance
   Maximally caffeine stimulated muscle decreased endurance
   Effect of caffeine in hot and humid conditions during endurance exercise
   No effect of caffeine on endurance after nonselective beta-adrenergic blockade
Effects of caffeine on strength
   Isometric maximal force
   Isolated skeletal muscle experiments with caffeine
   Effects on torque and muscle activity during resistance exercise men
   Caffeine potentiates low frequency skeletal muscle force
   Effects on resistance training
   Strength and endurance
   Neuromuscular and perceptual factors
   Effect on delayed-onset muscle soreness
Effects of caffeine on skill performance
   Effect on athletic agility
Effects of performance after chronic use of caffeine
   Effects of caffeine after a withdrawal period

**EFFECT OF CAFFEINE IN DIFFERENT SPORTS**

**Running**
Caffeine and ephedrine on 10-km run performance

**Iron-man**

**Biking**
Caffeine in 100-km cycling time-trial performance
Caffeine affects time to exhaustion and substrate oxidation during cycling

**Cross-country skiing**

**Rowing**

**Football**

**Rugby**

**Field hockey**

**Basketball**

**Volleyball**

**Tennis**

**Badminton**

**Wrestling**
Effect of caffeine on upper-body anaerobic performance

**Jiu-jitsu**

**Weight-lifting**
Paraplegic and tetraplegic compared to able-bodied individuals
Vertical jump height

**Golf**

**Effect on sedentary men**

**PHYSIOLOGICAL EFFECTS OF CAFFEINE ON THE NERVOUS SYSTEM**

Effects of caffeine on the brain
   Effect on morning reduction in neuromuscular performance
Relationship between daily caffeine consumption and accuracy of time estimation

Caffeine lowers threshold for exercise-induced beta-endorphin and cortisol release

Caffeine in central fatigue
Dose-dependent neuromuscular effects
Caffeine's ergogenic effects on neuromuscular and perceptual factors

Ratings of perceived exertion
Pre-existent expectancy regarding the effects of the caffeine
Impact of caffeine on pain perception
Moderated effect of caffeine on anxiety
Psychological effects of caffeine
Experimental: performance-enhancing task considerations
Influence of caffeine, cold and exercise on multiple choice reaction time

Effects of caffeine on sleep and arousal
Caffeine's effect on autonomic nervous activity
Effect on sleep
Effects of caffeine on arousal
Effect on alertness

Morning coffee
Effect on insomnia, nervousness, and activeness
Physical performance during 24 h of active wakefulness
Influence on circadian rhythms

CAFFEINE EFFECTS ON GLUCOSE HOMEOSTASIS
Effect of caffeine on glycogen
Caffeine's effect of inhibition of glycogen phosphorylase
Impact on glycogen accumulation
Caffeine at low muscle glycogen availability
Caffeine ingestion increases estimated glycolytic metabolism
Caffeine increase of exogenous carbohydrate oxidation during exercise
Caffeine in combination with carbohydrate supplement
Effects of caffeine and carbohydrates on hydration status

CAFFEINE’S EFFECT ON ENERGY EXPENDITURE
Effect of caffeine on thermogenesis and lipolysis
Caffeine as a lipolytic food component
Caffeine’s effect on individuals with negative energy balance
Impact of caffeine on post-exercise oxygen consumption
Effects of caffeine on performance after a fat meal
Duration of coffee- and exercise-induced changes in the fatty acid profile
Experimental
Increases in VO_{2max} and metabolic markers of fat oxidation by caffeine

IMPACT OF CAFFEINE ON THE HEART
Caffeine’s effect on cardiac blood flow
Caffeine-reduced myocardial blood flow during exercise
Caffeine decreased exercise-induced myocardial flow reserve
Effects of caffeine on linear and nonlinear measures of heart rate variability

EFFECT OF CAFFEINE ON RENAL FUNCTIONS
Effect of caffeine on hydration
Diuretic effects
Body fluid-electrolyte balance and exercise performance
Effect on urea formation

**IMPACT OF CAFFEINE ON IMMUNOLOGICAL FACTORS**
Impact on the inflammatory response
Effect of caffeine ingestion on lymphocyte counts
Effect on NK cells
Immuoendocrine effects

**OTHER PHYSIOLOGICAL EFFECTS OF CAFFEINE**
Gastrointestinal function during exercise with caffeine
Impact of caffeine on ventilation
Impact on sweating
Effect of caffeine on delayed onset muscle soreness
Lack of effect on oxidative stress
   Modulation of oxidative stress markers in the liver of trained rats
Caffeine improves performance at high altitude
Effect of caffeine on liver during training

**POSSIBLE HEALTH-PROMOTING EFFECTS OF CAFFEINE**
Specific diagnoses
Caffeine in exercise-induced bronchoconstriction
Caffeine in diabetics

**POSSIBLE ADVERSE EFFECTS OF CAFFEINE ON HEALTH**
Addiction
Withdrawal effects
Cerebral problems
Cardiovascular problems
   Hypertension
Core body temperature
Increased diuresis
Respiratory problems
   Experimental
Muscle fatigue
Interference with females and female hormones
   Caffeine ingestion enhances perceptual responses in females
Interference of caffeine with alcohol consumption
Effects in children

**SOCIO-MEDICAL, SOCIAL AND PSYCHOLOGICAL ASPECTS OF CAFFEINE**
Athletes’ knowledge of effects of caffeine

**COMBINATION OF PHARMACOLOGICAL SUBSTANCES WITH CAFFEINE**
Combination with ephedrine
   Caffeine and ephedrine ingestion on anaerobic exercise performance
Combination with pseudoephedrine
Combination with synephrine
Combination with theobromine
Combination with creatine
   Effect on strength and sprint
Combination with salbutamol
Combination with sodium bicarbonate
Combination with sodium citrate
Combination with carbohydrates
   Feeling smart: effects of caffeine and glucose on cognition, mood and self-judgment
   Caffeinated carbohydrate-gel ingestion
   In football
   In badminton
   Caffeine plus carbohydrates or fat
Combination with epigallocatechin
Caffeine with phosphatidylserine
Combination with amitryptilin
Combination with amino acids
Combination with taurine
   Experimental
Combination with carnitine
   Caffeine combined with carnitine and choline decreases body fat and serum leptin
Combination with ecstasy (methyleneoxymethamphetamine, MDMA)
Combination with green tea and cayenne powder
Combination with sodium phosphate
Acceleration of caffeine metabolism of tobacco and cannabis

**INFLUENCE OF CAFFEINE ON BIOMONITORING DATA**
Effect of smoking and caffeine
Impact on testosterone levels
Impact on potassium levels
Impact on glutamine acid levels
Impact on creatinine levels
Impact on sex-hormone binding globulin levels
Impact on hematological variables
   Effect on lymphocyte counts and subset activation
Stability studies of caffeine in urine

**LABORATORY TECHNIQUES**

**RECOMMENDATIONS THE INTERNATIONAL SOCIETY OF SPORTS NUTRITION**

**THE CHANGING LANDSCAPE OF CAFFEINE RESEARCH**

**REFERENCES**
Caffeine (1,3,7-trimethylxanthine, \( \text{C}_8\text{H}_{10}\text{N}_4\text{O}_2 \)) is one of the most heavily consumed and widely studied stimulants in history. Caffeine-containing beverages, primarily coffee (\textit{Coffea arabica}) and tea (\textit{Camellia sinensis}), have been a mainstay in both Eastern and Western society for more than 500 years. The appearance of carbonated soft drinks or colas in the early 20th century often used kola nut (\textit{Cola acuminata}) as a flavoring agent and caffeine source, whereas the recent emergence of energy drinks incorporate guarana (\textit{Paulina cupana}), green tea (\textit{C sinensis}), and Yerba maté (\textit{Ilex paraguariensis}) as natural caffeine sources. Together, these beverages constitute the primary sources of caffeine in the modern diet. The popularity of these beverages stems from the mild stimulatory effects (e.g. increased wakefulness, improved cognition, and decreased fatigue) that caffeine has on the central nervous system (CNS) when ingested in moderate quantities (\( \leq 200\text{mg} \)). Because of its CNS stimulant properties, purified caffeine (\( \leq 200\text{mg} \)) can also be found in various nonprescription drug products. According to European and North American statistics, about 90 percent of the adult population consider themselves as daily coffee users with an average daily caffeine consumption of about 200 mg or 2.4 mg/kg/day (about 2 cups of coffee). The main pharmacologically active substance in is the purine alkaloid of the xanthines class. Caffeine is both water and fat soluble and is quickly distributed in the body after absorption mainly by the small intestine and the stomach. Due to its lipophilic nature, caffeine also crosses the blood-brain barrier, and is metabolized by the liver into paraxanthine, theophylline, and theobromine.

Chronic use of caffeine leads to dependence, tolerance, drug craving, and upon abrupt cessation unpleasant withdrawal symptoms. Thus, caffeine fulfills pharmacological criteria by which agents are classified as drugs of abuse. Nevertheless, its use is legal and only at high, but readily attainable, levels made it banned from sport as a doping substance for many years (not so now in 2015). Its use is widespread by athletes as young as 11 years of age who are seeking athletic advantage over fellow competitors. It is likely that its use will not decline any time soon because it is inexpensive, readily available, medically quite safe, socially acceptable, and by most measures legal. However, at levels allowed in sport, caffeine through its wide-ranging physiological and psychological effects increases endurance in well-trained athletes.

**Proposed effects of caffeine**

Caffeine does not improve maximal oxygen capacity directly, but could permit the athlete to train at a greater power output and/or to train longer. It has also been shown to increase speed and/or power output in simulated race conditions. These effects have been found in activities that last as little as 60 seconds or as long as 2 hours. There is less information about the effects of caffeine on strength; however, recent work suggests no effect on maximal ability, but enhanced endurance or resistance to fatigue. There is no evidence that caffeine ingestion before exercise leads to dehydration, ion imbalance, or any other adverse effects. Related compounds such as theophylline are also potent ergogenic aids. Caffeine may act synergistically with other drugs including ephedrine and anti-inflammatory agents. It appears that male and female athletes have similar caffeine pharmacokinetics, i.e., for a given dose of caffeine, the time course and absolute plasma concentrations of caffeine and its metabolites are the same. In addition, exercise or dehydration does not affect caffeine pharmacokinetics.

Caffeine improves concentration, reduces fatigue, and enhances alertness. Habitual intake does not diminish caffeine’s ergogenic properties. Routine caffeine consumption may cause tolerance or dependence, and abrupt discontinuation produces irritability, mood shifts, headache, drowsiness, or fatigue. The effect of caffeine to promote improvements in mood,
cognition, and exercise performance has been well established in young and athletic adults. The results of several studies demonstrate that caffeine reduces perception of effort and improves exercise performance. The positive effect of caffeine on perception of effort is associated with changes in motor-related cortical activity during exercise, most likely in areas upstream of the primary motor cortex. Caffeine can also reduce exercise-induced muscle pain, increase pleasure during exercise, and increase exercise enjoyment. Importantly, caffeine can reduce perception of effort and exercise-induced muscle pain even at relatively low doses and in habitual high caffeine consumers.

**Proposed underlying physiological ways of action**

Caffeine's stimulant effects on the cardiovascular system and CNS stem from 4 principal mechanisms: nonselective antagonism of G-coupled adenosine A₁ and A₂A receptors, nonselective inhibition of phosphodiesterases with the subsequent accumulation of cyclic adenosine monophosphate (cAMP) and an intensification of the effects of catecholamines, mobilization of intracellular calcium via activation of ryanodine receptor channels, and inhibition of gamma-aminobutyric acid neurotransmission. Only at higher serum concentrations (>25 microg/mL) do the later 3 mechanisms appear to contribute significantly to caffeine pharmacodynamics. Caffeine's dose-dependent CNS stimulant effects (e.g. mood enhancement, wakefulness, insomnia, anxiety, tremors, and seizures) stem from antagonism of brain adenosine receptors, whereas antagonism of A₁ and A₂A receptors in the heart and vasculature account for its hemodynamic effects (e.g. increased heart rate, coronary and peripheral vasoconstriction, and elevated blood pressure). As a result of adenosine antagonism, caffeine also stimulates the release of several neurotransmitters (e.g. dopamine, norepinephrine, and serotonin), which also accounts for many of the drug's indirect pharmacodynamic effects. Caffeine can also reduce cerebral, hepatic, and mesenteric blood flow and produce mild diuresis via increased glomerular filtration and enhanced sodium and water excretion. At higher doses, caffeine can also cause other pharmacodynamic effects, including bronchodilation, lipolysis, hyperglycemia, and hypokalemia. Caffeine-induced hypokalemia could contribute to ventricular arrhythmias and sudden death. Owing to the rapid development of tolerance, a person's response to caffeine depends on dose, dosing regularity, and their pharmacokinetic profile.

Caffeine acts as a nonselective competitive inhibitor of the phosphodiesterase enzymes. Phosphodiesterases hydrolyze the phosphodiesterase bond in molecules such as cyclic adenosine monophosphate (cAMP), inhibiting the breakdown of cAMP. cAMP activates lipolysis by activating HSL and is an important molecule in the epinephrine cascade. It further activates protein kinase A, which in turn can phosphorylate a number of enzymes involved in glucose and lipid metabolism.

**Overdosing**

Caffeine can have negative effects at high doses (from about 400 mg). Such high doses can reduce motivation, and potentially also cognitive performance. It was for example in 1994 reported that doses of 420 mg doses of caffeine resulted in more commission errors and slower processing rate in cognitive tasks than lower doses. Further, withdrawal of heavy caffeine consumption can result in adverse side effects including headaches, increased subjective stress, fatigue, and decreased alertness.

The lethal dose of caffeine is about 10 grams, which is equivalent to the amount of caffeine in 100 cups of coffee.
Pharmacokinetics

Caffeine is rapidly absorbed by the body, when consumed in coffee and capsules, and appears in the blood within 5-15 min and peaks between 40 and 80 min. Plasma caffeine levels rise to 15-20 mol/L with a low caffeine dose (3 mg/kg bm), 40 mol/L with a moderate dose (6 mg/kg bm), and 60-70 mol/L with a high dose of 9 mg/kg bm. Caffeine also has a long half-life (3-5 h), which makes it well suited to interact with many tissues in the body. However, since caffeine interacts with many tissues, it is difficult to independently study its effects on the CNS, the peripheral nervous system, and the many metabolic tissues in the body (skeletal muscle, liver, heart, and adipose tissue) at rest and during exercise. Moreover, it has been shown that the plasma caffeine levels needed to affect changes in the metabolic tissues are substantially higher than required to affect the adenosine receptors in the brain and peripheral nervous system, making it unlikely that there could be major ergogenic effects with caffeine doses of 3 mg/kg bm or less where plasma levels are 15-20 mol/L.

Caffeine is completely absorbed by the gastrointestional tract within 1 hour. Plasma caffeine concentrations have also been shown to rise in a dose-dependent manner and exhibit first order, linear kinetics resulting in a half-life of approximately 5 hours. Additionally, the nature of formulation can also directly influence the rate and extent of absorption following oral administration as caffeine has shown to have a greater rate of absorption from a capsule than from dietary sources such as coffee, cola, or chocolate.

On account of its excellent aqueous solubility and small molecular weight, caffeine readily enters the intracellular space and is widely distributed – its volume of distribution mimics that of total body water. Accordingly, caffeine readily crosses the blood brain barrier and can be found in almost all body fluids and tissues. The pharmacokinetic properties of caffeine are dose dependent, which likely contributes to toxic effects associated with many caffeine-containing dietary supplements. Caffeine biotransformation is mediated primarily via hepatic cytochrome P450 1A2 (CYP1A2), and saturation of this pathway can occur at doses as low as 5 mg/kg. Caffeine’s principal CYP1A2-mediated metabolite in humans is paraxanthine, which exhibits pharmacologic effects similar to its parent compound, whereas minor metabolites include theophylline and theobromine. Caffeine clearance is highly variable, and both genetic and environmental factors (e.g. diet, smoking, and oral contraceptive use) are contributors to this variability. Like the receptor polymorphisms mentioned above, allelic variants in CYP1A2 can affect caffeine’s pharmacokinetic properties and pharmacologic response. Among caffeine users, both slow and rapid metabolizer phenotypes have been described, each corresponding to respective allelic variants that give rise to loss or gain of enzyme function. Habitual coffee use and higher consumption of coffee appear to correlate with rapid metabolizer phenotypes (homozygous CYP1A2*1A), whereas slow metabolizer phenotypes (heterozygous CYP1A2*1F) have been linked to higher risks of hypertension and nonfatal myocardial infarction.

Environmental influences on blood levels

CYP1A2 allelic variants aside, caffeine metabolism is also susceptible to a host of environmental influences. Smoking and diets rich in cruciferous vegetables induce CYP1A2 gene expression, presumably through activation of the aryl hydrocarbon nuclear receptor, resulting in enhanced caffeine clearance. Conversely, alcohol consumption, oral contraceptives, fluvoxamine, and quinolone antibiotics are known to inhibit CYP1A2 activity, lower caffeine clearance, and increase both area under the plasma concentration time curve and elimination half-life. Other phytochemicals thought to affect the pharmacokinetic properties of caffeine when consumed concomitantly include tanshinone, quercetin, genistein, curcumin, daidzein, and naringenin. Given the multiplicity of botanical extracts that constitute caffeine-containing dietary supplement formulations, it is difficult to predict how
such complex phytochemical mixtures will affect caffeine pharmacokinetic and pharmacodynamic properties. What is well recognized, however, is that caffeine can potentiate the cardiovascular and CNS effects of other stimulants. Such stimulants include plant-derived alpha- and beta-adrenergic agonists such as those found in Ephedra species (e.g. ephedrine, pseudoephedrine, norephedrine, and methylephedrine) and alpha2- adrenergic antagonists from the African plant Pausinystalia yohimbe (e.g. yohimbine and rauwolscine), as well as synthetic stimulants such as amphetamine, methamphetamine, 3,4-methylenedioxyamphetamine, and cocaine. When combined with ephedrine alkaloids or amphetamines, especially in the context of vigorous exercise, caffeine may increase the likelihood of serious adverse health effects, such as arrhythmia, myocardial infarction, stroke, seizure, hypertensive crisis, and exertional heat illness.

Several studies suggest that caffeine disposition is not significantly altered during exercise, while other studies indicate that peak caffeine plasma levels may be enhanced. Likewise, obesity’s effect on caffeine pharmacokinetic properties is also difficult to predict. Such ambiguities may contribute to the questionable tolerability and efficacy of caffeine-containing dietary supplements.

**Individual sensitivity**

Individual sensitivity to the effects of caffeine is well recognized. Such sensitivities may be attributable, in part, to an individual’s genetic makeup. Only recently has an appreciation developed for the effects that human receptor gene polymorphisms can have on the pharmacodynamics of caffeine. Adenosine A2A and alpha2-adrenergic receptor polymorphisms have been linked to caffeine-induced insomnia, anxiety, habitual coffee consumption, and blood pressure elevation, whereas animal studies hint that cardiac ryanodine receptor mutations may increase caffeine’s arrhythmogenic potential. Another gene polymorphism associated with the adverse effects of caffeine is the enzyme catechol-O-methyltransferase (COMT). In the case of functional COMT polymorphisms, the sympathomimetic effects of endogenous catecholamines (e.g. norepinephrine) are enhanced; after caffeine ingestion, such mutations have been linked to rapid heart beat, elevated blood pressure, and the incidence of acute coronary events.

**No acceleration of fat metabolism**

Conversely to what was initially thought, CAF intake does not seem to be able to accelerate fat metabolism and to spare muscle glycogen during exercise, which would explain the increased performance observed in endurance tasks. Currently, this potential effect of CAF is credited to its affinity to adenosine receptors (A1 and A2A). When CAF molecules bind with these pre and post synaptic receptors, it inhibits adenosine action, promoting the release of excitatory neurotransmitters, increasing corticomotor excitability.

It was previously thought that caffeine mechanisms were associated with adrenaline (epinephrine)-induced enhanced free-fatty acid oxidation and consequent glycogen sparing, which is the leading hypothesis for the ergogenic effect. It would seem unlikely that the proposed theory would result in improved anaerobic performance, since exercise is dominated by oxygen-independent metabolic pathways.

**Mobilization of intracellular calcium**

It has been shown that caffeine can enhance calcium release from the sarcoplasmic reticulum and can also inhibit its reuptake. Via this mechanism, caffeine can enhance contractile force during submaximal contractions in habitual and nonhabitual caffeine consumers. Intracellular calcium favors the activation of endothelial nitric oxide synthase,
which increases nitric oxide. Some of the ergogenic effects of caffeine might therefore as well be mediated partly by effecting the neuromuscular system and increasing contractile force. There is, however, still controversy about the translation of results from in vitro studies on muscle preparations to caffeine dose and calcium release in vivo.

**Increased post-exercise muscle glycogen accumulation (neoglycogenesis)**

Enhanced recovery by increased rate of glycogen resynthesis following exercise. It has been reported that caffeine ingestion has no effect on glycogen accumulation during recovery in recreationally active individuals, but it has also been reported that caffeine (8 mg/kg body weight) co-ingested with carbohydrates (CHO) increases rates of postexercise muscle glycogen accumulation compared with consumption of CHO alone in well-trained athletes after exercise-induced glycogen depletion. Although this issue needs further study in different populations (untrained, trained) and at different time points (during exercise or recovery), caffeine added to postexercise CHO feeding seems to have the potential to improve glycogen resynthesis.

**Hypoalgesia**

The hypoalgesic effects of caffeine have resulted in dampened pain perception and blunted perceived exertion during exercise. This could potentially have favourable effects on negating decreased firing rates of motor units and possibly produce a more sustainable and forceful muscle contraction. The analgesic effect is possibly mediated by augmenting plasma endorphin concentrations.

**Sources of caffeine**

Caffeine is a naturally occurring plant alkaloid. It is classified as a methylxanthine. Other examples of methylxanthines include theophylline and theobromine. It is found in over 60 different plant species. It is also found in a variety of over the counter stimulants, appetite suppressants, analgesics, and cold and sinus preparations. In fact, caffeine is the world’s most commonly used and widely consumed pharmacologic substance. Approximately 75 percent of caffeine is consumed in the form of coffee. In terms of international commerce, coffee is second only to oil in dollar amount traded. Consumption of caffeine is highest in the United Kingdom and Scandinavian countries (400 mg/person/d compared with 238 mg/person/d in the United States).

The caffeine content of coffee varies greatly, depending on the beans, how they are roasted, and other factors, but the average for an 8-ounce cup is about 100 milligrams (mg). Tea has about half as much caffeine as coffee. Decaffeinated coffee has some caffeine, but the 2 to 4 mg in an 8-ounce cup is a smidgen compared with the caffeinated version.

Caffeine is also available in gels and bars and in some sports drinks for use by athletes before and during athletic events. It might be assumed that the appearance of caffeine in the blood would be slightly delayed with gels and bars compared with ingestion in coffee or tablets/capsules ingested with water but this does not appear to have been studied. Another form of delivery that has received some interest is chewing gum. The acute ingestion of caffeine via chewing gum attenuates fatigue during repeated, high-intensity sprint exercise in competitive cyclists.

The efficacy of time-release caffeine capsules appears to be no different than regular caffeine capsules. Investigations have demonstrated that time-release caffeine can enhance alertness and reaction performance for up to 13 hours following ingestion, and improve vigilance and cognitive function during sleep deprivation as compared to a placebo.
Another emerging area for exposing the body to caffeine is mouth rinsing. The premise is that small volumes of fluid containing high concentrations of caffeine could be mouthrinsed for 5-10 s periods. While this is unlikely to result in significant caffeine absorption, it would test the possibility that caffeine is sensed in the mouth with signals sent to the CNS [054]. A dose of 100 mg of caffeine (equivalent to one cup of coffee) will produce a urine concentration of approximately 1.5 mg/mL caffe ine content (mg) of common substances in 2005:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Volume</th>
<th>Caffeine Content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee</td>
<td>7.5 oz</td>
<td>100</td>
</tr>
<tr>
<td>Coca-Cola</td>
<td>12 oz</td>
<td>46</td>
</tr>
<tr>
<td>Diet Coke</td>
<td>12 oz</td>
<td>46</td>
</tr>
<tr>
<td>Mountain Dew</td>
<td>12 oz</td>
<td>54</td>
</tr>
<tr>
<td>Dr. Pepper</td>
<td>12 oz</td>
<td>40</td>
</tr>
<tr>
<td>Sprite</td>
<td>12 oz</td>
<td>0</td>
</tr>
<tr>
<td>Iced tea</td>
<td>12 oz</td>
<td>70</td>
</tr>
<tr>
<td>Over-the-counter stimulants</td>
<td>1 capsule</td>
<td>100</td>
</tr>
</tbody>
</table>

The content (mg) of an “ordinary” cup (8.4 ounce) of caffeine was in one study:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Caffeine Content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starbucks coffee</td>
<td>180</td>
</tr>
<tr>
<td>Red bull</td>
<td>80</td>
</tr>
<tr>
<td>Lipton green tea</td>
<td>35</td>
</tr>
</tbody>
</table>

**Effect versus dosage**

There is a scarcity of field-based studies and investigations involving elite performers. Researchers are encouraged to use statistical analyses that consider the magnitude of changes, and to establish whether these are meaningful to the outcome of sport. The available literature that follows such guidelines suggests that performance benefits can be seen with moderate amounts (about 3 mg/kg body mass) of caffeine. Furthermore, these benefits are likely to occur across a range of sports, including endurance events, stop-and-go events (e.g. team and racquet sports), and sports involving sustained high-intensity activity lasting from 1-60 min (e.g. swimming, rowing, and middle and distance running races). The direct effects on single events involving strength and power, such as lifts, throws, and sprints, are unclear. Further studies are needed to better elucidate the range of protocols (timing and amount of doses) that produce benefits and the range of sports to which these may apply. Individual responses, the politics of sport, and the effects of caffeine on other goals, such as sleep, hydration, and refuelling, also need to be considered.

Although the traditional supplementation regimen involves a single intake of about 6 mg/kg BM, 1 h pre-exercise, one studies show that ergogenic effects from caffeine intake may occur at very modest levels of intake (1-3 mg/kg bodyweight or 70-200 mg caffeine). In fact, several studies suggest there is no dose-response relationship between caffeine intake and benefits to endurance exercise or, if it exists, there is a plateau at about 3 mg/kg or about 200 mg.

**Users versus non-users**

Some studies used caffeine-naïve whereas others used caffeine-habituated subjects. There seems to be a higher increase in plasma adrenalin in caffeine-naïves compared to caffeine habituated subjects after caffeine ingestion. However, no differences between habitual caffeine intake and 1500 m running performance or force of contraction could be observed. For both caffeine-naïve as well as caffeine-habituated subjects, moderate to high doses of caffeine are ergogenic during prolonged moderate intensity exercise. The differences
between users and non-users do not seem to be major.

*Duration of effect*

In terms of variations to the timing of intake of caffeine doses, it appears, at least in endurance sports, that caffeine can be consumed pre-event or as single or multiple doses spread throughout an exercise bout or just prior to the onset of fatigue. The effects of caffeine can be long lasting, with one study showing that people who ingest caffeine to enhance a morning exercise task may still receive benefits during a session undertaken later in the day.

*Optimum time to exercise after caffeine ingestion*

There have been numerous studies and reviews indicating that caffeine ingested before exercise causes rapid and significant improvements in performance, especially in aerobic exercise capacity. The dose of caffeine studied has ranged from 1 to 15 mg/kg of body mass. The optimal dose has not been determined because it may vary according to the sensitivity of the individual to caffeine. However, doses between 3 and 6 mg/kg produce an equivalent ergogenic effect to higher doses, and this has led to the suggestion that the optimal dose thus lies in this lower range. Even though caffeine has a half-life of 4-6 h that implies high levels of caffeine will be in the blood for up to 3-4 h after ingestion, most studies have focused on exercise performance about 1 h after ingestion. Thus maximal effects are assumed to occur about 1 h after ingestion, when peak blood concentrations are observed.

Dividing a caffeine dose provides no ergogenic effect over a bolus dose but reduces postexercise urinary concentration.

*Low doses of caffeine*

A low dose of caffeine is defined as ingesting 3 mg/kg body mass or less, which is 200 mg of caffeine for a 70 kg individual. This is no more caffeine than may be consumed in 1-2 small cups of coffee or one large coffee.

The ingestion of high caffeine doses also produced troubling side effects of gastrointestinal upset, nervousness, mental confusion, inability to focus, and disturbed sleeping in some subjects, especially those who were habitual light caffeine users. When the caffeine dose was reduced to a moderate level (5-6 mg/kg bm), the ergogenic effects were maintained and the physiological responses and side effects were also reduced but were still present. There have also been many attempts over the years to link these caffeine-induced peripheral physiological responses to the ergogenic benefits of caffeine. However, the administration of a low caffeine dose (3 mg/kg bm) also produced an ergogenic effect, with no changes in exercise heart rate and the levels of catecholamines, lactate, FFA, and glycerol. This strongly suggested that the ergogenic effect of caffeine is mediated through the central nervous system (CNS).

Low doses of caffeine (<3 mg/kg body mass, about 200 mg) are also ergogenic in some exercise and sport situations. Lower caffeine doses has in studies been shown to:

- not alter the peripheral whole-body responses to exercise
- improve vigilance, alertness, and mood and cognitive processes during and after exercise
- be associated with few, if any, side effects
**Effects on exercise of caffeine**

Numerous studies to date have shown the efficacy of acute caffeine ingestion for improving prolonged endurance exercise performance. It has been concluded that in one meta-analysis that investigated caffeine intake (1-6 mg CAF/kg BW), performance was improved by about 3 percent. It is often cited that caffeine induces its ergogenic effects by an increase in fat oxidation through the sympathetic nervous system, and a sequential sparing of muscle glycogen. In the literature to date, the ergogenic effects are well documented with the time to exhaustion test at a fixed power output being the predominant performance measure used. A number of studies have confirmed the ergogenic effects of caffeine using time trial protocols, which involves completing an energy based target or set distance in as fast as time possible, thus simulating variable intensities that are likely to occur during competitive events. In most of these studies pure (anhydrous) caffeine was ingested through capsules or dissolved in water. Based on this research it is often assumed that ingesting caffeine in a variety of dietary sources, such as coffee, will result in the same ergogenic effect. Coffee improved performance in some, but not all studies. Amongst the current studies, only a few investigations have actually used coffee rather than decaffeinated coffee plus anhydrous caffeine, with even fewer of these studies showing an ergogenic effect of the coffee.

A large body of scientific evidence describes the beneficial effects of human caffeine consumption on a number of physiologic systems, which is useful for good physical and psychological performance. The consumption of moderate amounts of caffeine thus:

- increases energy availability
- increases daily energy expenditure
- decreases fatigue
- decreases the sense of effort associated with physical activity
- enhances motor performance
- enhances cognitive performance
- increases alertness, wakefulness, and feelings of "energy"
- decreases mental fatigue
- quickens reactions
- increases the accuracy of reactions
- increases the ability to concentrate and focus attention
- enhances short-term memory
- increases the ability to solve problems requiring reasoning
- increases the ability to make correct decisions
- enhances cognitive functioning capabilities and neuromuscular coordination

From this list it is obvious that when stating that caffeine enhances performance it is not a question of only influence one bodily function, but caffeine simultaneously influence several functions, which also will influence each other. This makes practical research of “causes-effect” difficult from a scientific point of view, as it is probable that caffeine rather gives a cascade of effects than just one single effect.

Further, post-exercise caffeine intake seems to benefit recovery be increasing rates of glycogen resynthesis.

<table>
<thead>
<tr>
<th>Acute effect</th>
<th>Effect on performance</th>
<th>Caffeine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater reliance on fat metabolism; increased FFAs; lower respiratory exchange ratio (RER)</td>
<td>Increased time trial performance</td>
<td>6 mg/kg body mass</td>
</tr>
<tr>
<td>Effect</td>
<td>Dosage Details</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Counteract central fatigue, maintenance of MVC</td>
<td>3 % PMAX increase, increase in voluntary activation 6 mg/kg body mass</td>
<td></td>
</tr>
<tr>
<td>directed effect on the CNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No clear mechanism; effect on CNS (greater motor unit recruitment and altered neurotransmitter function) or direct effect on skeletal muscle</td>
<td>Enhanced time trial performance 6 mg/kg caffeine 1 h pre-exercise and about 1.5 mg/kg after 2 h of exercise</td>
<td></td>
</tr>
<tr>
<td>Direct effect on skeletal muscle; interaction with ryanodine receptor; potentiated calcium release from the SR</td>
<td>Increase of contraction force at low frequency stimulation (20 Hz) 6 mg/kg 100 min before stimulation</td>
<td></td>
</tr>
<tr>
<td>Blunted pain response</td>
<td>Significantly higher reps during leg press set 3 with caffeine, same RPE 6 mg/kg 1 h prior to 10 RM bench and leg press</td>
<td></td>
</tr>
<tr>
<td>Glycogen-sparing effect and increased utilization of intramuscular TGs and plasma FFAs with caffeine</td>
<td>Increased cycling time trial performance with caffeine 9 mg/kg body mass 1 h before exercise</td>
<td></td>
</tr>
</tbody>
</table>

**Meta-analyses of the effects of caffeine ingestion on exercise testing**

One study used the meta-analytic approach to examine the effects of caffeine ingestion on exercise testing. Forty double-blind studies with 76 effect sizes (ES) met the inclusion criteria. The type of exercise test was classified as endurance, graded, or short-term. In comparison with placebo, caffeine improved test outcome by 12.3 percent (95 % confidence interval 9.1 to 15.4), which was equivalent to an overall ES of 0.41 (95 % confidence interval 0.31 to 0.51). Endurance exercise significantly improved test outcome more than either graded or short-term exercise. When exercise protocol was examined, time-to-exhaustion (Tlim) protocols had a significantly greater ES than either the graded or the non-Tlim protocol(s). The results from this meta-analysis thus confirm the ergogenic effects of caffeine, particularly for endurance testing that use Tlim protocols.

Another review of the literature revealed 29 studies that measured alterations in short-term performance after caffeine ingestion. Each study was critically analyzed using the Physiotherapy Evidence Database (PEDro) scale. The mean PEDro score was 7.76 ± 0.87. Eleven of 17 studies revealed significant improvements in team sports exercise and power-based sports with caffeine ingestion, yet these effects were more common in elite athletes who do not regularly ingest caffeine. Six of 11 studies revealed significant benefits of caffeine for resistance training. Some studies show decreased performance with caffeine ingestion when repeated bouts are completed. The exact mechanism explaining the ergogenic effect of caffeine for short-term exercise is unknown.

**Effects of caffeine on skill performance**

Popular use of caffeine is often at high concentrations (4-9 mg/kg) on the basis that these are more efficacious, but the proof of this is low with individual variability and consumption habits being the more dominant factors. Assessing its effects on performance is however difficult, especially in team sports where multiple physical and skill components are involved. While overt physical components such as power don’t appear affected by acute deprivation a
few studies do however suggest acute deprivation can affect certain sport skill and physical performance. Caffeine, for example, has been shown to improve both mood and mental function following sleep deprivation. The psychostimulant effects of caffeine appear to be related to the pre and post synaptic brakes that adenosine imposes on dopaminergic neurotransmission by acting on different adenosine receptor heteromers, although numerous mechanisms are likely to be involved. It is not known how much mood and other cognitive function, particularly motivation on repeat skill tasks, interact. The absorption of caffeine in plasma following consumption has been estimated at between 30 and 90 min with half life of several hours. Effective doses of caffeine (and their dose response nature) remain contentious in literature possibly reflecting larger inter-subject variability in responses and different sensitivities of various physical and behavioural expressions.

However, results from one study indicate that a 6 mg/kg dose of caffeine does not impact agility as measured by the proagility run test or power output as measured by the 30-second Wingate test in recreationally active young adult males who are not habituated to caffeine.

**Caffeine effects on glucose homeostasis**

Caffeine intake has also been proposed to increase symptomatic warning signs of hypoglycemia in patients with type 1 diabetes and elevate blood glucose levels in patients with type 2 diabetes. Other effects include potential increases in glucose counter-regulatory hormones such as epinephrine, which can also decrease peripheral glucose disposal. Despite these established physiological effects, increased coffee intake has been associated with reduced risk of developing type 2 diabetes in large-scale epidemiological studies. One review highlighted the known effects of caffeine on glucose homeostasis and diabetes metabolism during rest and exercise.

There are evidence that in trained subjects coingestion of large amounts of caffein (8 mg/kg) with CHO has an additive effect on rates of postexercise muscle glycogen accumulation compared with consumption of CHO alone.

The reduction in performance associated with low CHO availability is reversed with caffeine ingestion due to a higher anaerobic contribution, suggesting that caffeine could access an anaerobic "reserve" that is not used under normal conditions.

**Caffeine-reduced myocardial blood flow during exercise**

Acute ingestion of caffeine usually increases cardiac work; however, caffeine impairs the expected proportional increase in myocardial blood flow to match this increased work of the heart, most notably during exercise. This appears to be mainly due to caffeine's effect on blocking adenosine-induced vasodilatation in the coronary arteries in normal healthy subjects.

**Effect of caffeine on hydration**

Acute and chronic caffeine intakes have no impact on hydration status: a moderate caffeine dose, equivalent to approximately 5 espresso cups of coffee or 7 servings of tea, does not alter total body water and fluid distribution in healthy men, regardless of body composition, or daily water ingestion.

However, the available literature also suggests that acute ingestion of caffeine in large doses (at least 250-300 mg, equivalent to the amount found in 2-3 cups of coffee or 5-8 cups of tea) results in a short-term stimulation of urine output in individuals who have been deprived of caffeine for a period of days or weeks. A profound tolerance to the diuretic and other effects
of caffeine develops, however, and the actions are much diminished in individuals who regularly consume tea or coffee. Doses of caffeine equivalent to the amount normally found in standard servings of tea, coffee and carbonated soft drinks appear to have no diuretic action.

**Combination of coffee with ephedrine**

Unfortunately, there have been multiple deaths linked to the use of caffeine in combination with ephedra. It is felt that, when used in combination, the potential deadly effects are secondary to ephedra, rather than caffeine. However, the cardiovascular effects of ephedra are likely increased with concomitant stimulant use (e.g. caffeine).

From the metabolic point of view, combined ingestion of caffeine and ephedrine has been observed to increase blood glucose and lactate concentrations during exercise, whereas qualitatively similar effects on lipid fuels (free fatty acids and glycerol) are less pronounced. In parallel, epinephrine and dopamine concentrations are significantly increased, whereas the effects on norepinephrine are less clear. With respect to pulmonary gas exchange during short-term intense exercise, no physiologically significant effects have been reported following ingestion of caffeine, ephedrine or their combination. Yet, during longer and/or more demanding efforts, some sporadic enhancements have indeed been shown. On the other hand, a relatively consistent cardiovascular manifestation of the latter preparation is an increase in heart rate, in addition to that caused by exercise alone. Finally, evidence to date strongly suggests that caffeine and ephedrine combined are quite effective in decreasing the rating of perceived exertion and this seems to be independent of the type of activity being performed. In general, our knowledge and understanding of the physiological, metabolic and performance-enhancing effects of caffeine-ephedrine mixtures are still in their infancy.
INTRODUCTION

Caffeine (1,3,7-trimethylxanthine) is one of the most heavily consumed and widely studied stimulants in history. Caffeine-containing beverages, primarily coffee (Coffea arabica) and tea (Camellia sinensis), have been a mainstay in both Eastern and Western society for more than 500 years. The appearance of carbonated soft drinks or colas in the early 20th century often used kola nut (Cola acuminata) as a flavoring agent and caffeine source, whereas the recent emergence of energy drinks incorporate guarana (Paulinia cupana), green tea (C sinensis), and Yerba maté (Ilex paraguariensis) as natural caffeine sources. Together, these beverages constitute the primary sources of caffeine in the modern diet. In fact, almost 90 percent of US adults consume caffeine in forms of coffee, tea, or other caffeinated food products. The popularity of these beverages stems from the mild stimulatory effects (e.g. increased wakefulness, improved cognition, and decreased fatigue) that caffeine has on the central nervous system (CNS) when ingested in moderate quantities (≤200 mg). Because of its CNS stimulant properties, purified caffeine (≤200 mg) can also be found in various nonprescription drug products [001].

Caffeine (C8H10N4O2) is a unique compound. It is a drug with no nutritive value so entrenched in our food supply that it enjoys social acceptance and widespread use by the majority of adults around the world. Together with nicotine and alcohol, caffeine is among the most prevalent and culturally accepted drugs in western society. Its well-known effects of reducing fatigue and increasing alertness are prized by populations who need to prolong their capacity for occupational activities, for example, students studying for exams, shiftworkers, long-haul truck drivers, members of the military forces and athletes. In fact, new products such as non-prescription medications, “energy drinks”, confectionery and sports supplements containing caffeine or guarana are now being specifically manufactured to allow caffeine to be consumed as an ergogenic (work-enhancing) aid [002].

According to European and North American statistics, about 90 percent of the adult population consider themselves as daily coffee users with an average daily caffeine consumption of about 200 mg or 2.4 mg/kg/day (about 2 cups of coffee), and its trade exceeds USD10 billion worldwide. Caffeine is not only common in the general population, but have also made their way into elite sports because of their purported performance-altering potential. However, only caffeine – compared to nicotine and alcohol – has enough scientific evidence indicating an ergogenic effect. The main pharmacologically active substance in both is the purine alkaloid of the xanthines class, 1,3,7,-trimethylxanthine or caffeine. Caffeine is both water and fat soluble and is quickly distributed in the body after absorption mainly by the small intestine and the stomach with peaking plasma levels after 15-120 min and a half-life of about 5-6 hours with individual variation. Due to its lipophilic nature, caffeine also crosses the blood-brain barrier, and is metabolized by the liver into paraxanthine, theophylline, and theobromine [002].

Caffeine is thus the most widely ingested psychoactive drug in the world. As many know, chronic use of caffeine leads to dependence, tolerance, drug craving, and upon abrupt cessation unpleasant withdrawal symptoms. Thus, caffeine fulfills pharmacological criteria by which agents are classified as drugs of abuse. Nevertheless, its use is legal and only at high, but readily attainable, levels made it banned from sport as a doping substance for many years (not so now in 2015). Its use is widespread by athletes as young as 11 years of age who are seeking athletic advantage over fellow competitors. It is likely that its use will not decline any time soon because it is inexpensive, readily available, medically quite safe, socially acceptable, and by most measures legal. However, at levels allowed in sport, caffeine through its wide-ranging physiological and psychological effects increases endurance in well-trained athletes. If the goal of drug-testing and education programs in sport is to protect the health of athletes, prevent unfair advantage (cheating) and encourage ethical
behavior then it seems obvious that the allowable levels of caffeine ingestion may be discussed [003].

Proposed effects of caffeine

Caffeine is a common substance in the diets of most athletes and it is now appearing in many new products, including energy drinks, sport gels, alcoholic beverages and diet aids. It can be a powerful ergogenic aid at levels that are considerably lower than the acceptable limit of the International Olympic Committee and could be beneficial in training and in competition. Caffeine does not improve maximal oxygen capacity directly, but could permit the athlete to train at a greater power output and/or to train longer. It has also been shown to increase speed and/or power output in simulated race conditions. These effects have been found in activities that last as little as 60 seconds or as long as 2 hours. There is less information about the effects of caffeine on strength; however, recent work suggests no effect on maximal ability, but enhanced endurance or resistance to fatigue. There is no evidence that caffeine ingestion before exercise leads to dehydration, ion imbalance, or any other adverse effects. The ingestion of caffeine as coffee appears to be ineffective compared to doping with pure caffeine. Related compounds such as theophylline are also potent ergogenic aids. Caffeine may act synergistically with other drugs including ephedrine and anti-inflammatory agents. It appears that male and female athletes have similar caffeine pharmacokinetics, i.e., for a given dose of caffeine, the time course and absolute plasma concentrations of caffeine and its metabolites are the same. In addition, exercise or dehydration does not affect caffeine pharmacokinetics. The limited information available suggests that caffeine non-users and users respond similarly and that withdrawal from caffeine may not be important. The mechanism(s) by which caffeine elicits its ergogenic effects are unknown, but the popular theory that it enhances fat oxidation and spares muscle glycogen has very little support and is an incomplete explanation at best. Caffeine may work, in part, by creating a more favourable intracellular ionic environment in active muscle. This could facilitate force production by each motor unit [004].

Caffeine is the most commonly consumed drug in the world, and athletes frequently use it as an ergogenic aid. It improves performance and endurance during prolonged, exhaustive exercise. To a lesser degree it also enhances short-term, high-intensity athletic performance. Caffeine improves concentration, reduces fatigue, and enhances alertness. Habitual intake does not diminish caffeine's ergogenic properties. Several mechanisms have been proposed to explain the physiologic effects of caffeine, but adenosine receptor antagonism most likely accounts for the primary mode of action. It is relatively safe and has no known negative performance effects, nor does it cause significant dehydration or electrolyte imbalance during exercise. Routine caffeine consumption may cause tolerance or dependence, and abrupt discontinuation produces irritability, mood shifts, headache, drowsiness, or fatigue. Major sport governing bodies ban excessive use of caffeine, but current monitoring techniques are inadequate, and ethical dilemmas persist regarding caffeine intake by athletes [005].

Improvements in mood, cognition and perception

Caffeine is the most widely used pharmacologically active compound, and it has been estimated that 80-90 percent of users report habitual consumption, with a daily average intake of approximately 200-250 mg. Caffeine has been shown to enhance cognitive function and feelings of mental alertness, mood, and arousal. In addition, caffeine ingestion has been demonstrated to maintain or enhance vigilance and choice reaction time, and is commonly used to alleviate the effects of sleep deprivation and fatigue [006].

The effect of caffeine to promote improvements in mood, cognition, and exercise performance has been well established in young and athletic adults. However, acute caffeine
ingestion may not be as an effective ergogenic aid for improving muscular strength in older adults but could, possibly be used as a nutrition supplement for enhancing mood and improving cognitive performance in daily living tasks where interceptive timing skills are required [007].

The results of several studies demonstrate that caffeine reduces perception of effort and improves exercise performance, and this is one of the main reasons why three out of four elite athletes consume caffeine before or during competitions. The positive effect of caffeine on perception of effort is associated with changes in motor-related cortical activity during exercise, most likely in areas upstream of the primary motor cortex. Caffeine can also reduce exercise-induced muscle pain, increase pleasure during exercise, and increase exercise enjoyment. Importantly, caffeine can reduce perception of effort and exercise-induced muscle pain even at relatively low doses and in habitual high caffeine consumers. It should also be considered that, in real-life applications, the efficacy of caffeine would be enhanced by its placebo effect and associated changes in motor-related cortical activity. In addition to these positive psychobiological effects, caffeine can also create a greater energy deficit after exercise thus helping with the prevention and treatment of obesity. Although very promising, most studies demonstrating the positive effects of caffeine on perception of effort and discomfort during exercise are acute studies conducted in physically active participants. Therefore, we need to investigate further the acute and chronic effects of caffeine on perception of effort and other psychological responses to exercise in sedentary people. After this developmental research, we need to establish whether caffeine can actually change physical activity behaviour. Examples of this research include a randomized placebo-controlled trial to establish the effect of pre-exercise caffeine supplementation on adherence to vigorous exercise, followed by a larger pragmatic trial to evaluate the effectiveness of caffeine in increasing physical activity in the long term [008].

Proposed underlying physiological ways of action

Caffeine’s stimulant effects on the cardiovascular system and CNS stem from 4 principal mechanisms: nonselective antagonism of G-coupled adenosine A₁ and A₂A receptors, nonselective inhibition of phosphodiesterases with the subsequent accumulation of cyclic adenosine monophosphate (cAMP) and an intensification of the effects of catecholamines, mobilization of intracellular calcium via activation of ryanodine receptor channels, and inhibition of gamma-aminobutyric acid neurotransmission. Only at higher serum concentrations (>25 microg/mL) do the latter 3 mechanisms appear to contribute significantly to caffeine pharmacodynamics. Caffeine’s dose-dependent CNS stimulant effects (e.g. mood enhancement, wakefulness, insomnia, anxiety, tremors, and seizures) stem from antagonism of brain adenosine receptors, whereas antagonism of A₁ and A₂A receptors in the heart and vasculature account for its hemodynamic effects (e.g. increased heart rate, coronary and peripheral vasoconstriction, and elevated blood pressure). As a result of adenosine antagonism, caffeine also stimulates the release of several neurotransmitters (e.g. dopamine, norepinephrine, and serotonin), which also accounts for many of the drug’s indirect pharmacodynamic effects. Caffeine can also reduce cerebral, hepatic, and mesenteric blood flow and produce mild diuresis via increased glomerular filtration and enhanced sodium and water excretion. At higher doses, caffeine can also cause other pharmacodynamic effects, including bronchodilation, lipolysis, hyperglycemia, and hypokalemia. Caffeine-induced hypokalemia could contribute to ventricular arrhythmias and sudden death. Long-term consumption of caffeine, however, can lead to pharmacologic tolerance, which can occur within a few days. Owing to the rapid development of tolerance, a person’s response to caffeine depends on dose, dosing regularity, and their pharmacokinetic profile [009].
Caffeine is an adenosine receptor antagonist, applicable inter alia in the forms of coffee, tea, or energy drinks. It is assumed that caffeine stimulates neural activity through higher noradrenaline emission. Several studies have shown that caffeine improves sustained attention and alertness in simple tasks. The beneficial effects in complex tasks, however, are less consistent. Further, caffeine can improve both encoding and response speed to new stimuli, as well as long-term memory consolidation. However, it is not clear whether reported memory improvements could be due to an increase in attention during encoding. Effects of caffeine are moderated by level of habitual intake, age, and even personality. Caffeine can have negative effects at high doses (from about 400 mg). Such high doses can reduce motivation, and potentially also cognitive performance. It was for example in 1994 reported that doses of 420 mg doses of caffeine resulted in more commission errors and slower processing rate in cognitive tasks than lower doses. Further, withdrawal of heavy caffeine consumption can result in adverse side effects including headaches, increased subjective stress, fatigue, and decreased alertness [010].

**Ergogenic claims**

Caffeine has been demonstrated to be ergogenic at doses lower than those doses that result in a urine concentration of 12 microg/ml, and higher doses appear to exhibit no additional performance-enhancing effect. Furthermore, caffeine is metabolized at very different rates in individuals and hence urinary concentrations can vary considerably and do not always correlate to the dose ingested [011].
HISTORY OF ANTI-DOPING WITH REGARD TO CAFFEINE

Caffeine has been consumed in the form of coffee since around 850 AD when its use was popularized in Egypt. Caffeine has long held interest as a potential ergogenic aid. In fact, the fatigue-masking effects of caffeine have been known since the early 1900s [012].

From 1962 to 1972 and again from 1984 to 2003 caffeine was on the WADA banned list, with a concentration >12 microg/ml in the urine considered as doping. Caffeine has been demonstrated to be ergogenic at doses lower than those doses that result in a urine concentration of 12 microg/ml, and higher doses appear to exhibit no additional performance-enhancing effect. During the second banned period, many athletes tested positive for caffeine. The sanctions ranged from warnings up to 2 year suspensions (maximum penalty, usually only 2-6 months). Since 2004, caffeine has been removed from the prohibited list, however, it is still part of WADAs monitoring program (stimulants but in competition only) in order to monitor the possible potential of misuse in sport. According to WADA, one of the reasons caffeine was removed from the Prohibited List was that many experts believe it to be ubiquitous in beverages and food and that having a threshold might lead to athletes being sanctioned for social or dietary consumption of caffeine. Furthermore, caffeine is metabolized at very different rates in individuals and hence urinary concentrations can vary considerably and do not always correlate to the dose ingested. In addition, caffeine is added to a wide range of popular food products such as coffee, tea, energy drinks and bars, and chocolate [011].

Caffeine is thus a stimulant that is not currently banned by WADA, despite its proven ergogenicity. In the past it was included on the banned list at urine concentrations above (12 microg/mL), on the basis that concentrations below this level may be attained from the consumption of coffee, coca cola and similar sources, whereas above this concentration indicated a deliberate consumption, probably via tablets, with the intent of performance enhancement. It was removed from the banned list in 2004 but is still subject to monitoring, although it should be noted that the ergogenic benefits for a range of sports appear to be attained at modest doses (3 mg/kg) doses that are easily achieved via intake of everyday dietary sources such as coffee, cola drinks and energy drinks [013].

Caffeine levels before and after the removal of caffeine from the doping list

Caffeine concentrations were measured in the urine of 4633 athletes tested for doping control in the Ghent Doping Control Laboratory in 2004. Determination of these concentrations was done using an alkaline extraction with a mixture of dichloromethane and methanol (9 : 1; v/v) followed by high performance liquid chromatography and ultraviolet detection (HPLC-UV). The method was validated according to ISO 17 025 standards (International Organisation for Standardisation). Quantification was done by using a linear calibration curve in the range from 0 to 20 microg/mL. The limit of quantification (LOQ) was 0.10 microg/ml. Because the results were not normally distributed, transformation of the data was done to evaluate the difference in detected concentrations in several sports. This resulted in an overall average concentration of 1.12 + 2.68 microg/mL. Comparison of the most frequently tested sports in 2004 demonstrated that caffeine concentrations in samples originating from power lifters are significantly higher in comparison to urines taken in other sports. Also, a significant difference between caffeine concentrations found in cycling and concentrations found in other sports, including athletics and some ball sports, was observed. A comparison was made between results obtained in 2004 and results obtained before the removal of caffeine from the WADA (World Anti-Doping Agency) doping list indicating that average caffeine concentrations decreased after the withdrawal of caffeine from the list of prohibited substances. The overall percentage of positive samples between the two periods
remained the same although the percentage of positive samples noticed in cycling increased after the removal of caffeine from the doping list [014].
DOCUMENTED USE OF CAFFEINE BY ATHLETES

UK

One study was undertaken to examine self-reported caffeine consumption and reasons for its use, amongst UK athletes, following its removal from the 2004 World Anti-Doping Agency (WADA) Prohibited List. A convenience sample of track and field athletes (n=193) and cyclists (n=287) completed a postal or Web-based questionnaire. Messages were posted on athletics and cycling club Web sites and mailing lists to direct athletes to the Web-based questionnaire. Postal questionnaires were distributed at domestic sporting events. A higher proportion of cyclists (60 %) compared with track and field athletes (33 %) consumed caffeine to enhance performance. A higher proportion of elite as opposed to sub-elite athletes representing cycling and athletics used caffeine to enhance performance. Of all caffeine containing products used, coffee, energy drinks, pharmaceutical preparations and caffeinated sports supplements were most prevalent. Results revealed that amongst UK athletes, the intention to use caffeine as an ergogenic aid was high, and that use was more widespread and accepted in competitive sport, especially at elite level, when compared to recreational sport [015].

Spain

One study showed that 3 out of 4 elite athletes consume caffeine prior to competing, based on the post-exercise urinary caffeine concentrations of 20,686 urine samples obtained for doping analysis. However, the manner in which athletes consume caffeine is diverse. Caffeine is present in coffee and chocolate beans, tea leaves and cola nuts and so can be consumed from natural sources (coffee, tea, chocolate, etc). In addition, caffeine can be artificially synthesized and included in food and drinks, like the recently created energy drinks. These beverages contain moderate amounts of caffeine (32 mg/100 mL) in addition to carbohydrates, taurine, glucoronolactone and B-group vitamins. Due to their low cost, accessibility, and the relatively low frequency of deleterious side-effects derived from their consumption, caffeine-containing energy drinks have become the most popular supplement in the sports population, with a prevalence of 73 percent in American college athletes, 75 percent in Canadian Varsity athletes and 42 percent in British elite athletes [016].

Canada

The purpose of one review was to examine the prevalence of coffee and (or) caffeine consumption among elite Canadian athletes, and to delineate the effects of coffee and caffeine on physical activity, weight maintenance, performance, and metabolism. A total of 270 self-reported 3-day food records were examined for caffeine intake from athletes registered with Canadian Sport Centres in 2005 and 2006. Athletes ranged in age from 16-45 years, and competed in 38 different sports. Results showed that 30 percent of athletes ingested >1 mg/kg per day from a variety of sources. Average daily intake was 0.85 mg/kg. Caffeine intake was not correlated with any one sport; the 10 highest caffeine users were athletes from 9 different sports, including skill, endurance, and power sports. No differences were noted for average caffeine ingestion between summer and winter sports. High caffeine intakes corresponded to coffee ingestion, with the 25 highest individual intakes (193-895 mg/day) from coffee drinkers. In summary, it could be concluded that the majority of high-level Canadian athletes consume dietary caffeine primarily in the form of coffee. However, levels consumed are insufficient to elicit performance enhancement. Potential detrimental effects of caffeine consumption on exercise performance include gastric upset, withdrawal, sleep disturbance, and interactions with other dietary supplements [017].
Belgium

Caffeine concentrations were measured in the urines of 11,361 athletes tested for doping control in the Ghent doping control laboratory during the period 1993-2002. Determination of these concentrations was done using an alkaline extraction with a mixture of dichloromethane and methanol (9:1; v/v) followed by high performance liquid chromatography and ultraviolet detection (HPLC-UV). The method was validated according to ISO 17 025 standards (International Organisation for Standardisation). Quantification was done by using a calibration curve in the range from 0 to 20 microg/ml. The limit of quantification (LOQ) was 0.10 microg/ml. Most caffeine concentrations were far below 12 microg/ml. Because the results were not normally distributed, transformation of the data was done to evaluate the difference in detected concentrations in several sports. This resulted in an overall average concentration of 1.22 ± 2.45 microg/mL. Comparison of those sports with more than 200 samples being analysed demonstrated that caffeine concentrations in urine samples from bodybuilders are significantly higher in comparison to urines taken in the other sports. Also, a significant difference between caffeine concentrations found in cycling and concentrations found in other sports, including athletics and some ball sports, was observed [018].

Use as a flavor for consuming behavior

Using sweeteners as controls, it was assessed whether caffeine has flavor activity in a cola soft-drink. A forced-choice triangle discrimination methodology was used to determine detection thresholds of caffeine in sweeteners and a cola beverage. The subjects (n=30, 28 female, 23 years old) were trained tasters and completed over 1600 discrimination tests during the study. The mean detection thresholds for caffeine in the sweet solutions were: 0.333 ± 0.1mM sucrose; 0.467 ± 0.29 mM aspartame; 0.462 ± 0.3mM sucralose, well below the concentration in common cola beverages (0.55-0.67 mM). A fixed concentration of caffeine, corresponding to the concentration of caffeine in a common cola beverage (0.67 mM) was added to the sweeteners and a non-caffeinated cola beverage. Subjects could distinguish between caffeinated and non-caffeinated sweeteners, but all subjects failed to distinguish between caffeinated and non-caffeinated cola beverage. Caffeine has no flavor activity in soft-drinks yet will induce a physiologic and psychologic desire to consume the drink [019].

Emergency medicine residents’ use

It was evaluated the frequency that emergency medicine house staff report use of stimulants and sedatives to aid in shift work and circadian transitions. It was surveyed residents from 12 regional emergency medicine programs inviting them to complete a voluntary, anonymous electronic questionnaire regarding their use of stimulants and sedatives. Out of 485 eligible residents invited to participate in the survey, 226 responded (47 % response frequency). The reported use of prescription stimulants for shift work is uncommon (3 % of respondents.) In contrast, 201 residents (89 %) report use of caffeine during night shifts, including 118 residents (52 %) who use this substance every night shift. Eighty-six residents (38 %) reported using sedative agents to sleep following shift work with the most common agents being anti-histamines (31 %), nonbenzodiazepine hypnotics such as zolpidem (14 %), melatonin (10 %), and benzodiazepines (9 %). It was concluded that emergency medicine residents report substantial use of several classes of hypnotics to aid in shift work. Despite anecdotal reports, use of prescription stimulants appears rare, and is notably less common
than use of sedatives and non-prescription stimulants [020].
PHARMACOLOGY OF CAFFEINE

Absorption, blood levels and half-life

Caffeine is rapidly absorbed by the body, when consumed in coffee and capsules, and appears in the blood within 5-15 min and peaks between 40 and 80 min. Plasma caffeine levels rise to 15-20 lmol/L with a low caffeine dose (3 mg/kg bm), 40 lmol/L with a moderate dose (6 mg/kg bm), and 60-70 mol/L with a high dose of 9 mg/kg bm. Caffeine also has a long half-life (3-5 h), which makes it well suited to interact with many tissues in the body. However, since caffeine interacts with many tissues, it is difficult to independently study its effects on the CNS, the peripheral nervous system, and the many metabolic tissues in the body (skeletal muscle, liver, heart, and adipose tissue) at rest and during exercise. However, it has been shown that the plasma caffeine levels needed to affect changes in the metabolic tissues are substantially higher than required to affect the adenosine receptors in the brain and peripheral nervous system, making it unlikely that there could be major ergogenic effects with caffeine doses of 3 mg/kg bm or less where plasma levels are 15-20 lmol/L. The lack of changes in heart rate and levels of catecholamines, lactate, FFA and glycerol with this low dose of caffeine supports this argument [021].

Absorption of caffeine

Previous investigations have determined that caffeine is completely absorbed by the gastrointestinal tract within 1 hour, with peak plasma concentrations occurring between 15 and 120 minutes following ingestion. Plasma caffeine concentrations have also been shown to rise in a dose-dependent manner and exhibit first order, linear kinetics resulting in a half-life of approximately 5 hours. However, the half-life of caffeine has also been reported to range between 2.5 and 10 hours by other investigators. Additionally, the nature of formulation can also directly influence the rate and extent of absorption following oral administration as caffeine has shown to have a greater rate of absorption from a capsule than from dietary sources such as coffee, cola, or chocolate [006].

Pharmacokinetics

Caffeine’s physicochemical and pharmacokinetic properties set it apart from most phytochemicals. Caffeine is one of the few phytochemicals whose oral bioavailability is almost complete. Peak blood concentrations of caffeine are usually achieved within an hour of ingestion. On account of its excellent aqueous solubility and small molecular weight, caffeine readily enters the intracellular space and is widely distributed – its volume of distribution mimics that of total body water. Accordingly, caffeine readily crosses the blood brain barrier and can be found in almost all body fluids and tissues. The pharmacokinetic properties of caffeine are dose dependent, which likely contributes to toxic effects associated with many caffeine-containing dietary supplements. Caffeine biotransformation is mediated primarily via hepatic cytochrome P450 1A2 (CYP1A2), and saturation of this pathway can occur at doses as low as 5 mg/kg. Caffeine’s principal CYP1A2-mediated metabolite in humans is paraxanthine, which exhibits pharmacologic effects similar to its parent compound, whereas minor metabolites include theophylline and theobromine. Caffeine clearance is highly variable, and both genetic and environmental factors (e.g. diet, smoking, and oral contraceptive use) are contributors to this variability. Like the receptor polymorphisms mentioned above, allelic variants in CYP1A2 can affect caffeine’s pharmacokinetic properties and pharmacologic response. Among caffeine users, both slow and rapid metabolizer phenotypes have been described, each corresponding to respective allelic variants that give rise to loss or gain of enzyme function. Habitual coffee use and higher consumption of coffee appear to correlate with rapid metabolizer phenotypes (homozygous CYP1A2*1A), whereas slow metabolizer phenotypes (heterozygous
CYP1A2*1F) have been linked to higher risks of hypertension and nonfatal myocardial infarction [001].

**Urinary caffeine levels**

Because some were afraid that the misuse of caffeine might increase after its removal from the doping list, the urinary concentrations have been monitored since. Data presented show that the misuse did not increase, although in some sport disciplines such as cycling some misuse of caffeine was still found. Some advocated than that if unfair play should be prevented it might be reconsidered to add caffeine to the list again with a urinary threshold level of 12 microg/mL. However, it should be emphasized that research has shown that caffeine has performance enhancing properties up to approximately 5 mg/kg, above which no additional effect on performance was found. However, when dosages up to 5 mg/kg are taken the urine levels generally stay below 12 microg/mL. So, there is no scientific basis to support the statement that re-establishing a threshold of 12 microg/ml would avoid unfair competition. The misuse found in some sports may be attributed to lack of knowledge and education which appears to be supported by the facts in several doping cases. An important, but too often underscored aspect of the fight against doping is education of athletes and people around the athlete. The recommendation to add caffeine to the doping list again ignores the reasons why it was removed some years ago. Proper education in those sports where caffeine is still abused may be a more effective approach [022].

**Environmental influences on blood levels**

CYP1A2 allelic variants aside, caffeine metabolism is also susceptible to a host of environmental influences. Smoking and diets rich in cruciferous vegetables induce CYP1A2 gene expression, presumably through activation of the aryl hydrocarbon nuclear receptor, resulting in enhanced caffeine clearance. Conversely, alcohol consumption, oral contraceptives, fluvoxamine, and quinolone antibiotics are known to inhibit CYP1A2 activity, lower caffeine clearance, and increase both area under the plasma concentration time curve and elimination half-life. Other phytochemicals thought to affect the pharmacokinetic properties of caffeine when consumed concomitantly include tanshinone, quercetin, genistein, curcumin, daidzein, and naringenin. Given the multiplicity of botanical extracts that constitute caffeine-containing dietary supplement formulations, it is difficult to predict how such complex phytochemical mixtures will affect caffeine pharmacokinetic and pharmacodynamic properties. What is well recognized, however, is that caffeine can potentiate the cardiovascular and CNS effects of other stimulants. Such stimulants include plant-derived alpha- and beta-adrenergic agonists such as those found in Ephedra species (e.g. ephedrine, pseudoephedrine, norephedrine, and methylephedrine) and alpha2- adrenergic antagonists from the African plant Pausinystalia yohimbe (e.g. yohimbine and rauwolscine), as well as synthetic stimulants such as amphetamine, methamphetamine, 3,4-methylenedioxyamphetamine, and cocaine. When combined with ephedrine alkaloids or amphetamines, especially in the context of vigorous exercise, caffeine may increase the likelihood of serious adverse health effects, such as arrhythmia, myocardial infarction, stroke, seizure, hypertensive crisis, and exertional heat illness [001].

**Pharmacokinetic interactions between dietary caffeine and medications**

Caffeine from dietary sources (mainly coffee, tea and soft drinks) is the most frequently and widely consumed CNS stimulant in the world today. Because of its enormous popularity, the consumption of caffeine is generally thought to be safe and long term caffeine intake may be disregarded as a medical problem. However, it is clear that this compound has many of the features usually associated with a drug of abuse. Furthermore, physicians should be aware of the possible contribution of dietary caffeine to the presenting signs and symptoms of
patients. The toxic effects of caffeine are extensions of their pharmacological effects. The most serious caffeine-related CNS effects include seizures and delirium. Other symptoms affecting the cardiovascular system range from moderate increases in heart rate to more severe cardiac arrhythmia. Although tolerance develops to many of the pharmacological effects of caffeine, tolerance may be overwhelmed by the nonlinear accumulation of caffeine when its metabolism becomes saturated. This might occur with high levels of consumption or as the result of a pharmacokinetic interaction between caffeine and over-the-counter or prescription medications. The polycyclic aromatic hydrocarbon-inducible cytochrome P450 (CYP) 1A2 participates in the metabolism of caffeine as well as of a number of clinically important drugs. A number of drugs, including certain selective serotonin reuptake inhibitors (particularly fluvoxamine), antiarrhythmics (mexiletine), antipsychotics (clozapine), psoralens, idrocilamide and phenylpropanolamine, bronchodilators (furafylline and theophylline) and quinolones (enoxacin), have been reported to be potent inhibitors of this isoenzyme. This has important clinical implications, since drugs that are metabolised by, or bind to, the same CYP enzyme have a high potential for pharmacokinetic interactions due to inhibition of drug metabolism. Thus, pharmacokinetic interactions at the CYP1A2 enzyme level may cause toxic effects during concomitant administration of caffeine and certain drugs used for cardiovascular, CNS (an excessive dietary intake of caffeine has also been observed in psychiatric patients), gastrointestinal, infectious, respiratory and skin disorders. Unless a lack of interaction has already been demonstrated for the potentially interacting drug, dietary caffeine intake should be considered when planning, or assessing response to, drug therapy. Some of the reported interactions of caffeine, irrespective of clinical relevance, might inadvertently cause athletes to exceed the urinary caffeine concentration limit set by sports authorities at 12 mg/L. Finally, caffeine is a useful and reliable probe drug for the assessment of CYP1A2 activity, which is of considerable interest for metabolic studies in human populations [023].

**Urinary concentration of caffeine after ad libitum caffeinated carbohydrate solution**

The purpose of one study was to examine the effect of ad libitum ingestion of a carbohydrate-electrolyte solution (CES) with 150 mg/L caffeine (CAF) on urinary CAF concentration after 4 h of endurance exercise. Fifty-eight healthy and well-trained male subjects ingested ad libitum a 7 percent CES with 150 mg/L CAF during 4 h cycling at 50 percent of maximal work capacity. Total fluid consumption was 2799 ± 72 mL and CAF intake was 420 ± 11 mg (5.7 ± 0.2 mg/kg body weight). The post-exercise urinary CAF concentration (4.53 ± 0.25 microg/mL) was below the doping level of the International Olympic Committee (12 microg/mL) in all subjects (range 1.20 to 10.84 microg/mL). A highly positive correlation was observed between CAF intake and post-exercise urinary CAF concentration. It is concluded that ad libitum ingestion of a CES with 150 mg/L CAF during 4 h cycling resulted in post-exercise urinary concentration below the doping level in all subjects [024].

**Individual sensitivity**

Individual sensitivity to the effects of caffeine is well recognized. Such sensitivities may be attributable, in part, to an individual’s genetic makeup. Only recently has an appreciation developed for the effects that human receptor gene polymorphisms can have on the pharmacodynamics of caffeine. Adenosine A2A and alpha-2-adrenergic receptor polymorphisms have been linked to caffeine-induced insomnia, anxiety, habitual coffee consumption, and blood pressure elevation, whereas animal studies hint that cardiac ryanodine receptor mutations may increase caffeine’s arrhythmogenic potential. Another gene polymorphism associated with the adverse effects of caffeine is the enzyme catechol-O-methyltransferase (COMT). In the case of functional COMT polymorphisms, the
sympathomimetic effects of endogenous catecholamines (eg, norepinephrine) are enhanced; after caffeine ingestion, such mutations have been linked to rapid heart beat, elevated blood pressure, and the incidence of acute coronary events. Despite these emerging gene-caffeine associations, more work is required before the functional variants involved in the caffeine response can be delineated [001].

Exercise and obesity

Because many caffeine-containing dietary supplements are marketed as exercise performance enhancers and weight loss aids, exercise and obesity have exhibited equivocal effects on caffeine pharmacokinetic properties. Several studies suggest that caffeine disposition is not significantly altered during exercise, while other studies indicate that peak caffeine plasma levels may be enhanced. Likewise, obesity’s effect on caffeine pharmacokinetic properties is also difficult to predict. Such ambiguities may contribute to the questionable tolerability and efficacy of caffeine-containing dietary supplements. What is less ambiguous is that vigorous exercise may exacerbate the pharmacodynamic effects of caffeine. Of particular concern is the recent finding that caffeine reduces myocardial blood flow during exercise. Such consequences could have significant health repercussions, especially in caffeine-naïve, untrained athletes. Collectively, these genetic and environmental influences can have a significant bearing on the tolerability of caffeine-containing dietary supplements [001].
**PHYSIOLOGICAL MODE OF ACTION OF CAFFEINE**

Caffeine is lipophilic and readily crosses most bodily membranes. It crosses to blood-brain barrier (BBB) and also crosses the placenta. Caffeine has been theorized to exert its effects through fat oxidation, central nervous system (CNS) stimulation, and direct action at skeletal muscle. There are several purported mechanisms for these effects including antagonism of adenosine receptors, inhibition of cyclic AMP, phosphodiesterase activity, increased calcium mobilization, and antagonism of benzodiazepine receptors [06183]. As for many pharmacological substances, there is generally more than one potential mechanism explaining the ergogenic effects. This is also true for caffeine which might affect both the central nervous system (CNS) and skeletal muscle [011].

**Methylxanthines**

One two-part investigation compared the ergogenic and metabolic effects of theophylline and caffeine. Initially (part A), the ergogenic potential of theophylline on endurance exercise was investigated. Eight men cycled at 80 percent maximum \( \text{O}_2 \) consumption to exhaustion 90 min after ingesting either placebo (dextrose), caffeine (6 mg/kg; Caff), or theophylline (4.5 mg/kg Theolair; Theo). There was a significant increase in time to exhaustion in both the Caff (41.2 ± 4.8 min) and Theo (37.4 ± 5.0 min) trials compared with placebo (32.6 ± 3.4 min). In part B, the effects of Theo on muscle metabolism were investigated and compared with Caff. Seven men cycled for 45 min at 70 percent maximum \( \text{O}_2 \) consumption (identical treatment protocol as in part A). Neither methylxanthines (MX) affected muscle glycogen utilization. Only Caff increased plasma epinephrine, but both MX increased blood glycerol levels. Muscle cAMP was increased by both MX at 15 min and remained elevated at 45 min with Theo. This demonstrates that both MX are ergogenic and that this can be independent of muscle glycogen [025].

Three possible mechanisms through which the methylxanthines may exert their metabolic effects include increased intracellular \( \text{Ca}^{2+} \) release, inhibition of cAMP phosphodiesterase, and antagonism of adenosine receptors. It is now established that adenosine receptor antagonism is the most relevant mechanism in vivo because pharmacological doses of methylxanthines (mM) rather than physiological doses (micrM) are needed to elicit a \( \text{Ca}^{2+} \) or phosphodiesterase inhibition effect. Many studies examining the mechanism behind the ergogenic effect of caffeine have focused on the methylxanthine-induced increase in circulating plasma epinephrine and the metabolic changes that occur with exercise. However, recent studies have provided evidence that an ergogenic effect of caffeine has been demonstrated without an increase in plasma epinephrine. In addition, an increase in free fatty acid (FFA) mobilization without a corresponding catecholamine response has been demonstrated, indicating a direct effect of caffeine on fat cells. Carbohydrate metabolism has been shown to be unaltered when epinephrine was infused to mimic the caffeine-induced epinephrine response. Glycogen sparing has not always been found during exercise after caffeine ingestion, and an increase in performance has been observed in exercise situations in which muscle glycogen is not the limiting factor and when no glycogen sparing was observed. A direct effect of caffeine on the central nervous system has also been postulated to explain the ergogenic effect of this methylxanthine; however, it has been demonstrated that this is not a critical mechanism [025].

Methylxanthines are nonselective adenosine receptor antagonists at \( A_1 \) and \( A_2 \) receptors, and in vitro theophylline, a dimethylxanthine, is a more potent adenosine receptor antagonist than caffeine. It was demonstrated an attenuation of adenosine-induced cardiovascular effects after theophylline administration. In addition, it was reported that adenosine administration increases muscle sympathetic nervous system activity and that this increase
was dampened by theophylline infusion, providing evidence of a methylxanthine-induced antagonism of adenosine receptors in various human tissues. It was also found that adenosine receptor antagonism by caffeine stimulated rather than inhibited net glycogenolysis in a contracting isolated rat hindlimb perfusion. The study demonstrated that adenosine inhibits glycogenolysis in contracting oxidative muscle fibers and may be a potential modulator of carbohydrate metabolism. When it was used stable isotopes and indirect calorimetry to determine the effect of theophylline on substrate metabolism during 30 min of moderate submaximal exercise glucose rate of disappearance was less after theophylline administration, suggesting that adenosine antagonism decreased glucose uptake during exercise. Estimation of muscle glycogen utilization, based on respiratory exchange ratio (RER) data, led to the conclusion that adenosine may play a role in regulating carbohydrate metabolism by decreasing glycogenolysis in contracting skeletal muscle. These studies suggest that methylxanthines should increase muscle glycogen use via adenosine antagonism, yet previous investigations of exercising humans demonstrated a glycogen sparing effect of caffeine [025].

**Activation of 5’AMP-activated protein kinase (AMPK)**

Caffeine activates 5’AMP-activated protein kinase (AMPK), a signalling intermediary implicated in the regulation of glucose, lipid, and energy metabolism in skeletal muscle. Skeletal muscle expresses two catalytic alpha subunits of AMPK, alpha1 and alpha2, but the isoform specificity of caffeine-induced AMPK activation is unclear. The aim of one study was to determine which alpha isoform is preferentially activated by caffeine in vitro and in vivo using rat skeletal muscle. Rat epitrochlearis muscle was isolated and incubated in vitro in the absence or presence of caffeine. In another experiment, the muscle was dissected after intravenous injection of caffeine. Isoform-specific AMPK activity, the phosphorylation status of AMPKalph Thr(172) and acetyl-CoA carboxylase (ACC) Ser(79), the concentrations of ATP, phosphocreatine (PCr), and glycogen, and 3-O-methyl-d-glucose (3MG) transport activity were estimated. Incubation of isolated epitrochlearis muscle with 1 mM of caffeine for 15 min increased AMPKalpha1 activity, but not AMPKalpha2 activity; concentrations of ATP, PCr and glycogen were not affected. Incubation with 3 mM of caffeine activated AMPKalpha2 and reduced PCr and glycogen concentrations. Incubation with 1 mM of caffeine increased the phosphorylation of AMPK and ACC and enhanced 3MG transport. Intravenous injection of caffeine (5 mg/kg) predominantly activated AMPKalpha1 and increased 3MG transport without affecting energy status. The results suggest that of the two alpha isoforms of AMPK, AMPKalpha1 is predominantly activated by caffeine via an energy-independent mechanism and that activation of AMPKalpha1 increases glucose transport and ACC phosphorylation in skeletal muscle [026].

Studies have proposed that caffeine-induced activation of glucose transport in skeletal muscle is independent of AMP-activated protein kinase (AMPK) because alpha-AMPK Thr172 phosphorylation was not increased by caffeine. However, previous studies, as well as the present, show that AMPK phosphorylation measured in whole muscle lysate is not a good indicator of AMPK activation in rodent skeletal muscle. In lysates from incubated rat soleus muscle, a predominant model in previous caffeine-studies, both acetyl-CoA carboxylase-beta (ACCbeta) Ser221 and immunoprecipitated alpha1-AMPK activity increased with caffeine incubation, without changes in AMPK phosphorylation or immunoprecipitated alpha2-AMPK activity. This pattern was also observed in mouse soleus muscle, where only ACCbeta and alpha1-AMPK phosphorylation were increased following caffeine treatment. Preincubation with the selective CaMKK inhibitor STO-609 (5 microM), the CaM-competitive inhibitor KN-93 (10 microM), or the SR Ca2+ release blocking agent dantrolene (10 microM) all inhibited ACCbeta phosphorylation and alpha1-AMPK phosphorylation, suggesting that SR Ca(2+) release may work through a CaMKK-AMPK...
pathway. Caffeine-stimulated 2-deoxyglucose (2DG) uptake reflected the AMPK activation pattern, being increased with caffeine and inhibited by STO-609, KN-93, or dantrolene. The inhibition of 2DG uptake is likely causally linked to AMPK activation, since muscle-specific expression of a kinase-dead AMPK construct greatly reduced caffeine-stimulated 2DG uptake in mouse soleus. It was concluded that a SR Ca2+-activated CaMKK may control alpha1-AMPK activation and be necessary for caffeine-stimulated glucose uptake in mouse soleus muscle [027].

**Effect on adenosine receptors**

Caffeine probably has multiple targets in the brain, but the main one seems to be adenosine receptors. Adenosine is a brain chemical that dampens brain activity. By hogging adenosine’s receptors, caffeine sets off a chain of events that affects the activity of dopamine, another important brain chemical, and the areas of the brain involved in arousal, pleasure, and thinking. The part of the brain affected by Parkinson’s disease, called the striatum, has many adenosine receptors; by docking on them, caffeine seems to have some protective effects [028].

Current research suggests that the main mechanism responsible for the physiologic effects of caffeine is blockade of CNS adenosine receptors. Because it easily crosses the blood-brain barrier, caffeine can readily have an effect on the CNS. The dosage of caffeine required to block adenosine receptors is much less than that required for caffeine to perform most of the other theorized physiologic mechanisms. Due to its close chemical resemblance of adenosine, caffeine blocks adenosine receptors (mainly A1 and A2A receptor subtypes), thereby competitively inhibiting its action. Caffeine promotes wakefulness by blocking adenosine A(2A) receptors (A(2A)Rs) in the brain, but the specific neurons on which caffeine acts to produce arousal have not been identified. Using selective gene deletion strategies based on the Cre/loxP technology in mice and focal RNA interference to silence the expression of A(2A)Rs in rats by local infection with adeno-associated virus carrying short-hairpin RNA, it was reported that the A(2A)Rs in the shell region of the nucleus accumbens (NAc) are responsible for the effect of caffeine on wakefulness. Caffeine-induced arousal was not affected in rats when A(2A)Rs were focally removed from the NAc core or other A(2A)R-positive areas of the basal ganglia. The observations suggest that caffeine promotes arousal by activating pathways that traditionally have been associated with motivational and motor responses in the brain [029].

Caffeine can decrease cerebral blood flow as well as antagonize A1, A2A and A2B adenosine receptors in blood vessels, thereby reducing adenosine-mediated vasodilatation and consequently decrease myocardial blood flow [13343]. A study using laboratory animals compared the results of centrally administered caffeine (an adenosine antagonist) with 5’-N-ethylcarboxamidoadenosine (NECA), an adenosine agonist. Caffeine improved run time to fatigue whereas NECA reduced it. Administration of caffeine peripherally failed to produce the same effect. Adenosine is a modulator of CNS neurotransmission. It is a potent vasodilator. It also decreases catecholamine release and inhibits lipolysis. Caffeine non-selectively blocks adenosine receptors, thus competitively inhibiting the action of adenosine. Up-regulation of these receptors occurs with regular consumption of caffeine [012].

*Caffeine and contraction synergistically stimulate 5’-AMP-activated protein kinase*

5’-Adenosine monophosphate-activated protein kinase (AMPK) has been identified as a key mediator of contraction-stimulated insulin-independent glucose transport in skeletal muscle. Caffeine acutely stimulates AMPK in resting skeletal muscle, but it is unknown whether caffeine affects AMPK in contracting muscle. Isolated rat epitrochlearis muscle was preincubated and then incubated in the absence or presence of 3 mmol/L caffeine for 30 or
120 min. Electrical stimulation (ES) was used to evoke tetanic contractions during the last 10 min of the incubation period. The combination of caffeine plus contraction had additive effects on AMPKαThr(172) phosphorylation, alpha-isoform-specific AMPK activity, and 3-O-methylglucose (3MG) transport. In contrast, caffeine inhibited basal and contraction-stimulated Akt Ser(473) phosphorylation. Caffeine significantly delayed muscle fatigue during contraction, and the combination of caffeine and contraction additively decreased ATP and phosphocreatine contents. Caffeine did not affect resting tension. Next, rats were given an intraperitoneal injection of caffeine (60 mg/kg body weight) or saline, and the extensor digitorum longus muscle was dissected 15 min later. ES of the sciatic nerve was performed to evoke tetanic contractions for 5 min before dissection. Similar to the findings from isolated muscles incubated in vitro, the combination of caffeine plus contraction in vivo had additive effects on AMPK phosphorylation, AMPK activity, and 3MG transport. Caffeine also inhibited basal and contraction-stimulated Akt phosphorylation in vivo. These findings suggest that caffeine and contraction synergistically stimulate AMPK activity and insulin-independent glucose transport, at least in part by decreasing muscle fatigue and thereby promoting energy consumption during contraction [030].

Experimental

Inhibition of adenosine receptor agonist-induced decreases in motor performance

It was examined the effects of an adenosine receptor agonist on caffeine-induced changes in thermoregulation, neurotransmitter release in the preoptic area and anterior hypothalamus, and endurance exercise performance in rats. One hour before the start of exercise, rats were intraperitoneally injected with either saline alone (SAL), 10 mg/kg caffeine and saline (CAF), a non-selective adenosine receptor agonist (5'-N-ethylcarboxamidoadenosine [NECA]: 0.5mg/kg) and saline (NECA), or the combination of caffeine and NECA (CAF+NECA). Rats ran until fatigue on the treadmill with a 5 percent grade at a speed of 18 m/min at 23°C. Compared to the SAL group, the run time to fatigue (RTTF) was significantly increased by 52 percent following caffeine administration and significantly decreased by 65 percent following NECA injection. NECA decreased the core body temperature (Tcore), oxygen consumption, which is an index of heat production, tail skin temperature, which is an index of heat loss, and extracellular dopamine (DA) release at rest and during exercise. Furthermore, caffeine injection inhibited the NECA-induced decreases in the RTTF, Tcore, heat production, heat loss, and extracellular DA release. Neither caffeine nor NECA affected extracellular noradrenaline or serotonin release. These results support the findings of previous studies showing improved endurance performance and overrides in body limitations after caffeine administration, and imply that the ergogenic effects of caffeine may be associated with the adenosine receptor blockade-induced increases in brain DA release [031].

Acceleration of fat metabolism

Recent studies have shown that caffeine (CAF) can act as an ergogenic aid, both in short and long-term exercise at both central and peripheral level. Conversely to what was initially thought, CAF intake does not seem to be able to accelerate fat metabolism and to spare muscle glycogen during exercise, which would explain the increased performance observed in endurance tasks. Currently, this potential effect of CAF is credited to its affinity to adenosine receptors (A1 and A2a). When CAF molecules bind with these pre and post synaptic receptors, it inhibits adenosine action, promoting the release of excitatory neurotransmitters, increasing corticomotor excitability. This stimulatory effect of CAF on the central nervous system may be responsible for modifying the motivation parameters that cause sustain discomfort during physical exercise, reducing the rating of perceived exertion (RPE) during exercise [032].
Delay fatigue through CNS mechanisms by blocking adenosine receptors

Caffeine ingestion can delay fatigue during exercise, but the mechanisms remain elusive. One study was designed to test the hypothesis that blockade of central nervous system (CNS) adenosine receptors may explain the beneficial effect of caffeine on fatigue. Initial experiments were done to confirm an effect of CNS caffeine and/or the adenosine A(1)/A(2) receptor agonist 5'-N-ethylcarboxamidoadenosine (NECA) on spontaneous locomotor activity. Thirty minutes before measurement of spontaneous activity or treadmill running, male rats received caffeine, NECA, caffeine plus NECA, or vehicle during four sessions separated by approximately 1 wk. CNS caffeine and NECA (intracerebroventricular) were associated with increased and decreased spontaneous activity, respectively, but caffeine plus NECA did not block the reduction induced by NECA. CNS caffeine also increased run time to fatigue by 60 percent and NECA reduced it by 68% vs. vehicle. However, unlike the effects on spontaneous activity, pretreatment with caffeine was effective in blocking the decrease in run time by NECA. No differences were found after peripheral (intraperitoneal) drug administration. Results suggest that caffeine can delay fatigue through CNS mechanisms, at least in part by blocking adenosine receptors [033].

Mobilization of intracellular calcium

It has been shown that caffeine can enhance calcium release from the sarcoplasmic reticulum and can also inhibit its reuptake. Via this mechanism, caffeine can enhance contractile force during submaximal contractions in habitual and nonhabitual caffeine consumers. Intracellular calcium favors the activation of endothelial nitric oxide synthase, which increases nitric oxide. Some of the ergogenic effects of caffeine might therefore as well be mediated partly by effecting the neuromuscular system and increasing contractile force. There is, however, still controversy about the translation of results from in vitro studies on muscle preparations to caffeine dose and calcium release in vivo [011].

Aerobic exercise training elicits adaptations in coronary smooth muscle that result in a novel intracellular Ca$^{2+}$ signaling phenomenon termed sarcoplasmic reticulum (SR) Ca$^{2+}$ unloading. Sarcoplasmic reticulum Ca$^{2+}$ unloading is defined as a time-dependent depletion and then repletion of the caffeine-sensitive SR Ca$^{2+}$ store. Male, Yucatan swine (8 months old) were maintained: sedentary or exercise trained (treadmill running performed 5 d/wk for 16 weeks). Smooth muscle cells were isolated from the right coronary artery and loaded with the intracellular Ca$^{2+}$-indicator, fura-2. Sarcoplasmic reticulum Ca$^{2+}$ content was assessed as the change in the caffeine (5 mM)-induced intracellular Ca$^{2+}$ peak after a 2-, 5-, 8-, 11- or 13-min recovery from high K$^+$ (depolarization)-induced Ca$^{2+}$ influx in a physiological (2 mM) Ca$^{2+}$ solution. The effect of Ca$^{2+}$ influx on SR Ca$^{2+}$ unloading was assessed by replacing the 2 mM Ca$^{2+}$ solution with a virtually Ca$^{2+}$-free (100 nM) solution during the recovery period. Consistent with previous studies, SR Ca$^{2+}$ unloading was not observed in cells from sedentary swine. In cells from exercise-trained swine, SR Ca$^{2+}$ depletion was observed in both the 2 mM and Ca$^{2+}$-free solutions, suggesting that Ca$^{2+}$-induced Ca$^{2+}$ release was not initiating SR Ca$^{2+}$ unloading during the recovery period. In addition, the reloading of the SR Ca$^{2+}$ store occurred even in the Ca$^{2+}$-free solution, suggesting that exercise training facilitates an internal cycling of Ca$^{2+}$ between the SR and another intracellular Ca$^{2+}$ store. It was concluded that in coronary smooth muscle from male swine, Ca$^{2+}$ influx is not necessary for the exercise training-induced phenomenon, SR Ca$^{2+}$ unloading [034].

During vigorous exercise, Pi concentration levels within the cytoplasm of fast-twitch muscle fibers may reach >30 mM. Cytoplasmic Pi may enter the sarcoplasmic reticulum (SR) and bind to Ca$^{2+}$ to form a precipitate (CaPi), thus reducing the amount of releasable Ca$^{2+}$. Using
mechanically skinned rat fast-twitch muscle fibers, which retain the normal action potential-mediated Ca\(^{2+}\) release mechanism, we investigated the consequences of Pi exposure on normal excitation-contraction coupling. The total amount of Ca\(^{2+}\) released from the SR by a combined caffeine/low-Mg\(^{2+}\) concentration stimulus was reduced by approximately 20 percent, and the initial rate of force development slowed after 2-min exposure to 30 mM Pi (with or without the presence creatine phosphate). Peak (50 Hz) tetanic force was also reduced (by approximately 25 percent and approximately 45 percent after 10 and 30 mM Pi exposure, respectively). Tetanic force responses produced after 30 mM Pi exposure were nearly identical to those observed in the same fiber after depletion of total SR Ca\(^{2+}\) by approximately 35 percent. Ca\(^{2+}\) content assays revealed that the total amount of Ca\(^{2+}\) in the SR was not detectably changed by exposure to 30 mM Pi, indicating that Ca\(^{2+}\) had not leaked from the SR but instead formed a precipitate with the Pi, reducing the amount of available Ca\(^{2+}\) for rapid release. These results suggest that CaPi precipitation that occurs within the SR could contribute to the failure of Ca\(^{2+}\) release observed in the later stages of metabolic muscle fatigue. They also demonstrate that the total amount of Ca\(^{2+}\) stored in the SR cannot drop substantially below the normal endogenous level without reducing tetanic force responses [035].

### Adrenaline-induced effects

It was previously thought that caffeine mechanisms were associated with adrenaline (epinephrine)-induced enhanced free-fatty acid oxidation and consequent glycogen sparing, which is the leading hypothesis for the ergogenic effect. It would seem unlikely that the proposed theory would result in improved anaerobic performance, since exercise is dominated by oxygen-independent metabolic pathways. Other mechanisms for caffeine have been suggested, such as enhanced calcium mobilization and phosphodiesterase inhibition. However, a normal physiological dose of caffeine in vivo does not indicate this mechanism plays a large role. Additionally, enhanced Na\(^+/K^+\) pump activity has been proposed to potentially enhance excitation contraction coupling with caffeine [036].

### A peripheral as opposed to a central neural mechanism of caffeine

One proposed mechanism is caffeine’s stimulatory effect on the central nervous system and thus, motor-unit excitation. The latter is non-invasively determined from surface electromyographic signal (EMG) frequency measures. The purpose of one study was to determine if power output and surface EMG frequency variables during high-intensity cycling were altered following caffeine ingestion. Eighteen recreationally active college males (mean age, 22) performed the Wingate test (WG) after ingestion of gelatin capsules containing either placebo (dextrose) or caffeine (CAFF; 5 mg/kg body mass). The trials were separated by 1 week and subjects were asked to withdraw from all caffeine-containing products for 48 h before each trial. From the resulting power-time records, peak power (PP; highest power output in 5 s), minimum power (MP; lowest power output in 5 s), and the percent decline in power (Pd) were calculated. Surface EMG records of the right vastus lateralis (VL) and the gastrocnemius (GA) muscles corresponding to the PP and MP periods were collected and used to determine the integrated electromyogram (IEMG), the mean (MNPF), and the median (MDPF) of the signal's power spectrum. Caffeine ingestion had no effect on PP, MP, or the Pd compared with the placebo. For both muscles, MNPF and MDPF diminished significantly across time and to a similar degree in both the CAFF and PL trials. Regardless of muscle, CAFF had no effect on the percent change in IEMG from the first 5 s to the last 5 s. For both treatments, the GA displayed a significantly greater pre versus post percent decline in the EMG signal amplitude compared with the VL. These results indicate that caffeine does not impact power output during a 30 s high-intensity cycling bout. Furthermore,
these data suggest that caffeine does not impact the neuromuscular drive as indicated by the similar IEMG scores between treatments. Similarly, caffeine does not seem to impact the frequency content of the surface EMG signal and thus the nature of recruited motor units before and after the expression of fatigue. The lack of decline in the IEMG in the VL despite the decline in power output over the course of the WG suggests a peripheral as opposed to a neural mechanism of fatigue in this muscle. The significant difference in the pre versus post percent decline in the GA IEMG score further supports this notion. The pre versus post decline in the IEMG noted in the GA may suggest a fatigue-triggered change in pedaling mechanics that may promote dominance of knee extensors with less reliance on plantar flexors [037].

**Effects of neural recovery**

The purpose of one study was to test the hypothesis that prior caffeine ingestion would enhance neural recovery after isometric fatiguing maximal intermittent plantar flexions, and thus would enhance the recovery of voluntary muscle strength. After a familiarisation session, 13 males randomly participated in two experimental trials where they ingested either caffeine (approximately 6 mg/kg) or identical placebo pills 1 h prior to testing. Subjects were tested for electromyogram (EMG) activity and evoked V-waves in the soleus and gastrocnemius medialis muscles. These measurements were obtained during brief plantar flexion maximum voluntary isometric contractions (MVICs), and normalised by the superimposed maximal M-wave (EMG/M(SUP) and V/M(SUP), respectively), before and after (20 s, 10 min and 20 min) a fatigue protocol (seven 25 s MVICs, 5 s rest). There were no effects (P > 0.05) of caffeine ingestion on EMG/M(SUP), V/M(SUP), MVIC or M(SUP). The central neural modulation (EMG/M(SUP) and V/M(SUP)) and voluntary strength changes followed a similar time-course with a substantial reduction 20 s post-fatigue and a gradual return towards baseline values. Thus, there was no effect of prior caffeine ingestion on neuromuscular recovery after maximal fatiguing contractions [038].

**Inhibition of the phosphodiesterase**

Caffeine acts as a nonselective competitive inhibitor of the phosphodiesterase enzymes. Phosphodiesterases hydrolyze the phosphodiesterase bond in molecules such as cyclic adenosine monophosphate (cAMP), inhibiting the breakdown of cAMP. cAMP activates lipolysis by activating HSL and is an important molecule in the epinephrine cascade. It further activates protein kinase A, which in turn can phosphorylate a number of enzymes involved in glucose and lipid metabolism [011].

**Effect on lipolysis**

Caffeine has been reported to increase lipolysis throughout the body with a resultant increase in plasma free fatty acid levels. It is thought that by having increased levels of fatty acids available for use by the body, muscle glycogen can be spared. Increased lipolysis leads to decreased reliance on glycogen use. Caffeine switches the substrate preference from glycogen to fat by increasing hormone sensitive lipase (HSL) activity and inhibition of glycogen phosphorylase activity [029].

**Mobilization of fat**

Part of caffeine's intrigue is that it is still not know the exact mechanism by which it enhances performance, with a number of effects on different body tissues being possible. Furthermore, individuals respond differently to caffeine (as with many drugs), across a range from positive
to negative outcomes, and some tissues become tolerant to repeated caffeine use, while others do not. The potentially beneficial effects of caffeine include the mobilisation of fat from adipose tissue and the muscle cell, stimulation of the release and activity of adrenaline, effects on cardiac muscle, direct changes to muscle contractility and alterations to the central nervous system to change perceptions of effort or fatigue. Most scientists believe that the last factor is the most important and consistent factor in explaining performance enhancement. Recent evidence has changed our perspective on two of the widely promoted effects of caffeine. Whereas caffeine was believed to enhance endurance performance via increased utilisation of fat as an exercise fuel and reduced use of the limited muscle stores of glycogen, studies now show that the effect of caffeine on “glycogen sparing” during submaximal exercise is short-lived and inconsistent. It is often warned that caffeine-containing drinks have a diuretic effect and will cause an athlete to become dehydrated. In fact, small to moderate doses of caffeine have minor effects on urine losses or the overall hydration in people who are habitual caffeine users. In addition, caffeine-containing drinks such as tea, coffee and cola drinks provide a significant source of fluid in the everyday diets of many people [002].

Duration of coffee- and exercise-induced changes in the fatty acid profile

Utilization of blood-borne nonesterified fatty acids (NEFA) in working muscles is important for aerobic ATP resynthesis during prolonged exercise of moderate intensity. Although an increase in the total concentration of plasma NEFA (as a result of augmented lipolysis in adipose tissue) during such efforts is well documented, little is known about the effect of exercise on their percent distribution. Studies have found that exercise changes the percentage of individual plasma NEFA, although there is no consensus on this issue. The most striking finding of our studies was an increase in the ratio of unsaturated to saturated (U/S) NEFA in the plasma of athletes and untrained individuals. This change may add to the health benefits of exercise, given the protective role of dietary unsaturated fatty acids against cardiovascular disease and the development of insulin resistance. It is reasonable to think that the magnitude of the effect(s) of this change will depend on its duration; that is, the longer the U/S remains elevated, the higher its impact on human metabolism will probably be. Because our findings and the findings of the relevant studies cited above were based on blood samples taken solely at the end of exercise, we deemed it worthwhile to investigate how far into the recovery period the changes in individual NEFA are extended. Numerous studies have investigated the influence of coffee and caffeine on metabolism, with emphasis on their probable glycogen-sparing effect as the explanation for the increase in endurance performance caused by their intake. On the basis of measurements of glycerol and NEFA release from adipose tissue, the majority of the relevant studies have shown caffeine to stimulate lipolysis. The vast majority of these studies have measured total NEFA; to our knowledge, there is only one report on the behavior of individual plasma NEFA after caffeine ingestion, an issue that deserves attention for the reasons presented above [039].

Prolonged moderate exercise increases the concentration of nonesterified fatty acids (NEFA) and the ratio of unsaturated to saturated (U/S) NEFA in human plasma. The present study examined the duration of these effects and compared them with the effects of coffee ingestion. On separate days and in random order, seven men and six women 1) cycled for 1 h, 2) ingested coffee containing 5 mg caffeine/kg body mass, 3) ingested coffee followed by exercise 1 h later, and 4) did nothing. Blood samples were drawn at 0, 1, 2, 4, 8, 12, and 24 h. Serum was analyzed for lactate, glucose, glycerol, individual NEFA, triacylglycerols, total cholesterol, and HDL cholesterol. Exercise elevated the U/S NEFA and the percentage of oleate, while decreasing the percentages of palmitate and stearate, at the end of exercise but not subsequently. Consumption of coffee triggered a lower lipolytic response with no alterations in U/S or percentages of individual NEFA. These findings may prove useful in discovering mechanisms mediating the effects of exercise training on the fatty acid profile of human tissues [039].
Increased post-exercise muscle glycogen accumulation (neoglycogenesis)

Enhanced recovery by increased rate of glycogen resynthesis following exercise. It has been reported that caffeine ingestion has no effect on glycogen accumulation during recovery in recreationally active individuals, but it has also been reported that caffeine (8 mg/kg body weight) co-ingested with carbohydrates (CHO) increases rates of postexercise muscle glycogen accumulation compared with consumption of CHO alone in well-trained athletes after exercise-induced glycogen depletion. Although this issue needs further study in different populations (untrained, trained) and at different time points (during exercise or recovery), caffeine added to postexercise CHO feeding seems to have the potential to improve glycogen resynthesis [011].

The purpose of one study was to examine the effects of caffeine (Caf) ingestion on pro- (PG) and macroglycogen (MG) resynthesis in 10 healthy men. Subjects completed two trials, consisting of a glycogen-depleting exercise, while ingesting either Caf or placebo capsules. Throughout recovery, biopsies were taken at 0 (exhaustion), 30, 120, and 300 min, and 75 g of carbohydrate were ingested at 0, 60, 120, 180, and 240 min. Whereas Caf ingestion resulted in a higher blood glucose concentration and decreased glycogen synthase fractional velocity, no effect was observed in either the amount or rate of PG and MG resynthesis. PG concentration increased significantly at each time point during recovery, whereas MG concentration remained unchanged until 120 min. The net rate of PG resynthesis was 115 mmol/kg/dw/h during the first 30 min of recovery, and then it significantly decreased by 62 percent throughout the remaining 4.5 h of recovery. The net rate of MG resynthesis was 77 percent lower than the net rate of PG resynthesis during the first 30 min of recovery and remained constant throughout 5 h of recovery despite increasing levels of insulin. In conclusion, Caf ingestion does not impede the resynthesis of PG or MG after an extensive depletion of muscle glycogen and with the provision of exogenous dietary carbohydrate [040].

Hypoalgesia

The hypoalgesic effects of caffeine have resulted in dampened pain perception and blunted perceived exertion during exercise. This could potentially have favourable effects on negating decreased firing rates of motor units and possibly produce a more sustainable and forceful muscle contraction. The exact mechanisms behind caffeine's action remain to be elucidated [041].

A double-blind, within-subjects experiment examined the effect of ingesting a large dose of caffeine on perceptions of leg muscle pain during moderate intensity cycling exercise. Low-caffeine-consuming college-aged males (n=16) ingested either caffeine (10 mg/kg body weight) or placebo and 1 hour later completed 30 minutes of moderate intensity cycling exercise (60 % VO2peak). The order of drug administration was counter-balanced. Perceptions of leg muscle pain as well as work rate, heart rate, and oxygen uptake (VO2) were recorded during exercise. Leg muscle pain ratings were significantly and moderately reduced after a high dose of caffeine. This observation suggests that prior reports showing caffeine improves endurance exercise performance might be partially explained by caffeine's hypoalgesic properties. It also suggests that moderate intensity cycling exercise has promise as a useful experimental model for the study of naturally occurring muscle pain [041].

The analgesic effect is possibly mediated by augmenting plasma endorphin concentrations [011].
### Effects on muscles

Caffeine (1,3,7-trimethylxanthine) has been implicated in the regulation of glucose and lipid metabolism including actions such as insulin-independent glucose transport, glucose transporter 4 expression, and fatty acid utilization in skeletal muscle. These effects are similar to the exercise-induced and 5′adenosine monophosphate-activated protein kinase (AMPK)-mediated metabolic changes in skeletal muscle, suggesting that caffeine is involved in the regulation of muscle metabolism through AMPK activation. It was explored whether caffeine acts on skeletal muscle to stimulate AMPK. Incubation of rat epitrochlearis and soleus muscles with Krebs buffer containing caffeine (>3 mmol/L, >15 minutes) increased the phosphorylation of AMPKalpha Thr(172), an essential step for full kinase activation, and acetyl-coenzyme A carboxylase Ser(79), a downstream target of AMPK, in dose- and time-dependent manners. Analysis of isoform-specific AMPK activity revealed that both AMPKalpha1 and alpha2 activities increased significantly. This enzyme activation was associated with a reduction in phosphocreatine content and an increased rate of 3-O-methyl-d-glucose transport activity in the absence of insulin. These results suggest that caffeine has similar actions to exercise by acutely stimulating skeletal muscle AMPK activity and insulin-independent glucose transport with a reduction of the intracellular energy status.

Caffeine activates 5′AMP-activated protein kinase (AMPK), a signalling intermediary implicated in the regulation of glucose, lipid and energy metabolism in skeletal muscle. Skeletal muscle expresses two catalytic α subunits of AMPK, alpha1 and alpha2, but the isoform specificity of caffeine-induced AMPK activation is unclear. The aim of this study was to determine which α isoform is preferentially activated by caffeine in vitro and in vivo using rat skeletal muscle. Rat epitrochlearis muscle was isolated and incubated in vitro in the absence or presence of caffeine. In another experiment, the muscle was dissected after intravenous injection of caffeine. Isoform-specific AMPK activity, the phosphorylation status of AMPKalpha Thr(172) and acetyl-CoA carboxylase (ACC) Ser(79), the concentrations of ATP, phosphocreatine (PCr) and glycogen, and 3-O-methyl-d-glucose (3MG) transport activity were estimated. Incubation of isolated epitrochlearis muscle with 1 mm of caffeine for 15 min increased AMPKalpha1 activity, but not AMPKalpha2 activity; concentrations of ATP, PCr and glycogen were not affected. Incubation with 3 mm of caffeine activated AMPKα2 and reduced PCr and glycogen concentrations. Incubation with 1 mm of caffeine increased the phosphorylation of AMPK and ACC and enhanced 3MG transport. Intravenous injection of caffeine (5 mg/kg) predominantly activated AMPKalpha1 and increased 3MG transport without affecting energy status. The results suggest that of the two α isoforms of AMPK, AMPKalpha1 is predominantly activated by caffeine via an energy-independent mechanism and that the activation of AMPKalpha1 increases glucose transport and ACC phosphorylation in skeletal muscle.

The mechanism of action underlying the ergogenic effect of caffeine is still unclear. Caffeine increases the force of muscular contraction during low-frequency stimulation by potentiating calcium release from the sarcoplasmic reticulum. Studies have also suggested an enhancement of lipid oxidation and glycogen sparing as potential mechanisms. Given that several studies have found an ergogenic effect of caffeine with no apparent metabolic effects, it is likely that a direct effect upon muscle is important. Twelve healthy male subjects were classified as habitual (n=6) or nonhabitual (n=6) caffeine consumers based on a 4-day diet record analysis, with a mean caffeine consumption of 771 and 14 mg/day for each group, respectively. Subjects were randomly allocated to receive caffeine (6 mg/kg) and placebo (citrate) in a double-blind, cross-over fashion approximately 100 min before a 2-min tetanic stimulation of the common peroneal nerve in a custom-made dynamometer (2 trials each of 20 and 40 Hz). Tetanic torque was measured every 30 s during and at 1, 5, and 15 min after the stimulation protocol. Maximal voluntary contraction strength and peak twitch torque were measured before and after the stimulation protocol. Caffeine potentiated the force of contraction during the final minute of the 20-Hz stimulation with no effect of...
habituation. There was no effect of caffeine on 40-Hz stimulation strength nor was there an effect on maximal voluntary contraction or peak twitch torque. These data support the hypothesis that some of the ergogenic effect of caffeine in endurance exercise performance occurs directly at the skeletal muscle level [044].

No effects on endothelial function

Endothelial function plays an important role in circulatory physiology. There has been differing reports on the effect of energy drink on endothelial function. It was set out to evaluate the effect of 3 energy drinks and coffee on endothelial function. Endothelial function was evaluated in healthy volunteers using a device that uses digital peripheral arterial tonometry measuring endothelial function as the reactive hyperemia index (RHI). Six volunteers (25 ± 7 years) received energy drink in a random order at least 2 days apart. Drinks studied were 250 ml "Red Bull" containing 80 mg caffeine, 57 mL "5-hour Energy" containing 230 mg caffeine, and a can of 355 mL "NOS" energy drink containing 120 mg caffeine. Sixteen volunteers (25 ± 5 years) received a cup of 473 ml coffee containing 240 mg caffeine. Studies were performed before drink (baseline) at 1.5 and 4 hours after drink. Two of the energy drinks (Red Bull and 5-hour Energy) significantly improved endothelial function at 4 hours after drink, whereas 1 energy drink (NOS) and coffee did not change endothelial function significantly. RHI increased by 82 ± 129 percent and 63 ± 37 percent after 5-hour Energy and Red Bull, respectively. The RHI changed after NOS by 2 ± 30 percent and by 7 ± 30 percent after coffee. In conclusion, some energy drinks appear to significantly improve endothelial function. Caffeine does not appear to be the component responsible for these differences [045].
METABOLISM OF CAFFEINE

Caffeine gets is rapidly absorbed through the gastrointestinal tract, with approximately 90 percent cleared from the stomach within 20 minutes, and is then distributed throughout the body, including the brain. Peak plasma concentrations of caffeine are achieved in 40 to 60 minutes. Its half-life is approximately 3 to 5 hours and only small amounts are around 8 to 10 hours later. In between, the amount circulating declines as caffeine gets metabolized in the liver [046].

Caffeine, theophylline, theobromine, and paraxanthine administered to animals and humans distribute in all body fluids and cross all biological membranes. They do not accumulate in organs or tissues and are extensively metabolized by the liver, with less than 2 percent of caffeine administered excreted unchanged in human urine. Dose-independent and dose-dependent pharmacokinetics of caffeine and other dimethylxanthines may be observed and explained by saturation of metabolic pathways and impaired elimination due to the immaturity of hepatic enzyme and liver diseases. While gender and menstrual cycle have little effect on their elimination, decreased clearance is seen in women using oral contraceptives and during pregnancy. Obesity, physical exercise, diseases, and particularly smoking and the interactions of drugs affect their elimination owing to either stimulation or inhibition of CYP1A2. Their metabolic pathways exhibit important quantitative and qualitative differences in animal species and man. Chronic ingestion or restriction of caffeine intake in man has a small effect on their disposition, but dietary constituents, including broccoli and herbal tea, as well as alcohol were shown to modify their plasma pharmacokinetics. Using molar ratios of metabolites in plasma and/or urine, phenotyping of various enzyme activities, such as cytochrome monooxygenases, N-acetylation, 8-hydroxylation, and xanthine oxidase, has become a valuable tool to identify polymorphisms and to understand individual variations and potential associations with health risks in epidemiological surveys [047].

Fate in the liver

Caffeine is metabolized through the liver via the cytochrome P450 enzyme system [012].

Factors influencing serum caffeine concentrations

To determine whether differences in training status, body composition and/or habitual caffeine intake influenced serum caffeine concentrations following caffeine ingestion trained cyclists/triathletes (n=14) and active (n=14) males consumed 6 mg/kg anhydrous caffeine were studied. Peak, total and time to peak serum caffeine concentrations were determined from venous blood samples at baseline and 6 time-points over 4 h following intake. Body composition was assessed by dual energy X-ray absorptiometry and habitual caffeine intake by a questionnaire. Trained cyclists/triathletes had 16 percent lower peak caffeine concentrations following caffeine ingestion compared to active individuals, although this was not statistically significant. There was no significant difference between trained cyclists/triathletes and active males in total or time to peak serum caffeine concentrations. Fat mass was significantly associated with total but not peak or time to peak serum caffeine concentration. There were no associations between habitual caffeine intake and peak, total or time to peak serum caffeine concentrations. It was concluded that following caffeine ingestion three findings from the study it was evident that endurance-trained athletes trended towards lower peak caffeine concentrations compared to active males; that higher fat mass was associated with higher concentrations of caffeine in the blood over 4h, and that habitual caffeine intake does not appear to influence serum caffeine concentrations. Identification of the optimal conditions to ensure peak availability of caffeine within the blood and/or
overcoming some of the variation in how individuals respond to caffeine requires consideration of the training status and body composition of the athlete [048].

**Dependence on time of the day of caffeine’s effects**

To determine whether the ergogenic effects of caffeine ingestion on neuromuscular performance are similar when ingestion takes place in the morning and in the afternoon. In a double blind, cross-over, randomized, placebo controlled design study 13 resistance-trained males carried out bench press and full squat exercises against four incremental loads (25 %, 50 %, 75 % and 90 % 1RM), at maximal velocity. Trials took place 60 min after ingesting either 6 mg/kg of caffeine or placebo. Two trials took place in the morning (AMPLAC and AMCAFF) and two in the afternoon (PMPLAC and PMCAFF), all separated by 36-48 h. Tympanic temperature, plasma caffeine concentration and side-effects were measured. Plasma caffeine increased similarly during AMCAFF and PMCAFF. Tympanic temperature was lower in the mornings without caffeine effects. AMCAFF increased propulsive velocity above AMPLAC to levels similar to those found in the PM trials for the 25, 50, and 75 percent 1RM loads in the SQ exercise (5.4-8.1 %). However, in the PM trials, caffeine ingestion did not improve propulsive velocity at any load during BP or SQ. The negative side effects of caffeine were more prevalent in the afternoon trials (13 vs 26 %). It was concluded that the ingestion of a moderate dose of caffeine counteracts the muscle contraction velocity declines observed in the morning against a wide range of loads. Caffeine effects are more evident in the lower body musculature. Evening caffeine ingestion not only has little effect on neuromuscular performance, but increases the rate of negative side-effects reported [049].

**Time for abstention from drunken caffeine**

Seventy patients undergoing adenosine myocardial perfusion scintigraphy were studied. All patients reported abstention from products containing caffeine in the 12 h prior to the test. Blood samples were drawn prior to initiation of the stress test, and serum caffeine levels were determined using high-performance liquid chromatography. All patients were also asked about their coffee and tea drinking habits. Seventy-four percent of patients had measurable serum caffeine levels (n=52) ranging from 0.1 to 8.8 mg/L. Results were correlated with maximum pulse rate, systolic and diastolic blood pressure changes and clinical symptoms during the test. There was no correlation between coffee or tea drinking habits and serum caffeine levels. A serum caffeine level of 2.9 mg/L was considered a cut-off point for comparing patients. No significant difference was seen in mean maximum change of pulse rate, systolic and diastolic blood pressure between patients with serum caffeine levels > 2.9 mg/L and those with lower serum caffeine levels. Of eight patients with serum caffeine levels > 2.9 mg/L, six had no symptoms (75 %). When patients were classified as patients with no symptoms or patients with symptoms (mild, moderate or severe), a significant difference was demonstrated between patients with serum caffeine levels > 2.9 mg/L and those with lower levels. This suggests 12 h abstention from caffeine may be insufficient. Whether this translates into false-negative perfusion scans should be the subject of a larger study [050].
DOSING OF CAFFEINE

Sources of caffeine

Caffeine is a naturally occurring plant alkaloid. It is classified as a methylxanthine. Other examples of methylxanthines include theophylline and theobromine. It is found in over 60 different plant species including Caffea arabica (coffee), Thea sinenis (tea), and Cola acuminate (cola). Caffeine is consumed in a variety of forms, including coffee, soft drinks, and chocolate. It is also found in a variety of over the counter stimulants, appetite suppressants, analgesics, and cold and sinus preparations. In fact, caffeine is the world's most commonly used and widely consumed pharmacologic substance. Approximately 75 percent of caffeine is consumed in the form of coffee. In terms of international commerce, coffee is second only to oil in dollar amount traded. Consumption of caffeine is highest in the United Kingdom and Scandinavian countries (400 mg/person/d compared with 238 mg/person/d in the United States) [012].

Roasting

The caffeine content of coffee varies greatly, depending on the beans, how they are roasted, and other factors, but the average for an 8-ounce cup is about 100 milligrams (mg). Tea has about half as much caffeine as coffee. Decaffeinated coffee has some caffeine, but the 2 to 4 mg in an 8-ounce cup is a smidgen compared with the caffeinated version [028].

Powder or capsules

Most of the previous caffeine research has focused on supplying caffeine in a powder or capsule form. Additionally, caffeine has been typically dosed on a per kg body weight either before or during the exercise. It is unlikely, however, that athletes and recreational athletes dose their supplement ingestion based upon their body weight. Such dosing may not be truly representative of athletes' habits during training or competition. Rather, products are typically ingested by a given serving size or volume of a given commercially available product. It is quite rare, however, that one would find a caffeine-only product in the energy shot and drink market. Oftentimes, caffeine is combined with ingredients such as carbohydrates, taurine, and niacin in the hope of improving performance [051].

In one study plasma concentrations of caffeine were similar whether ingested in the form of coffee or capsule. However, enhancement of endurance was seen only when caffeine was consumed independent of coffee. Likely, there are substances in coffee that antagonize the ergogenic potential of caffeine. Another source of caffeine that has been studied in terms of its ergogenic potential is decaffeinated soft drinks. There is a practice among some endurance athletes to use a “defizized” soft drink as a replacement for sports drinks during the latter stages of such events, believing that the caffeine intake produces an ergogenic effect. A study out of Australia suggests that the use of Coca-Cola produces an ergogenic effect similar to that of more conventional forms of caffeine intake. These findings are of undetermined significance, however, as the dose of caffeine consumed through Coca-Cola in this study are less than dosages of caffeine previously proven to be ergogenic [012].

In preparations against common cold

Caffeine may also be a constituent of some common medicines such as cold preparations and pain relief treatments, usually in quantities of less than 100 mg per dose [012].
Phenolic compounds such as chlorogenic acids

It has been shown that coffee, by containing phenolic compounds such as chlorogenic acids, elicits metabolic effects independent of caffeine. These compounds may have the potential to antagonize the physiological responses of caffeine. The question therefore remains whether ingesting the same amount of caffeine via a food source (e.g. energy bar or coffee) is as effective as ingesting isolated caffeine in the form of a tablet. Only a few studies, however, have shown a positive effect of coffee on performance. Whereas some studies found enhanced performance after coffee consumption, others did not. One earlier works reported increases in time trial performance of competitive cyclists only in the coffee trial group (containing 330 mg caffeine 1 h prior to exercise) but not in the decaffeinated coffee trial. It was also studied exercise endurance in runners after ingestions of a caffeine (4.45 mg/kg BW) or placebo capsule with water or either decaffeinated coffee, decaffeinated coffee with added caffeine or regular coffee. The authors found that only caffeine significantly improved running time to exhaustion at 75 percent VO2max but neither did regular coffee or decaffeinated coffee plus caffeine. Based on these results, the authors speculated that some component(s) in coffee possibly interfere with the ergogenic response of caffeine alone.

Caffeinated “energy shots”

Caffeine (1,3,7-trimethylxanthine) is widely used among athletes, and it was in 2007 found that 73 percent of 140 athletes surveyed at the 2005 Ironman Triathlon World Championships believed caffeine improved performance. Via ingestion of coffee, capsules, or anhydrous powder, caffeine improves performance of moderate to high intensity endurance exercise. However, most studies examining caffeine utilized anhydrous caffeine, which is not readily accessible to coaches and athletes. Additionally, most researchers utilize doses relative to body weight instead of the absolute doses commonly found in commercially available caffeine products. While it could be argued that weighing out a relative dose may be plausible for elite athletes, who have access to dietitians and other trained staff, most track and field/cross country running coaches in the United States have large numbers of athletes to supervise, and this is relatively impractical. Energy drink usage among athletes is also quite widespread, and it was reported 48 percent of 401 collegiate athletes regularly consumed energy drinks. Thus, a coach is far more likely to tell an athlete to “Drink this” prior to a competition instead of calculating a target caffeine dose for each athlete. Recent research has examined effects of more accessible forms of caffeine, such as energy drinks, on exercise performance in athletes. A, yet to be evaluated, caffeine supplement is the energy “shot” which is smaller in volume (generally 59-88 mL), as it lacks the large amounts of sugars, carbohydrates, and/or carbonated water of energy drinks containing caffeine. This low volume and energy content may make their intake practical for runners, who typically avoid supplements due to the onset of gastrointestinal disturbances, as running has a higher occurrence of GI symptoms than cycling. Despite the large amount of literature examining the ergogenic properties of caffeine, few studies have evaluated the efficacy of caffeine ingestion on running performance using ecologically valid assessments, such as time trials. Energy shots may prove to be a viable pre-competition supplement for runners. Six male runners (mean ± SD age 22.5 ± 1.8 years) completed three trials [placebo (PLA; 0 mg caffeine), Guayakí Yerba Maté Organic Energy Shot™ (YM; 140 mg caffeine), or Red Bull Energy Shot™ (RB; 80 mg caffeine)]. Treatments were ingested following a randomized, placebo-controlled crossover design. Participants ran a five kilometer time trial on a treadmill. No differences in performance were detected with RB or YM ingestion compared to placebo. Thus, ingestion of two commercially available energy shots with differing levels of caffeine does not alter treadmill five kilometer time-trial performance, RPE, or physiological variables in well-trained runners, compared to a placebo. The results must be considered preliminary due to the small sample size, and further studies should examine the effects of energy shot ingestion on performance in a variety of sport and field settings. While some research has
been conducted on energy drinks, this is the first study to examine the efficacy of energy shots on exercise performance. Therefore, additional study is needed to examine their long-term effects on body composition and health, in addition to athletic performance, before recommendations about their usage can be provided to coaches and athletes [052].

**Caffeinated beverages**

The purpose of one study was to assess the influence of rehydration with a caffeinated beverage during nonexercise periods on hydration status throughout consecutive practices in the heat. Ten (7 women, 3 men) partially heat-acclimated athletes (age 24 years) completed 3 successive days of 2-a-day practices (2 h/practice, 4 h/d) in mild heat (WBGT = 23°C). The 2 trials (double-blind, random, cross-over design) included; 1) caffeine (CAF) rehydrated with Coca-Cola and 2) caffeine-free (CF) rehydrated with Caffeine-Free Coca-Cola. Urine and psychological measures were determined before and after each 2-h practice. A significant difference was found for urine color for the post-AM time point. No differences were found among other variables (P > 0.05). In summary, there is little evidence to suggest that the use of beverages containing caffeine during nonexercise might hinder hydration status [053].

**Caffeinated chewing gum**

Caffeine administration in most research settings is delivered in coffee or in tablets/capsules along with water, where there is a known amount of caffeine ingested. Caffeine is also available in gels and bars and in some sports drinks for use by athletes before and during athletic events. It might be assumed that the appearance of caffeine in the blood would be slightly delayed with gels and bars compared with ingestion in coffee or tablets/capsules ingested with water but this does not appear to have been studied. Another form of delivery that has received some interest is chewing gum. It was compared the rate of absorption of 50, 100 and 200 mg caffeine in chewing gum versus the same doses in capsules in healthy volunteers. All subjects had abstained from caffeine for 20 h and there were 12 subjects in each treatment group. Eight blood samples were taken from 5 to 90 min after caffeine ingestion, and eight more were taken from 2 to 29 h postadministration. The rate of caffeine absorption was significantly faster from the gum versus the capsules, suggesting that absorption from the buccal mucosa in the mouth was a contributing factor when chewing gum was administered. However, over time, the gum and capsule formulations provided essentially the same amounts of caffeine for the 100 and 200 mg doses. If rapid caffeine absorption is required in a sport situation, chewing gum may be the desired form of delivery. A second study demonstrated that plasma caffeine levels can be maintained at desired concentrations with repeated doses (2 h apart) of caffeine delivered in gum. A few studies have examined the potential ergogenic effect of caffeine administration in gum. On study administered two pieces of caffeinated chewing gum (200 mg total) at one of three time points, either 35 or 5 min before exercise or 15 min into cycling at 85 percent VO2max to exhaustion lasting 30-35 min. A placebo was given at the other two time points and all three points during the control trial. The subjects were college-age, physically active male volunteers. The caffeine in the gum did not improve endurance performance at any of the administration times [69]. In a follow-up study it was given 300 mg of caffeine in gum either at 120 min, 60 min or 5 min before exercise. In the placebo trial, subjects received no caffeine. Caffeine improved cycling performance only in the trial where the caffeine was administered 5 min before exercise compared with the placebo trial. One report examined the effects of caffeine given as chewing gum on repeated cycle sprint ability. Competitive cyclists completed four sets of 30 s maximal sprints, with five sprints/set and each sprint was separated by 30 s of active recovery. Caffeine (240 mg or 3 mg/kg bm) was administered following the second set and the rate of power output decline in the final two sets (10 sprints) was significantly reduced by the caffeinated gum compared with the placebo group [054].
One investigation reports the effects of caffeinated chewing gum on fatigue and hormone response during repeated sprint performance with competitive cyclists. Nine male cyclists completed four high-intensity experimental sessions, consisting of four sets of 30 s sprints (5 sprints each set). Caffeine (240 mg) or placebo was administered via chewing gum following the second set of each experimental session. Testosterone and cortisol concentrations were assayed in saliva samples collected at rest and after each set of sprints. Mean power output in the first 10 sprints relative to the last 10 sprints declined by 5.8 ± 4.0 percent in the placebo and 0.4 ± 7.7 percent in the caffeine trials, respectively. The reduced fatigue in the caffeine trials equated to a 5.4 percent performance enhancement in favour of caffeine. Salivary testosterone increased rapidly from rest (53 %) and prior to treatments in all trials. Following caffeine treatment, testosterone increased by a further 12 ± 14 percent relative to the placebo condition. In contrast, cortisol concentrations were not elevated until after the third exercise set; following the caffeine treatment cortisol was reduced by 21 ± 31 percent relative to placebo. The acute ingestion of caffeine via chewing gum attenuated fatigue during repeated, high-intensity sprint exercise in competitive cyclists. Furthermore, the delayed fatigue was associated with substantially elevated testosterone concentrations and decreased cortisol in the caffeine trials [055].

Low-dose caffeine administered in chewing gum does not enhance cycling to exhaustion. The purpose of the current investigation was to examine the effect of low-dose caffeine (CAF) administered in chewing gum at 3 different time points during submaximal cycling exercise to exhaustion. Eight college-aged (26 ± 4 years), physically active (46 ± 6 mL/kg/min) volunteers participated in 4 experimental trials. Two pieces of caffeinated chewing gum (100 mg per piece, total quantity of 200 mg) were administered in a double-blind manner at 1 of 3 time points (-35, -5, and +15 minutes) with placebo at the other 2 points and at all 3 points in the control trial. The participants cycled at 85 percent of maximal oxygen consumption until volitional fatigue and time to exhaustion (TTE) were recorded in minutes. Venous blood samples were obtained at -40, -10, and immediately postexercise and analyzed for serum-free fatty acid and plasma catecholamine concentrations. Oxygen consumption, respiratory exchange ratio, heart rate, glucose, lactate, ratings of perceived exertion, and perceived leg pain measures were obtained at baseline and every 10 minutes during cycling. The results showed that there were no significant differences between the trials for any of the parameters measured including TTE. These findings suggest that low-dose CAF administered in chewing gum has no effect on TTE during cycling in recreational athletes and is, therefore, not recommended [056].

Research has shown that standard chewing gum can affect aspects of both attention and memory. One study examined the effects of Think Gum®, a caffeinated-herbal chewing gum, on both concentration and memory using a series of paper-based and online testing. Compared to standard chewing gum and a no-gum control, chewing caffeinated-herbal gum during testing improved aspects of memory, but did not affect concentration. The findings suggest that caffeinated-herbal chewing gum is an effective memory aid [057].

The purpose of one study was to determine the most efficacious time to administer caffeine (CAF) in chewing gum to enhance cycling performance. Eight male cyclists participated in 5 separate laboratory sessions. During the first visit, the subjects underwent a graded exercise test to determine maximal oxygen consumption (VO2max). During the next 4 visits, 3 pieces of chewing gum were administered at 3 time points (120-minute precycling, 60-minute precycling, and 5-minute precycling). In 3 of the 4 visits, at 1 of the time points mentioned previously, 300 mg of CAF was administered. During the fourth visit, placebo gum was administered at all 3 time points. The experimental trials were defined as follows: trial A (-120), trial B (-60), trial C (-5), and trial D (Placebo). After baseline measurements, time allotted for gum administration, and a standard warm-up, the participants cycled at 75% VO2max for 15 minutes then completed a 7kJ/kg cycling time trial. Data were analyzed using
a repeated measures analysis of variance. Cycling performance was improved in trial C (-5), but not in trial A (-120) or trial B (-60), relative to trial D (Placebo). CAF administered in chewing gum enhanced cycling performance when administered immediately prior, but not when administered 1 or 2 hours before cycling [056].

**Caffein gel**

It was investigated the effects of ingesting carbohydrate gels with and without caffeine on a 90 minute, four blocks intermittent sprint test (IST), in 12 recreationally trained male athletes. Using a cross-over design, one 70 ml dose of gel containing either 25 g of carbohydrate with (CHOCAF) or without (CHO) 100 mg of caffeine, or a non-caloric placebo (PL) was ingested on three occasions: one hour before, immediately prior to and during the IST. Blood glucose, rating of perceived exertion (RPE) and fatigue index (FI) were analysed. Glucose showed significantly higher values for both CHOCAF and CHO at the first, second and third blocks when compared with PL, while only CHOCAF was significantly different to PL at the fourth block. CHOCAF showed an improved FI compared with CHO and PL, a significantly lower RPE compared with PL and a trend in respect of CHO after the third block. In conclusion, ingesting CHOCAF one hour before, prior to and during an IST is effective at transiently reducing fatigue and RPE whilst maintaining higher glucose levels at the final stages of the exercise [058].

**Time-release caffeine containing supplement**

The efficacy of time-release caffeine capsules appears to be no different than regular caffeine capsules. Investigations have demonstrated that time-release caffeine can enhance alertness and reaction performance for up to 13 hours following ingestion, and improve vigilance and cognitive function during sleep deprivation as compared to a placebo. However, these previous studies have not compared the efficacy of time-release caffeine directly to regular caffeine capsule ingestion, nor have they examined performance changes relative to differences in the pharmacokinetics of caffeine uptake into the plasma. One study compared caffeine pharmacokinetics, glycerol concentrations, metabolic rate, and performance measures following ingestion of a time-release caffeine containing supplement (TR-CAF) versus a regular caffeine capsule (CAF) and a placebo (PL). Following a double-blind, placebo-controlled, randomized, cross-over design, ten males (26 ± 3 years) who regularly consume caffeine ingested capsules containing either TR-CAF, CAF, or PL. Blood draws and performance measures occurred at every hour over an 8-hour period. Plasma caffeine concentrations were significantly greater in CAF compared to TR-CAF during hours 2-5 and significantly greater in TR-CAF compared to CAF at hour 8. There were no significant differences between trials in glycerol concentrations or metabolic measures. Physical reaction time was significantly improved for CAF at hour 5 compared to PL. Average upper body reaction time was significantly improved for CAF and TR-CAF during hours 1-4 and over the 8-hour period compared to PL. Average upper body reaction time was also significantly improved for TR-CAF compared to PL during hours 5-8. TR-CAF and CAF showed distinct pharmacokinetics yielding modest effects on reaction time, yet did not alter glycerol concentration, metabolic measures, or other performance measures. Thus, time-release caffeine and regular caffeine showed distinct pharmacokinetics over an 8-hour period following ingestion. Time-release caffeine and regular caffeine yielded modest effects on reaction time over an 8-hour period following ingestion. Time-release caffeine and regular caffeine did not alter glycerol concentration, metabolic measures, or other performance measures over an 8-hour period following ingestion [059].

**Guarana**

Exercise undertaken in a fasted state can lead to higher post-exercise mental fatigue. The
administration of a vitamin and mineral complex with guaraná (MVM + G) has been shown to attenuate mental fatigue and improve performance during cognitively demanding tasks. This placebo-controlled, double-blind, randomized, balanced cross-over study examined the effect of MVM + G consumed prior to morning exercise on cognitive performance, affect, exertion, and substrate metabolism. Forty active males (age 21.4 ± 3.0 year; body mass index (BMI) 24.0 ± 2.4 kg/m²; maximal oxygen consumption (VO₂max) 57.6 ± 7.3 mL/min/kg) completed two main trials, consuming either MVM + G or placebo prior to a 30-min run at 60 percent VO₂max. Supplementation prior to exercise led to a small but significant reduction in Rating of Perceived Exertion (RPE) during exercise compared to the placebo. The MVM + G combination also led to significantly increased accuracy of numeric working memory and increased speed of picture recognition, compared to the placebo. There were no significant effects of supplementation on any other cognitive or mood measures or on substrate metabolism during exercise. These findings demonstrate that consuming a vitamin and mineral complex containing guaraná, prior to exercise, can positively impact subsequent memory performance and reduce perceived exertion during a moderate-intensity run in active males [060].

Guarana is an Amazonian plant that is an excellent source of caffeine and also contains high concentrations of catechin polyphenols. Catechin polyphenols include epigallocatechin-3-gallate (EGCG), epigallocatechin, epicatechin, among others. The catechins are readily absorbed from the gastrointestinal tract and undergo significant presystemic metabolism, primarily via methylation, glucuronidation, and sulfation. Catechins and their conjugated metabolites are widely distributed in tissues. Catechins and even their metabolites can inhibit COMT – an enzyme involved in the peripheral metabolism of catecholamine neurotransmitters – and by doing so exacerbate the pharmacologic effects of ephedrine and caffeine. Recent findings also indicate that catechins, particularly EGCG, can inhibit the human intestinal uptake transporter OATP1A2, thereby precluding absorption of drugs such as the antihypertensive nadolol, which are substrates for this protein. Thus, catechins present in green tea or guarana may give rise to pharmacokinetic-based herb-drug interactions if taken concomitantly with OATP1A2 substrates. Moreover, certain catechins elicit their own inotropic effect on the heart, which may have contributed to the adverse cardiovascular effects of Ephedra supplements [001].

Guarana (Paullinia cupana), a climbing plant in the maple family, native to the Amazon basin and especially common in Brazil, contains a high amount of guaraná, a chemical substance with the same characteristics as caffeine. Guaranine, a synonym for caffeine, is defined only as the caffeine chemical in guarana and is identical to the caffeine chemical derived from other sources (e.g. coffee, tea, maté). Guarana features large leaves, clusters of flowers, and a fruit similar in size to the coffee bean. As a dietary supplement, guarana is a useful caffeine source with guarana seeds containing approximately twice the amount of caffeine (2-4.5 %) compared with 1-2 percent for coffee beans. Guarana, alongside other natural sources of caffeine, also contains varying mixtures of other xanthine alkaloids such as theobromine and theophylline. Guarana is generally recognised as an acceptable ingredient and can be found in drinks, “energy shots”, herbal teas or capsules. Consequently, guarana is best known for its stimulatory properties, providing similar benefits to caffeine, such as reducing fatigue, increasing alertness, and as an ergogenic aid in the athletic arena. The maximal ergogenic benefits of caffeine and guarana can be seen at small to moderate caffeine doses (2-3 mg/kg). Theoretically, it is possible to overdose on caffeine or guarana, with the fatal dose being estimated at a single dose of 10 g pure caffeine/guaranine [061].

Guarana is widely consumed by athletes, either in supplements or in soft drinks, under the belief that it presents ergogenic and "fat burning" effects. It was examined the effect of guarana supplementation (14 days) upon aspects of lipid metabolism in sedentary (C) and trained rats (T). To isolate the effect of caffeine from that of other components of guarana, it was adopted two different doses of whole extract (G1-0.130 g/kg; G2-0.325 g/kg) or...
decaffeinated extract (DG1, DG2). Body weight, food and water intake; muscle fat content, oleate incorporation, glycogen content, and carnitine palmitoyltransferase I (CPT I) activity and mRNA expression; along with plasma lactate concentration, were assessed. Muscle oleate incorporation was decreased in rats receiving decaffeinated guarana in relation to G1 and G2; as was CPT I mRNA expression in the gastrocnemius. Whole extract supplementation, but not DG induced reduced plasma lactate concentration in trained rats. G1 showed higher muscle glycogen content compared with all other groups. The results show an effect of guarana on aspects of lipid metabolism, which is abolished by decaffeination. It was concluded that the changes in lipid metabolism of supplemented rats herein reported are associated with the methylxanthine content of guarana [062].

Guarana, a herbal extract from the seeds of Paullinia cupana Mart. has been evaluated in comparison with caffeine on mouse behaviour in forced swimming and open field tests. Guarana (25 and 50 mg/kg, p.o.) and caffeine (10 and 20 mg/kg, p.o.) each significantly reduced the duration of immobility in the forced swimming test suggesting an antidepressant-like effect in mice. At these doses, neither substance affected ambulation in the open field test. However, a high dose of guarana (100 mg/kg) and caffeine (30 mg/kg) significantly enhanced the locomotor activity in the open field test. Caffeine, but not guarana, could effectively block an adenosine agonist, cyclopentyl adenosine (CPA)-induced increase in swimming immobility suggesting that mechanism(s) other than the adenosinergic mechanism are involved in the antidepressant-like activity of guarana [063].

*Mouth rinsing*

Another emerging area for exposing the body to caffeine is mouth rinsing. The premise is that small volumes of fluid containing high concentrations of caffeine could be mouthrinsed for 5–10 s periods. While this is unlikely to result in significant caffeine absorption, it would test the possibility that caffeine is sensed in the mouth with signals sent to the CNS. Further work will be needed to determine whether mouth rinsing with caffeine is ergogenic in the absence of absorption into the blood [054].

*Aerosol form*

Lastly, there are commercially available products where caffeine can be delivered in aerosol form, with some products claiming to deliver 100 mg of caffeine per spray or squirt of aerosol. There are no published reports measuring the time of caffeine absorption into the blood using these products, and it seems unlikely that these claims are true. However, delivering caffeine in a gas form into the lungs sets up the possibility that rapid absorption could occur. In this case the absorbed caffeine would be delivered straight from the lungs to the heart and this would not be desirable in some cases. An absorption study measuring the effectiveness of these products is needed [054].

*Coffee, tea and cola drinks*

The intake of caffeine from the traditionally available sources (coffee, tea and cola drinks) is typically around 50–150 mg of caffeine per serving. However, it is possible to find products that provide 300–500 mg of caffeine per serving [002].

The most common form of caffeine consumption is coffee. One cup of coffee contains approximately 100 mg of caffeine. This is the same dosage of caffeine that is contained in most over the counter preparations that are used for promoting wakefulness. Soft drinks are another common form of caffeine consumption. Levels vary depending on the type of soft drink. A 12-oz Coca-Cola can contains approximately 46 mg of caffeine, a 12-oz glass of iced tea contains approximately 70 mg of caffeine. The average American consumes about
200 mg of caffeine daily; adults average about 2.4 mg/kg/d whereas children average about 1.1 mg/kg/d. Interestingly, studies have shown that caffeine can produce its ergogenic potential at doses much less than 800 mg, probably as low as 250 mg. Most studies that show ergogenic potential of caffeine have used dosages of around 400 to 600 mg of caffeine which is equivalent to the amount of caffeine in four to six cups of coffee. A dose of 100 mg of caffeine (equivalent to one cup of coffee) will produce a urine concentration of approximately 1.5 mg/mL caffeine content (mg) of common substances in 2005 [012]:

<table>
<thead>
<tr>
<th>Substances</th>
<th>Content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee</td>
<td>7.5 oz</td>
</tr>
<tr>
<td>Coca-Cola</td>
<td>12 oz</td>
</tr>
<tr>
<td>Diet Coke</td>
<td>12 oz</td>
</tr>
<tr>
<td>Mountain Dew</td>
<td>12 oz</td>
</tr>
<tr>
<td>Dr. Pepper</td>
<td>12 oz</td>
</tr>
<tr>
<td>Sprite</td>
<td>12 oz</td>
</tr>
<tr>
<td>Iced tea</td>
<td>12 oz</td>
</tr>
<tr>
<td>Over-the-counter stimulants</td>
<td>1 capsule</td>
</tr>
</tbody>
</table>

The content (mg) of an “ordinary” cup (8.4 ounce) of caffeine in another study was [028]:

<table>
<thead>
<tr>
<th>Substances</th>
<th>Content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starbucks coffee</td>
<td>180</td>
</tr>
<tr>
<td>Red bull</td>
<td>80</td>
</tr>
<tr>
<td>Lipton green tea (1 bag)</td>
<td>35</td>
</tr>
</tbody>
</table>

**Caffeinated versus decaffeinated coffee**

One study examined the effect of coffee ingestion on physiological responses and ratings of perceived exertion (RPE) during submaximal endurance exercises by 10 healthy young adults. Participants performed a submaximal endurance cycling exercise corresponding to 60 percent of maximum oxygen uptake capacity for 60 min. They drank either caffeinated coffee with a caffeine content of 6 mg/kg body-mass of each participant or a decaffeinated coffee 60 min before starting exercise. Participants participated in the blind design experiment under both conditions at a one-week interval. Oxygen uptake, respiratory exchange ratio, heart rate, RPE, and plasma lactate concentration were measured during the endurance exercise. The RPE under the caffeinated coffee condition during the last 60 min of endurance exercise was significantly lower than that in the decaffeinated coffee condition. However, no significant differences in any physiological response were observed between conditions. Thus, caffeine ingestion 60 min before starting exercise had an insignificant effect on the physiological responses, except for RPE during submaximal endurance exercises for 60 min. Caffeine ingestion before endurance exercise of relatively low intensity may have a beneficial effect on psychological responses [064].

Although coffee is largely consumed by adults in Western countries, controversy exists about its impact on the cardiovascular system. It was recently demonstrated that caffeinated and decaffeinated espresso coffee have different acute effects on endothelial function in healthy subjects, measured using flow-mediated dilation of the brachial artery. In one study, it was measured the anti-oxidant capacity of two coffee substances in terms of free stable radical 2,2-diphenyl-1-picryl-hydrazyl 50 percent inhibition (I50 DPPH). The caffeinated coffee had a slightly higher anti-oxidant capacity than decaffeinated espresso coffee. It was suggested that the unfavourable effects observed after caffeinated coffee ingestion are due to caffeine and that the antioxidant activity is responsible for the increased FMD observed after decaffeinated coffee ingestion. Further clinical and epidemiological studies are needed to understand the chronic effects of coffee consumption on health [065].
Caffeine versus anhydrous caffeine

Caffeine and coffee are widely used among active individuals to enhance performance. The purpose of the current study was to compare the effects of acute coffee (COF) and caffeine anhydrous (CAF) intake on strength and sprint performance. Fifty-four resistance-trained males completed strength testing, consisting of one-rep max (1RM) and repetitions to fatigue (RTF) at 80 percent of 1RM for leg press (LP) and bench press (BP). Participants then completed five, 10-second cycle ergometer sprints separated by one minute of rest. Peak power (PP) and total work (TW) were recorded for each sprint. At least 48 hours later, participants returned and ingested a beverage containing CAF (300 mg flat dose; yielding 3.5 mg/kg bodyweight), COF (8.9 g; 303 mg caffeine), or placebo (PLA; 3.8 g non-caloric flavouring) 30 minutes before testing. LP 1RM was improved more by COF than CAF, but not PLA. Significant interactions were not observed for BP 1RM, BP RTF, or LP RTF. There were no sprint × treatment interactions for PP or TW. 95 percent confidence intervals revealed a significant improvement in sprint 1 TW for CAF, but not COF or PLA. For PLA, significant reductions were observed in sprint 4 PP, sprint 2 TW, sprint 4 TW, and average TW; significant reductions were not observed with CAF or COF. Neither COF nor CAF improved strength outcomes more than PLA, while both groups attenuated sprint power reductions to a similar degree. Coffee and caffeine anhydrous may be considered suitable pre-exercise caffeine sources for high-intensity exercise [066].

Turkish coffee

Coffee consumption has vast commercial, agricultural, and social importance, is pharmacologically active, and is often consumed for its stimulatory effects. Coffee is a highly-concentrated source of caffeine (2 %). The stimulatory effects of coffee are attributed to the pharmacological activity of caffeine, acting as an antagonist of adenosine receptors in the brain. However, the wide variety of coffee species, roasting conditions, and extraction procedures employed results in a considerable amount of biological variance. Unlike coffee traditionally consumed in the western world, Turkish coffee is not drip filtered, but rather its method of preparation involves slowly boiling water that is mixed with thin powdery grounds. This style of preparation results in a greater amount of biologically active components remaining in the liquid, and likely contributes to the higher concentration of caffeine found in Turkish coffee compared to other coffee types and preparation styles. The ingestion of caffeine has been reported to spare muscle glycogen, and increase fat oxidation through increased sympathetic nervous system activity. Several reviews examining the ergogenic benefits of caffeine use and endurance performance have concluded that caffeine use is positively related to greater performance in time trials and in exercise to exhaustion. Caffeine anhydrous has long been thought to be superior for improving endurance performance as compared to coffee due to the presence of chlorogenic acid in coffee. Recently, it was compared the effects of decaffeinated coffee, regular coffee, caffeine anhydrous, and a placebo and demonstrated regular coffee to be as effective as anhydrous caffeine, when provided at the same relative dose, for improving endurance performance. Differences in their study and others were partly attributed to the performance test used. Previous studies examining the ergogenic benefits of coffee have used prolonged submaximal runs, or using time to exhaustion tests, however, it was than employed a time trial as their assessment. Considering that time to exhaustion tests have been shown to be highly variable from day to day, the use of time trials may provide a more reliable measure of endurance performance [067].

The purpose of one study was to examine the ergogenic benefits of Turkish coffee consumed an hour before exercise. In addition, metabolic, cardiovascular, and subjective measures of energy, focus and alertness were examined in healthy, recreationally active adults who were regular caffeine consumers (>200 mg per day). Twenty males (n=10) and
females (n=10), age 24.1 ± 2.9 years, ingested both Turkish coffee (3 mg/kg BW of caffeine, (TC)), and decaffeinated Turkish coffee (DC) in a double-blind, randomized, cross-over design. Performance measures included a 5 km time trial, upper and lower body reaction to visual stimuli, and multiple object tracking. Plasma caffeine concentrations, blood pressure (BP), heart rate and subjective measures of energy, focus and alertness were assessed at baseline (BL), 30-min following coffee ingestion (30+), prior to endurance exercise (PRE) and immediately-post 5 km (IP). Metabolic measures (VO₂, VE), and respiratory exchange rate (RER) were measured during the 5 km. Plasma caffeine concentrations were significantly greater during TC at 30+, PRE, and IP compared to DC. Significantly higher energy levels were reported at 30+ and PRE for TC compared to DC. Upper body reaction performance and RER were significantly higher for TC compared to DC. Although no significant differences were observed in 5 km run time, 12 of the 20 subjects ran faster during TC (1662 ± 252 s) compared to DC (1743 ± 296 s). Systolic BP was significantly elevated during TC in comparison to DC. No other differences were noted in any of the other performance or metabolic measures. It was concluded that acute ingestion of TC resulted in a significant elevation in plasma caffeine concentrations within 30–min of consumption. TC ingestion resulted in significant performance benefits in reaction time and an increase in subjective feelings of energy in habitual caffeine users. No significant differences were noted in time for the 5 km between trials, however 60% of the participants performed the 5 km faster during the TC trial and were deemed responders. When comparing TC to DC in responders only, significantly faster times were noted when consuming TC compared to DC. No significant benefits were noted in measures of cognitive function [067].

Bioavailability of coffee

Coffee and green tea are two of the most widely consumed hot beverages in the world. Their respective bioavailability has been studied separately, but absorption of their respective bioactive phenolics has not been compared. In a randomized cross-over design, nine healthy subjects drank instant coffee and green tea. Blood samples were collected over 12 h and at 24 h to assess return to baseline. After green tea consumption, (-)-epigallocatechin (EGC) was the major catechin, appearing rapidly in the plasma; (-)-EGC gallate (EGCg) and (-)-epicatechin (EC) were also present, but (-)-EC gallate and C were not detected. Dihydroferulic acid and dihydrocaffeic acid were the major metabolites that appeared after coffee consumption with a long time needed to reach maximum plasma concentration, suggesting metabolism and absorption in the colon. Other phenolic acid equivalents (caffeic acid (CA), ferulic acid (FA) and isoflavonoids (iFA)) were detected earlier, and they peaked at lower concentrations. Summations of the plasma area under the curves (AUC) for the measured metabolites showed 1.7-fold more coffee-derived phenolic acids than green tea-derived catechins. Furthermore, it was found a significant correlation between coffee metabolites based on AUC. Inter-individual differences were observed, but individuals with a high level of CA also showed a correspondingly high level of FA. However, no such correlation was observed between the tea catechins and coffee phenolic acids. Correlation between AUC and maximum plasma concentration was also significant for CA, FA and iFA and for EGCg. This implies that the mechanisms of absorption for these two classes of compounds are different, and that a high absorber of phenolic acids is not necessarily a high absorber of catechins [068].

Effect versus dosage

There is a scarcity of field-based studies and investigations involving elite performers. Researchers are encouraged to use statistical analyses that consider the magnitude of changes, and to establish whether these are meaningful to the outcome of sport. The
available literature that follows such guidelines suggests that performance benefits can be seen with moderate amounts (about 3 mg/kg body mass) of caffeine. Furthermore, these benefits are likely to occur across a range of sports, including endurance events, stop-and-go events (e.g. team and racquet sports), and sports involving sustained high-intensity activity lasting from 1-60 min (e.g. swimming, rowing, and middle and distance running races). The direct effects on single events involving strength and power, such as lifts, throws, and sprints, are unclear. Further studies are needed to better elucidate the range of protocols (timing and amount of doses) that produce benefits and the range of sports to which these may apply. Individual responses, the politics of sport, and the effects of caffeine on other goals, such as sleep, hydration, and refuelling, also need to be considered [069].

Caffeine increase athletic performance, endurance, and mental chronometry at doses as low as 1-3 mg/kg [08305]. Several aspects of the relationship between caffeine and exercise are intriguing, and differ from the situation with other ergogenic aids. First, caffeine appears to exert positive effects on exercise capacity (prolonging the duration for which exercise of a given intensity can be maintained) over a diverse range of protocols including prolonged submaximal exercise (>90 min), sustained high-intensity work (20-60 min) and short duration supra-maximal exercise (1–5 min). Of course, athletes are more interested in the effects of caffeine in trained individuals on measurements of sports performance. A much smaller number of studies in laboratory and field conditions show that caffeine supplementation is likely to be beneficial across a range of sports including endurance events, “stop and go” events (e.g. team and racquet sports) and sports involving sustained high-intensity activity lasting from 1-60 min (e.g. swimming, rowing, middle and distance running races). The direct effects on single events involving strength and power such as lifts, throws and sprints are unclear. The benefits of caffeine appear to be achieved by a number of different protocols of use, with variables including the timing and amount of the caffeine dose. Although the traditional supplementation regimen involves a single intake of about 6 mg/kg BM, 1 h pre-exercise, one studies show that ergogenic effects from caffeine intake may occur at very modest levels of intake (1-3 mg/kg bodyweight or 70-200 mg caffeine). In fact, several studies suggest there is no dose-response relationship between caffeine intake and benefits to endurance exercise or, if it exists, there is a plateau at about 3 mg/kg or about 200 mg [002].

**Dosage versus endurance cycle time**

One study investigated the effects of two different doses of caffeine on endurance cycle time trial performance in male athletes. Using a randomized, placebo-controlled, double-blind crossover study design, sixteen well-trained and familiarized male cyclists (age 32 years) completed three experimental trials, following training and dietary standardization. Participants ingested either a placebo, or 3 or 6 mg/kg body mass of caffeine 90 min prior to completing a set amount of work equivalent to 75 percent of peak sustainable power output for 60 min. Exercise performance was significantly improved with both caffeine treatments as compared to placebo (4.2 % with 3 mg/kg body mass and 2.9 % with 6 mg/kg body mass). The difference between the two caffeine doses was not statistically significant. Caffeine ingestion at either dose resulted in significantly higher heart rate values than the placebo conditions, but no statistically significant treatment effects in ratings of perceived exertion (RPE) were observed. A caffeine dose of 3 mg/kg body mass appears to improve cycling performance in well-trained and familiarized athletes. Doubling the dose to 6 mg/kg body mass does not confer any additional improvements in performance [070].

**Users versus non-users**

Some studies used caffeine-naïve whereas others used caffeine-habituated subjects. There seems to be a higher increase in plasma adrenalin in caffeine-naïves compared to caffeine
habituated subjects after caffeine ingestion. However, no differences between habitual caffeine intake and 1500 m running performance or force of contraction could be observed. For both caffeine-naïve as well as caffeine-habituated subjects, moderate to high doses of caffeine are ergogenic during prolonged moderate intensity exercise. Although there is clearly the need to study caffeine habituation further, the differences between users and non-users do not seem to be major [011].

It appears that the ergogenic effect of caffeine occurs regardless of the timing of intake (either before or during the event). The effect of caffeine intake appears to be prolonged to as much as 6 hours following ingestion. This ergogenic effect is seen at a similar magnitude with both a one-time ingestion prior to exercise as well as with multiple smaller, but equal dosages given throughout a period of prolonged exercise. An interesting finding is that the ergogenic effect of caffeine is more pronounced in nonusers (< 50 mg daily) compared with regular users (> 300 mg daily) of caffeine. This is most likely explained by the upregulation of adenosine receptors with the regular consumption of caffeine [012].

Another factor that must be considered in the evaluation of the effect of caffeine is a tolerance to the effects from habitual consumption. Tolerance to the adenosine receptor-mediated effects of epinephrine release, FFA release, and increased blood pressure have been observed. Given that the dihydropyridine and ryanodine receptors form a macro-molecular complex and are not true receptors, it could be predicted that downregulation would not occur, as has been shown for the adenosine receptor-mediated effects [044].

**Duration of effect**

In terms of variations to the timing of intake of caffeine doses, it appears, at least in endurance sports, that caffeine can be consumed pre-event or as single or multiple doses spread throughout an exercise bout or just prior to the onset of fatigue. The effects of caffeine can be long lasting, with one study showing that people who ingest caffeine to enhance a morning exercise task may still receive benefits during a session undertaken later in the day [002].

**Optimum time to exercise after caffeine ingestion**

There have been numerous studies and reviews indicating that caffeine ingested before exercise causes rapid and significant improvements in performance, especially in aerobic exercise capacity. The dose of caffeine studied has ranged from 1 to 15 mg/kg of body mass. The optimal dose has not been determined because it may vary according to the sensitivity of the individual to caffeine. However, doses between 3 and 6 mg/kg produce an equivalent ergogenic effect to higher doses, and this has led to the suggestion that the optimal dose thus lies in this lower range. Even though caffeine has a half-life of 4-6 h that implies high levels of caffeine will be in the blood for up to 3-4 h after ingestion, most studies have focused on exercise performance about 1 h after ingestion. The assumption is that the ergogenic effect is related to the circulating level of the drug in the blood. Thus maximal effects are assumed to occur about 1 h after ingestion, when peak blood concentrations are observed. Some studies have suggested that waiting 3 h may be more optimal because the caffeine-induced effect on lipolysis is greater than at earlier times after ingestion. However, the hypothesis that the ergogenic effect from caffeine is due to an enhanced free fatty acid mobilization and tissue utilization has not found much support in the recent literature. For sustained operations, as is quite common in the military, or for athletes who might be faced with unplanned delays in competition, it would seem critical not only to know when a particular drug should be taken to produce its effect, but also it would seem important to understand for how long that ergogenic effect may last. Military operations or athletic events may be delayed or cancelled at the last minute, and information about the time course of the
effect of a drug would assist in the planning and subsequent rescheduling of activities. Caffeine acts as an $A_1$ and $A_{2a}$ adenosine receptor antagonist. Regular consumption of caffeine is associated with an upregulation of the number of these adenosine receptors in the vascular and neural tissues of the brain. One might expect, therefore, that users and nonusers of caffeine would respond differently to the same dose of the drug because it is known that some individuals are more sensitive than others to caffeine. Others have compared users and nonusers of caffeine during an incremental exercise test to maximum or during 1 h of submaximal exercise at 50 percent of maximal oxygen consumption ($VO_{2\text{max}}$). The purpose of one study was to examine the duration of caffeine's ergogenic effect and whether it differs between users and nonusers of the drug. Twenty-one subjects (13 caffeine users and 8 nonusers) completed six randomized exercise rides to exhaustion at 80% of maximal oxygen consumption after ingesting either a placebo or 5 mg/kg of caffeine. Exercise to exhaustion was completed once per week at either 1, 3, or 6 h after placebo or drug ingestion. Exercise time to exhaustion differed between users and nonusers with the ergogenic effect being greater and lasting longer in nonusers. For the nonusers, exercise times 1, 3, and 6 h after caffeine ingestion were 32.7 ± 8.4, 32.1 ± 8.6, and 31.7 ± 12.0 min, respectively, and these values were each significantly greater than the corresponding placebo values of 24.2 ± 6.4, 25.8 ± 9.0, and 23.2 ± 7.1 min. For caffeine users, exercise times 1, 3, and 6 h after caffeine ingestion were 27.4 ± 7.2, 28.1 ± 7.8, and 24.5 ± 7.6 min, respectively. Only exercise times 1 and 3 h after drug ingestion were significantly greater than the respective placebo trials of 23.3 ± 6.5, 23.2 ± 7.1, and 23.5 ± 5.7 min. In conclusion, both the duration and magnitude of the ergogenic effect that followed a 5 mg/kg dose of caffeine were greater in the nonusers compared with the users [071].

Divided doses or bolus?

One study compared the effects of a single and divided dose of caffeine on endurance performance and on postexercise urinary caffeine and plasma paraxanthine concentrations. Nine male cyclists and triathletes cycled for 90 min at 68 percent of maximal oxygen uptake, followed by a self-paced time trial (work equivalent to 80% of maximal oxygen uptake workload over 30 min) with three randomized, balanced, and double-blind interventions: 1) placebo 60 min before and 45 min into exercise (PP); 2) single caffeine dose (6 mg/kg) 60 min before exercise and placebo 45 min into exercise (CP); and 3) divided caffeine dose (3 mg/kg) 60 min before and 45 min into exercise (CC). Time trial performance was unchanged with caffeine ingestion, but it tended to be faster in the caffeine trials (CP: 24.2 min and CC: 23.4 min) compared with placebo (PP: 28.3 min). Postexercise urinary caffeine concentration was significantly lower in CC (3.8 micro g/ml) compared with CP (6.8 micro g/ml). Plasma paraxanthine increased in a dose-dependent fashion and did not peak during exercise. In conclusion, dividing a caffeine dose provides no ergogenic effect over a bolus dose but reduces postexercise urinary concentration [072].

Effect of a divided caffeine dose on endurance performance

As a central nervous system stimulant, caffeine was classed as a prohibited substance by the International Olympic Committee (IOC) and other sporting bodies. However, because it is present in many commonly ingested foodstuffs, 12 microg/mL was the permissible postexercise urinary threshold under which no doping offense is recorded. There is substantial intersubject variability in the metabolism and elimination of caffeine particularly during exercise. Thus urine caffeine concentration as a marker of caffeine consumption may not accurately reflect dose or plasma levels. It was for example measured postexercise urinary caffeine concentrations after caffeine ingestion during exercise. One study showed no effect of splitting the dose on urine concentrations, but another observed lower concentrations (2.5 microg/ml) after a split dose than previous studies with a bolus dose. It is possible that splitting the caffeine dose delays the appearance in the urine but still provides a similar ergogenic effect to a bolus dose. Paraxanthine, the primary metabolite of caffeine,
accounts for >80 percent of caffeine degradation. It is pharmacologically active as an adenosine-receptor antagonist and thus potentially ergogenic, presenting difficulties in determining whether caffeine alone is responsible for the effects on exercise performance. Little is known about paraxanthine kinetics during exercise. Caffeine is one of the most widely consumed drugs in the world and is known to be ingested by sportspeople to augment performance. Ample laboratory-based and some field-based evidence demonstrate the beneficial effects of caffeine on endurance exercise performance. However, few reports document the incidence of its use as an ergogenic aid in the athletic population and its ideal pattern of delivery. The majority of laboratory studies demonstrating the ergogenic effect of caffeine ingestion on performance administer caffeine as a single dose 1 h before exercise. This is largely to ensure a peak plasma concentration during exercise. However, it is unknown whether this is the optimal timing of caffeine administration to maximize its ergogenic effect. Few studies have measured the plasma concentration of caffeine during exercise or examined its variability in exercising subjects. To date, five studies have investigated the effects of repeated caffeine administration during exercise, and not all observed a performance-enhancing effect. Of these, only two have employed a self-paced time trial, a protocol more reliable and representative of competition, as an endurance performance measure. One study compared the effects of a single and divided dose of caffeine on endurance performance and on postexercise urinary caffeine and plasma paraxanthine concentrations. Nine male cyclists and triathletes cycled for 90 min at 68 percent of maximal oxygen uptake, followed by a self-paced time trial (work equivalent to 80% of maximal oxygen uptake workload over 30 min) with three randomized, balanced, and double-blind interventions: 1) placebo 60 min before and 45 min into exercise (PP); 2) single caffeine dose (6 mg/kg) 60 min before exercise and placebo 45 min into exercise (CP); and 3) divided caffeine dose (3 mg/kg) 60 min before and 45 min into exercise (CC). Time trial performance was unchanged with caffeine ingestion, but it tended to be faster in the caffeine trials (CP: 24.2 min and CC: 23.4 min) compared with placebo (PP: 28.3 min). Postexercise urinary caffeine concentration was significantly lower in CC (3.8 micro g/ml) compared with CP (6.8 micro g/ml). Plasma paraxanthine increased in a dose-dependent fashion and did not peak during exercise. In conclusion, dividing a caffeine dose provides no ergogenic effect over a bolus dose but reduces postexercise urinary concentration.

Lethal dosage

The lethal dose of caffeine is about 10 grams, which is equivalent to the amount of caffeine in 100 cups of coffee.

Low doses of caffeine

The world of sport has always had a high tolerance for the use of caffeine. For many years, caffeine use in sport was restricted or controlled, but athletes were still allowed high urinary caffeine levels (12 lg/mL), before it was considered illegal. Research in the laboratory had determined that athletes needed to ingest 10-13 mg caffeine/kg body mass in a fairly short period of time to reach this limit. For a 70 kg person, this amounted to the ingestion of 700-900 mg or the equivalent of 5-7 cups of coffee, which exceeds typical caffeine use in the general population. While studies using these high doses of caffeine reported ergogenic effects in endurance-type activities, there were also pronounced effects on the physiological responses to exercise, including increased heart rates, a doubling of the catecholamine levels, higher blood lactate levels, and increased blood free fatty acid (FFA) and glycerol levels in many subjects. The ingestion of high caffeine doses also produced troubling side effects of gastrointestinal upset, nervousness, mental confusion, inability to focus, and disturbed sleeping in some subjects, especially those who were habitual light caffeine users.
When the caffeine dose was reduced to a moderate level (5-6 mg/kg bm), the ergogenic effects were maintained and the physiological responses and side effects were also reduced but were still present. There have also been many attempts over the years to link these caffeine-induced peripheral physiological responses to the ergogenic benefits of caffeine. However, the administration of a low caffeine dose (3 mg/kg bm) also produced an ergogenic effect, with no changes in exercise heart rate and the levels of catecholamines, lactate, FFA, and glycerol. This strongly suggested that the ergogenic effect of caffeine was mediated through the central nervous system (CNS). Previous work demonstrating caffeine’s antagonistic effect on adenosine receptors in the body provided the likely mechanism of action. Work with animal models also demonstrated a direct effect of caffeine on the CNS and exercise performance [054].

The majority of research has examined the effects of moderate to high caffeine doses (5-13 mg/kg body mass) on exercise and sport. These caffeine doses have profound effects on the responses to exercise at the whole-body level and are associated with variable results and some undesirable side effects. Low doses of caffeine (<3 mg/kg body mass, about 200 mg) are also ergogenic in some exercise and sport situations, although this has been less well studied. Lower caffeine doses

- do not alter the peripheral whole-body responses to exercise
- improve vigilance, alertness, and mood and cognitive processes during and after exercise
- are associated with few, if any, side effects

Therefore, the ergogenic effect of low caffeine doses appears to result from alterations in the central nervous system. However, several aspects of consuming low doses of caffeine remain unresolved and suffer from a paucity of research, including the potential effects on high-intensity sprint and burst activities. The responses to low doses of caffeine are also variable and athletes need to determine whether the ingestion of about 200 mg of caffeine before and/or during training and competitions is ergogenic on an individual basis [054].

A low dose of caffeine is defined here as ingesting 3 mg/kg bm or less, which is 200 mg of caffeine for a 70 kg individual. This is no more caffeine than may be consumed in 1-2 small cups of coffee or one large coffee. It is ironic that more research has examined the efficacy of low caffeine doses for improving exercise and sport performance in the last 10 years, given that caffeine was removed from the World Anti-Doping Agency list of restricted or banned substances in 2004. It may have been expected that the use of higher caffeine doses would have increased but the majority of research continues to use moderate (5-6 mg/kg bm) or low (<3 mg/kg bm) doses [054].

Are low doses of caffeine ergogenic during endurance exercise?

The interest in caffeine as a potential ergogenic aid during endurance exercise began in large part due to the research in the late 1970s. Trained cyclists improved their ride times to exhaustion at 80 percent of maximal oxygen consumption (VO₂max), from 75 min in the placebo condition to 96 min following the ingestion of 330 mg of caffeine in coffee. This caffeine dose was not low at about 5 mg/kg bm, but a second study gave only 250 mg of caffeine at the beginning of exercise and then another 250 mg in seven doses during exercise and reported a 20 percent increase in the work completed during 2 h of cycling. This early work hinted that there may be an ergogenic effect of low doses of caffeine but it was not until 1995 that a dose response study examined the effects of 3, 6 and 9 mg/kg bm on the performance of well-trained runners. Subjects abstained from caffeine use for 48 h, then consumed a random dose of caffeine or placebo in capsule form 1 h before running to
exhaustion at 85 percent of VO\textsubscript{2max} on a treadmill in ambient laboratory conditions on four separate occasions. Endurance performance was enhanced by 22 percent over the placebo run of 49.4 ± 4.2 min following the ingestion of 3 and 6 mg/kg bm caffeine, but only by 11 percent and non-significantly following the highest caffeine dose. A later study examined the effects of two low caffeine doses and one moderate caffeine dose given with a CES on the ability to complete a set amount of work that required 1 h. Well-trained cyclists and triathletes randomly received either a placebo or a caffeine dose of 2.1, 3.2 or 4.5 mg/kg bm. The caffeine doses were partitioned with 60 percent of the dose administered 20 min before exercise, 20 percent after 20 min of cycling, and the remaining 20 percent at 40 min into the ride. The time-trial performance was 62.5 ± 1.3 min in the placebo trial and sequentially decreased with increasing caffeine doses to 61.5 ± 1.1, 60.4 ± 1.0, and 58.9 ± 1.2 min. Therefore, while the low doses of caffeine were performance enhancing, that study suggested that the moderate dose (4.5 mg/kg bm) was the most ergogenic [054].

Small doses of caffeine late in prolonged exercise

An interesting study was published in 2002 suggesting that well-trained athletes are very sensitive to small doses of caffeine late in prolonged exercise without taking any caffeine before exercise. Scientists at the Australian Institute of Sport were aware that endurance cyclists preferred to switch from a CES to flat cola in the later stages of 2- to 6-h road races. They then tested whether this practice was ergogenic and whether the active ingredient was in the cola was the extra carbohydrate (CHO) or the caffeine. The authors concluded that 67 percent of the improvement in time-trial performance was the effect of caffeine, with the remaining 33 percent due to the additional CHO. The average total caffeine intake at 80, 100 (and for some, 120) min of cycling was only 133 mg or 1.9 mg/kg bm, resulting in plasma levels of less than 10 lmol/L. These low levels of caffeine intake and plasma accumulation did not affect any of the physiological responses to exercise, suggesting that the beneficial effects of caffeine were manifested in the CNS late in exhaustive exercise. In a similar study, the effects of two low doses of caffeine on time-trial performance following a prolonged cycle were examined. A 200 mg dose was than more potent than 100 mg of caffeine. There were no differences in the physiological responses during the initial 120 min of submaximal exercise (heart rate, respiratory exchange ratio, and epinephrine, glucose, lactate, glycerol, and FFA levels) and prior to the time trials between the conditions, supporting a CNS mechanism for the improvement in performance [054].

Low caffeine doses ingested before endurance exercise

In other recent studies that examined the effects of low doses of caffeine given 1 h before prolonged exercise, improvements in performance have also been shown, but not at all doses when given well-trained cyclists either a placebo or 1, 2 or 3 mg/kg bm caffeine 1 h before exercise in a randomized design. The work done in 15 min was not improved by 1 mg/kg bm caffeine but increased significantly by 4 percent and 3 percent after 2 and 3 mg/kg bm, respectively. The authors also noted the considerable variability that existed between subjects. Another interesting study that was designed to determine whether a low acute dose of caffeine (3 g/kg bm) was ergogenic for endurance cycling performance following 4 days of caffeine withdrawal or no withdrawal in habitual caffeine users. In this study, the habitual caffeine-user athletes experienced a significant improvement in performance from ingesting a low caffeine dose 90 min before exercise, regardless of whether they withdrew from caffeine or not [054].

Running

It has been published a comprehensive study demonstrating that 150-200 mg of caffeine ingested as coffee 1 h before exercise improved 1,500 m running performance in well-trained
runners. In one experiment, 1,500 m time was improved by 4.2 s with caffeine and, in a second experiment, where the runners ran the first 1,100 m at a constant speed and then self-selected their speed over the final 400 m, running speed was improved over the final lap by 0.6 km/h, which amounted to 10 m. However, in a longer road race, 98 runners completed an 18 km run three times in 8 days in a cool environment and found no effect of a low dose of caffeine on performance. It was also reported a 24 s or 1.8 percent improvement in 8 km run time on a track with well-trained male runners when ingesting 3 mg/kg bm of caffeine 1 h before racing [054].

Stop-and-Go individual and team sports

There have been some studies examining the potential ergogenic effects of what might be called “stop-and-go” individual and team sports, most of which have not been conducted with low caffeine doses. A study with male collegiate tennis players demonstrated some improvements in forehand shot performance when 3 mg/kg bm was consumed 90 min before a simulated tennis match. A comprehensive study of golf putting performance and alertness when comparing an energy free, flavoured drink versus a CES with caffeine showed that the CES drink with caffeine improved putting performance and increased feelings of alertness. Two recent studies examined the effects of ingesting 3 mg/kg/bm caffeine on volleyball performance in females and males. In both studies, the caffeine was administered in an energy drink, with a caffeine-free energy drink serving as the control. The authors stressed that both physical performance and the accuracy of the volleyball skills were improved with caffeine ingestion in a commercially available energy drink. Two team-sport studies also suggested that low doses of caffeine may improve aspects of soccer and rugby playing, although the studies gave 3.7 and 4.0 mg/kg bm caffeine, respectively. The authors concluded that the co-ingestion of CHO and caffeine was likely to benefit performance [054].

Low caffeine doses and high-intensity exercise in anaerobic sports

Many forms of exercise and sports are reliant on bursts of activities or sprints, where the dominant portion of the energy production must be provided by non-oxidative or anaerobic energy sources. Phosphocreatine (PCr) and adenosine triphosphate (ATP) production in the glycolytic pathway are the two main pathways for the production of anaerobic energy. While the PCr store can be consumed in a few seconds and the heavy use of the glycolytic pathway can lead to acidosis in muscle cells, these pathways are able to provide energy very quickly and in large quantities for short periods of time to allow athletes to complete very powerful movements. In many sports, the ability to repeatedly burst or sprint is essential to success. In stop-and-go and power-based sports, these bursts often occur on the back of already high energy production from the aerobic system. Early reviews generally concluded that there was no benefit of caffeine for burst activities as the majority of studies reported no effects. However, as the number of studies examining this type of work increased, more recent reviews suggested that there were benefits in about 50 percent of the published studies in power-based sports, resistance training paradigms, repeated high-intensity intermittent exercise, and isometric and isokinetic muscle force production and endurance. For example, indices of strength in highly resistance-trained males were improved with caffeine ingestion of 7 mg/kg bm and more weight was lifted and a greater peak power was attained in a Wingate test in competitively trained males following the ingestion of 5 mg/kg bm caffeine. Short-term high-intensity cycling lasting about 1 min was also improved by the ingestion of 5 mg/kg bm caffeine in two studies. Almost no work exists in this area with low caffeine doses. However, a research group in France reported ergogenic effects of a 250 mg dose of caffeine on work maximum in a test of maximal anaerobic power and in repeated 100 m sprints in trained swimmers. The conclusion here must be that very little “low-dose”caffeine research has been done in this area, although it may be argued that this stems from the somewhat equivocal results that have been reported with moderate and high
doses of caffeine on burst and sprint activities [054].

Low caffeine doses and vigilance, alertness, mood and cognitive function

There is a large literature that has examined the use of caffeine for maintaining vigilance, alertness, mood, executive control, and related parameters. This research often investigates situations where maintaining vigilance and performance is critical, as in the military and other professions where people are awake for long periods of time. More recent work indicated that the optimal dose of caffeine is 200 mg when vigilance, mood, alerting, orienting, and executive control were assessed against other caffeine doses or no caffeine. The plateauing of beneficial effects at 200 mg of caffeine is believed to match the adenosine-mediated effects on dopamine-rich areas in the human brain and their involvement in the executive control of visual attention and alerting [49]. Results clearly demonstrated that the ability to concentrate and make decisions is improved by caffeine immediately after exhausting exercise, leading to the suggestion that this effect would also be present in the later stages of exercise. Other results suggest that low-dose caffeine ingestion during prolonged exercise helps with decision making and could be useful for all sports where critical decision making is important for success late in an event or game [054].

Gastrointestinal function

One study examined the effects of low doses of caffeine (95 mg) in a CES on gastrointestinal function given before exercise and at 20 and 40 min into 90 min of cycling at *70 percent VO_{2max}. Caffeine (285 mg in total) had no effect on gastric emptying, gastric pH, orocecal transit time, and intestinal permeability. Interestingly, glucose absorption was increased in the caffeine trial. A subsequent study examining the effects of caffeine on glucose absorption also reported an increase but with a high caffeine dose of 10 mg/kg bm during cycling, while two other studies reported no effect with 1.5, 3 and 5.3 mg/kg bm. So on balance, it seems unlikely that low doses of caffeine would affect glucose absorption on a consistent basis [054].

Reducing the dose of caffeine and ephedrine preserving the ergogenic effect

Ingestion of a combination of 5 mg/kg caffeine (C), and 1 mg/kg ephedrine (E) was reported to have an ergogenic effect on high intensity aerobic exercise performance, but 25 percent of the subjects experienced vomiting and nausea while engaging in hard exercise after the treatment. The present study was undertaken to investigate whether reduced levels of C+E would alleviate the problem and maintain the ergogenic effect. Twelve healthy untrained male subjects completed four randomized and double-blind, cycle ergometer trials to exhaustion at a power output equivalent to approximately 85 percent VO_{2peak}. 1.5-2 hours after ingesting a placebo (P) or a mixture of C+E in the following doses: 5 mg/kg of C plus 0.8 mg/kg of E (CLE); 4 mg/kg of C plus 1 mg x kg(-1) of E (LCE); or 4 mg/kg of C plus 0.8 mg/kg of E (LCLE). Trials were separated by 1 week. Venous blood samples were obtained and analyzed for caffeine and ephedrine levels 1.5 h post-drug ingestion. VO_{2}, VCO_{2}, VE, and RQ were measured every minute throughout the exhaustion ride. Heart rate and perceived exertion (RPE) were also recorded every 5 min and at the end of the exercise session. Plasma levels of C and E immediately before the exhaustion ride and the times to exhaustion for the treatment trials were similar and were significantly greater than placebo. The drugs did not affect VO_{2}, VCO_{2}, or VE. Heart rates were significantly higher for the drug trials while RPE was lower compared with P. No incidents of nausea or vomiting occurred with the lowest dose of the C+E, LCLE. It was concluded that a lower dose of C+E resulted in an ergogenic effect similar in magnitude to that reported previously with a higher dose, and with a reduced incidence of negative side effects [073].
**Mouth-rinse**

The purpose of one study was to investigate if acute caffeine exposure via mouth-rinse improved endurance cycling time-trial performance in well-trained cyclists. It was hypothesized that caffeine exposure at the mouth would enhance endurance cycling time-trial performance. Ten well-trained male cyclists (32.9 ± 7.5 years, 74.7 ± 5.3 kg, 176.8 ± 5.1 cm, VO$_{2\text{peak}}$ 59.8 ± 3.5 mL/kg/min) completed two experimental time-trials following 24 hr of dietary and exercise standardization. A randomized, double-blind, placebo-controlled, crossover design was employed whereby cyclists completed a time-trial in the fastest time possible, which was equivalent work to cycling at 75 percent of peak aerobic power output for 60 min. Cyclists were administered 25ml mouth-rinses for 10 s containing either placebo or 35mg of anhydrous caffeine eight times throughout the time-trial. Perceptual and physiological variables were recorded throughout. No significant improvement in time-trial performance was observed with caffeine (3918 ± 243 s) compared with placebo mouth-rinse (3940 ± 227 s). No elevation in plasma caffeine was detected due to the mouth-rinse conditions. Caffeine mouth-rinse had no significant effect on rating of perceived exertion, heart rate, rate of oxygen consumption or blood lactate concentration. Eight exposures of a 35 mg dose of caffeine at the buccal cavity for 10 s does not significantly enhance endurance cycling time-trial performance, nor does it elevate plasma caffeine concentration [074].

**Carbohydrate and caffeine mouth rinses**

Oral carbohydrate (CHO) rinsing has beneficial effects on endurance performance and caffeine (CAF) mouth rinsing either independently or in conjunction with CHO may enhance sprinting performance. However, the effects of CHO and CAF mouth rinses on resistance exercise have not been examined previously. The purpose of this study was to investigate the effects of CHO and CAF rinsing on maximum strength and muscular endurance performance. Fifteen recreationally resistance-trained males completed an exercise protocol, which involved a 1 repetition maximum (RM) bench press followed by 60 percent of their 1RM to failure in a double-blind, randomized, counterbalanced crossover design. Before exercise, 25 ml of a 6 percent (15 g; 0.20 ± 0.02 g/kg) CHO, 1.2 percent (300 mg; 3.9 ± 0.3 mg/kg) CAF, carbohydrate with caffeine (C + C) solutions, or water (placebo; PLA) were rinsed for 10 seconds. During the remaining session, no solution was rinsed (control; CON). All solutions were flavored with (200 mg) sucralose. Felt arousal was recorded pre- and post-rinse, and rating of perceived exertion (RPE) was recorded immediately after the repetitions to failure. There were no significant differences in 1RM, the number of repetitions performed, or the total exercise volume between conditions. Rating of perceived exertion was similar for all trials whereas Felt arousal increased as a consequence of rinsing, but was not different between trials. These results suggest that rinsing with a CHO and CAF solution either independently or combined has no significant effect on maximum strength or muscular endurance performance [075].

**Carbohydrate mouth rinse and caffeine improves high-intensity interval running**

It was tested the hypothesis that carbohydrate mouth rinsing, alone or in combination with caffeine, augments high-intensity interval (HIT) running capacity undertaken in a carbohydrate-restricted state. Carbohydrate restriction was achieved by performing high-intensity running to volitional exhaustion in the evening prior to the main experimental trials and further refraining from carbohydrate intake in the post-exercise and overnight period. On the subsequent morning, eight males performed 45-min steady-state (SS) exercise (65 %) followed by HIT running to exhaustion (1-min at 80 % interspersed with 1-min walking at 6 km/h). Subjects completed 3 trials consisting of placebo capsules (administered immediately prior to SS and immediately before HIT) and placebo mouth rinse at 4-min intervals during HIT (PLACEBO), placebo capsules but 10 percent carbohydrate mouth rinse (CMR) at
corresponding time-points or finally, caffeine capsules (200 mg per dose) plus 10 percent carbohydrate mouth rinse (CAFF + CMR) at corresponding time-points. Heart rate, capillary glucose, lactate, glycerol and NEFA were not different at exhaustion during HIT. However, HIT capacity was different between all pair-wise comparisons such that CAFF + CMR (65 ± 26 min) was superior to CMR (52 ± 23 min) and PLACEBO (36 ± 22 min). It was concluded that carbohydrate mouth rinsing and caffeine ingestion improves exercise capacity undertaken in carbohydrate-restricted states. Such nutritional strategies may be advantageous for those athletes who deliberately incorporate elements of training in carbohydrate-restricted states (i.e. the train-low paradigm) into their overall training program in an attempt to strategically enhance mitochondrial adaptations of skeletal muscle [076].

Caffeine and maltodextrin mouth rinsing

Caffeine (CAF) and maltodextrin (MALT) mouth rinses (MR) improve exercise performance. The current experiment aims to determine the effect of CAF and MALT MR on cognitive performance and brain activity. Ten healthy male subjects (age 27 ± 3 year) completed three experimental trials. Each trial included four Stroop tasks: two familiarization tasks, and one task before and one task after an MR period. The reaction time (in milliseconds) and accuracy (percent) of simple, congruent, and incongruent stimuli were assessed. Electroencephalography was applied throughout the experiment to record brain activity. The amplitudes and latencies of the P300 were determined during the Stroop tasks before and after the MR period. Subjects received MR with CAF (0.3 g/25 ml), MALT (1.6 g/25 ml), or placebo (PLAC) in a randomized, double-blind, crossover design. During MR, the brain imaging technique standardized low-resolution brain electromagnetic tomography was applied. Magnitude-based inferences showed that CAF MR is likely trivial (64 %) and likely beneficial (36 %) compared with PLAC MR, and compared with MALT MR likely beneficial to reaction time on incongruent stimuli (62 %). Additionally, both the orbitofrontal and dorsolateral prefrontal cortex were activated only during CAF MR, potentially explaining the likely beneficial effect on reaction times. MALT MR increased brain activity only within the orbitofrontal cortex. However, this brain activation did not alter the reaction time. Furthermore, no significant differences in the accuracy of stimuli responses were observed between conditions. In conclusion, only CAF MR exerted a likely beneficial effect on reaction time due to the subsequent activation of both the orbitofrontal and dorsolateral prefrontal cortexes [077].

Prior coffee consumption impact on subsequent effect of anhydrous caffeine

One study examined whether the prior consumption of coffee (COF) decreased the ergogenic effect of the subsequent ingestion of anhydrous caffeine (CAF). Thirteen subjects performed 6 rides to exhaustion at 80 percent VO2max 1.5 h after ingesting combinations of COF, decaffeinated coffee (DECOF), CAF, or placebo. The conditions were DECOF + placebo (A), DECOF + CAF (5 mg/kg) (B), COF (1.1 mg/kg caffeine) + CAF (5 mg/kg) (C), COF + CAF (3 mg/kg) (D), COF + CAF (7 mg/kg) (E), and colored water + CAF (5 mg/kg) (F). Times to exhaustion were significantly greater for all trials with CAF versus placebo. In conclusion, the prior consumption of COF did not decrease the ergogenic effect of the subsequent ingestion of anhydrous CAF [078].
EFFECTS ON EXERCISE OF CAFFEINE

Caffeine typically increases endurance performance; however, efficacy of caffeine ingestion for short-term high-intensity exercise is equivocal, which may be explained by discrepancies in exercise protocols, dosing, and subjects' training status and habitual caffeine intake found across studies [079].

Overviews

Numerous studies to date have shown the efficacy of acute caffeine ingestion for improving prolonged endurance exercise performance. The effects of caffeine on time trial endurance performance (>5 min) have recently been reviewed in a well conducted meta-analysis. The authors concluded that of the 12 studies that investigated caffeine intake (1-6 mg CAF/kg BW), performance was improved by about 3 percent. It is often cited that caffeine induces its ergogenic effects by an increase in fat oxidation through the sympathetic nervous system, and a sequential sparing of muscle glycogen. However, there is very little support for an increase in fat oxidation or an enhancement to the sympathetic nervous system being the principal mechanism of caffeine’s ergogenic effect. Since, recent investigations have elucidated that the principal mechanism of caffeine’s ergogenic effects is through its ability to act as an adenosine receptor antagonist to induce effects on both central and peripheral nervous system to reduce pain and exertion perception, improve motor recruitment and excitation-contraction coupling. In the literature to date, the ergonomic effects are well documented with the time to exhaustion test at a fixed power output being the predominant performance measure used. It was questioned whether assessing endurance capacity in this way would have sufficient ecological validity to translate results to real life events. However since then, a number of studies have confirmed the ergonomic effects of caffeine using time trial protocols, which involves completing an energy based target or set distance in as fast as time possible, thus simulating variable intensities that are likely to occur during competitive events. In most of these studies pure (anhydrous) caffeine was ingested through capsules or dissolved in water. Based on this research it is often assumed that ingesting caffeine in a variety of dietary sources, such as coffee, will result in the same ergonomic effect. Very few studies, however, have shown a positive effect of coffee on exercise performance. Coffee improved performance in some, but not all studies. This may seem surprising as reports have shown that coffee is the most concentrated dietary source of caffeine as well as being one of the largest sources of caffeine used by athletes prior to competition. Amongst the current studies, only a few investigations have actually used coffee rather than decaffeinated coffee plus anhydrous caffeine, with even fewer of these studies showing an ergonomic effect of the coffee. This further identifies the equivocal evidence surrounding the performance effects of coffee [080].

A large body of scientific evidence describes the beneficial effects of human caffeine consumption on a number of physiologic systems, which is useful for good physical and psychological performance. The consumption of moderate amounts of caffeine thus:

- increases energy availability
- increases daily energy expenditure
- decreases fatigue
- decreases the sense of effort associated with physical activity
- enhances motor performance
- enhances cognitive performance
- increases alertness, wakefulness, and feelings of "energy"
- decreases mental fatigue
- quickens reactions
increases the accuracy of reactions
increases the ability to concentrate and focus attention
enhances short-term memory
increases the ability to solve problems requiring reasoning
increases the ability to make correct decisions
enhances cognitive functioning capabilities and neuromuscular coordination

From this list it is obvious that when stating that caffeine enhances performance it is not a question of only influence one bodily function, but caffeine simultaneously influence several functions, which also will influence each other. This makes practical research of “causes-effect” difficult from a scientific point of view, as it is probable that caffeine rather gives a cascade of effects than just one single effect [081].

Caffeine, even at physiological doses (3-6 mg/kg), as well as coffee are proven ergogenic aids and as such – in most exercise situations, especially in endurance-type events – clearly work-enhancing. It most likely has a peripheral effect targeting skeletal muscle metabolism as well as a central effect targeting the brain to enhance performance, especially during endurance events. Also for anaerobic tasks, the effect of caffeine on the CNS might be most relevant. Further, post-exercise caffeine intake seems to benefit recovery by increasing rates of glycogen resynthesis [011].

<table>
<thead>
<tr>
<th>Acute effect</th>
<th>Effect on performance</th>
<th>Caffeine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater reliance on fat metabolism; increased FFAs; lower respiratory exchange ratio (RER)</td>
<td>Increased time trial performance</td>
<td>6 mg/kg body mass</td>
</tr>
<tr>
<td>Counteract central fatigue, maintenance of MVC directed effect on the CNS</td>
<td>3 % PMAX increase, increase in voluntary activation</td>
<td>6 mg/kg body mass</td>
</tr>
<tr>
<td>No clear mechanism; effect on CNS (greater motor unit recruitment and altered neurotransmitter function) or direct effect on skeletal muscle</td>
<td>Enhanced time trial performance</td>
<td>6 mg/kg caffeine 1 h pre-exercise and about 1.5 mg/kg after 2 h of exercise</td>
</tr>
<tr>
<td>Direct effect on skeletal muscle; interaction with ryanodine receptor; potentiated calcium release from the SR</td>
<td>Increase of contraction force at low frequency stimulation (20 Hz)</td>
<td>6 mg/kg 100 min before stimulation</td>
</tr>
<tr>
<td>Blunted pain response</td>
<td>Significantly higher reps during leg press set 3 with caffeine, same RPE</td>
<td>6 mg/kg 1 h prior to 10 RM bench and leg press</td>
</tr>
<tr>
<td>Glycogen-sparing effect and increased utilization of intramuscular TGs and plasma FFAs with caffeine</td>
<td>Increased cycling time trial performance with caffeine</td>
<td>9 mg/kg body mass 1 h before exercise</td>
</tr>
</tbody>
</table>

Meta-analysis of the effects of caffeine ingestion on exercise testing

One study used the meta-analytic approach to examine the effects of caffeine ingestion on exercise testing. Forty double-blind studies with 76 effect sizes (ES) met the inclusion criteria.
The type of exercise test was classified as endurance, graded, or short-term. In comparison with placebo, caffeine improved test outcome by 12.3 percent (95% confidence interval 9.1 to 15.4), which was equivalent to an overall ES of 0.41 (95% confidence interval 0.31 to 0.51). Endurance exercise significantly improved test outcome more than either graded or short-term exercise. When exercise protocol was examined, time-to-exhaustion (Tlim) protocols had a significantly greater ES than either the graded or the non-Tlim protocol(s). The results from this meta-analysis thus confirm the ergogenic effects of caffeine, particularly for endurance testing that use Tlim protocols [082].

**Confounding factors**

Coffee contains not only caffeine but also hundreds of other biologically active compounds, many of which are metabolically distinct from caffeine [083].

**Coffee polyphenol caffeic acid**

Chlorogenic acid is an ester of caffeic and quinic acids, and is one of the most widely consumed polyphenols because it is abundant in foods, especially coffee. We explored whether chlorogenic acid and its metabolite, caffeic acid, act directly on skeletal muscle to stimulate 5’-adenosine monophosphate-activated protein kinase (AMPK). Incubation of rat epitrochlearis muscles with Krebs buffer containing caffeic acid (≥0.1 mM, ≥30 min) but not chlorogenic acid increased the phosphorylation of AMPKalpha Thr(172), an essential step for kinase activation, and acetyl CoA carboxylase Ser(79), a downstream target of AMPK, in a dose- and time-dependent manner. Analysis of isoform-specific AMPK activity revealed that AMPKalpha2 activity increased significantly, whereas AMPKα1 activity did not change. This enzyme activation was associated with a reduction in phosphocreatine content and an increased rate of 3-O-methyl-d-glucose transport activity in the absence of insulin. These results suggest that caffeic acid but not chlorogenic acid acutely stimulates skeletal muscle AMPK activity and insulin-independent glucose transport with a reduction of the intracellular energy status [084].

Chlorogenic acids are a group of phenolic compounds that possess a quinic acid ester of hydroxycinnamic acid. It has been suggested that components, other than coffee, such as chlorogenic acids, may antagonize the physiological responses of caffeine. Coffee is about 2 percent caffeine, with the remainder composed of chlorogenic acids, ferulic acid, caffeic acid, nicotinic acid as well as other unidentifiable compounds. It is evident that the source of coffee beans, roasting, storage and preparation (brewing and filtering) dramatically alters the caffeine and chlorogenic acid content of the coffee. It has been shown in vitro that chlorogenic acids antagonize adenosine receptor binding of caffeine and cause blunting to heart rate, blood pressure and cause a dose-dependent relaxation of smooth muscle. In addition nicotinic acid, a fatty acid ester found in coffee known to inhibit lipolysis, has been shown to lower FA concentrations in patients suffering from hyperlipidemia. Chlorogenic acids are also believed to improve glucose uptake at the skeletal muscle when compared to caffeine, also by altering the antagonism of adenosine receptors. More recently, caffeic acid has been found to stimulate skeletal muscle glucose transport, independent of insulin, when accompanied with an elevation in AMPK in vitro. However, it has been unclear what role chlorogenic acids, found in coffee, will have on the physiological and metabolic effects of coffee and caffeine during exercise in humans. The consumption of chlorogenic acids varies significantly in coffee ranging from 20-675 mg per serving due to large variation of chlorogenic acids between coffee beverages [080].
Coffee versus caffeine

In one study it was investigated whether acute intake of coffee (5 mg CAF/kg bodyweight) and anhydrous caffeine (5 mg CAF/kg bodyweight) are ergogenic to cycling performance compared to decaffeinated coffee or placebo beverages when using a validated 45-minute time trial performance test and whether caffeine ingested through coffee has the same effects. In a single-blind, crossover, randomized counter-balanced study design, eight trained male cyclists/triathletes (age 41 ± 7 years) 30 min of steady-state cycling at approximately 55 percent $V_{O2\max}$ followed by a 45 min energy based target time trial. One hour prior to exercise each athlete consumed drinks consisting of caffeine, instant coffee, instant decaffeinated coffee, or placebo. The set workloads produced similar relative exercise intensities during the steady-state cycling for all drinks, with no observed difference in carbohydrate or fat oxidation. Performance times during the target time trial were significantly faster (4.9 and 4.5 %) for both caffeine and coffee when compared to placebo and decaffeinated coffee. The significantly faster performance times were similar for both caffeine and coffee. Average power for caffeine and coffee during the target time trial was significantly greater when compared to placebo and decaf. No significant differences were observed between placebo and decaf during the target time trial. It was observed that the significant increase in plasma glucose, FA and glycerol with caffeine was paralleled with an attenuated response for coffee, and a significantly blunted response with decaf coffee when compared to placebo. This is likely due to the compounds in coffee inducing subtle effects on antagonism of adenosine receptors in a variety of exercising and non exercising tissues. Thus, the present study illustrates that both caffeine and coffee consumed 1 h prior to exercise can improve endurance exercise performance with no differences observed. Despite conflicting evidence from other studies, the current study clearly demonstrates that coffee is as effective as caffeine at improving endurance exercise performance. The composition and preparation of coffee in each of the studies may also explain the discrepancies in the ergogenic effects of coffee [080].

Effect of caffeine on repeated exercise in team-sport like tests

Whereas the outcomes of caffeine ingestion (from natural sources and pills) are well known, the effects of caffeine-containing energy drinks on sports performance have been the object of fewer studies. The first report concerning the effects of energy drinks on physical performance was carried out by Alford and co-workers in 2001. These authors found that about 1 mg of caffeine per kg of body weight (one 250-mL serving of an energy drink) improved reaction time, alertness and aerobic and anaerobic performance. In contrast, subsequent investigations using energy drinks have shown that about 1 mg/kg of caffeine is not enough to enhance maximal oxygen uptake, peak power during three repetitions of the Wingate test, or running velocity during 24 “all-out” sprints. In addition, the ingestion of about 2 mg/kg of caffeine in the form of an energy drink was ergogenic during a cycling time trial but did not prolong time-to-exhaustion during a running test at 80 percent $V_{O2\max}$. The ergogenic effect of caffeine on endurance activities has been typically demonstrated with doses from 3 to 9 mg/kg, while the ingestion of 1 mg/kg of caffeine did not improve performance. Similar results have been found in team-sports specific activities: the ingestion of 6 mg/kg of caffeine increased repeated sprint ability, while the ingestion of 1 mg/kg of caffeine did not alter repeated sprint performance. Since the ingestion of one serving of an energy drink (typically 250-mL that contains 80 mg of caffeine) provides a dose of about 1 mg/kg of caffeine in a man of average weight, previous results about the inefficacy of energy drinks to improve performance may be explained by the low dose of caffeine provided for the subjects. During a soccer match, players combine periods of high-intensity exercise interspersed with periods of lower-intensity exercise or recovery. Thus, the ability to perform repeated sprints with minimal recovery between sprint bouts is one of the most crucial
capacities for team sport athletes. In addition, an enhanced ability to repeat sprints is related with playing at a higher competitive level, especially in soccer [016].

The effect of caffeine ingestion on repeated sprint performance is unclear. It was therefore investigated its effect on performance in a test that simulates the repeated sprints of team sports. In a randomized double-blind crossover experiment, 16 male team-sport athletes ingested either caffeine (6 mg/kg of body mass) or a placebo 60 min before performing a repeated 20-m sprint test. The test consisted of 10 sprints, each performed within 10 s and followed by rest for the remainder of each 10 s. The caffeine and placebo trials followed a familiarization trial, and the time between consecutive trials was 2-3 d. To allow estimation of variation in treatment effects between individuals, nine subjects performed three more trials without a supplement 7-14 d later. It was estimated the smallest worthwhile effect on sprint time in a team sport to be approximately 0.8 percent. The mean time to complete 10 sprints increased by 0.1 percent (95 % likely range -1.5 to 1.7 %) with caffeine ingestion relative to placebo. Individual variation in this effect was a standard deviation of 0.7 percent (-2.7 to 2.9 %). Time to complete the 10th sprint was 14.4 percent longer than the first; caffeine increased this time by 0.7 percent (-1.8 to 3.2 %) relative to placebo, and individual variation in this effect was 2.4 percent (-3.4 to 4.9 %). The observed effect of caffeine ingestion on mean sprint performance and fatigue over 10 sprints was negligible. The true effect on mean performance could be small at most, although the true effects on fatigue and on the performance of individuals could be somewhat larger. Pending confirmatory research, team-sport athletes should not expect caffeine to enhance sprint performance [085].

Recent studies incorporating trained subjects and paradigms specific to intermittent sports activity support the notion that caffeine is ergogenic to an extent with anaerobic exercise. Caffeine seems highly ergogenic for speed endurance exercise ranging in duration from 60 to 180 seconds. However, other traditional models examining power output (i.e. 30-second Wingate test) have shown minimal effect of caffeine on performance. Conversely, studies employing sport-specific methodologies (i.e. hockey, rugby, soccer) with shorter duration (i.e. 4-6 seconds) show caffeine to be ergogenic during high-intensity intermittent exercise [036].

The efficacy of caffeine ingestion in enhancing aerobic performance is well established. However, despite suggestions that caffeine may enhance resistance exercise performance, research is equivocal on the effect of acute caffeine ingestion on resistance exercise performance. It has also been suggested that dampened perception of perceived exertion and pain perception might be an explanation for any possible enhancement of resistance exercise performance due to caffeine ingestion. Therefore, the aim of one study was to examine the acute effect of caffeine ingestion on repetitions to failure, rating of perceived exertion (RPE) and muscle pain perception during resistance exercise to failure. Eleven resistance trained individuals (9 males, 2 females, mean age 26 years), took part in this double-blind, randomized cross-over experimental study whereby they ingested a caffeinated (5 mg/kg) or placebo solution 60 minutes before completing a bout of resistance exercise. Experimental conditions were separated by at least 48 hours. Resistance exercise sessions consisted of bench press, deadlift, prone row and back squat exercise to failure at an intensity of 60 percent 1 repetition maximum. Results indicated that participants completed significantly greater repetitions to failure, irrespective of exercise, in the presence of caffeine. Mean of repetitions to failure was 20 and 19 in caffeine and placebo conditions, respectively. There were no differences in peak heart rate or peak blood lactate values across conditions. RPE was significantly lower in the caffeine compared to the placebo condition and was significantly higher during lower body exercises compared to upper body exercises irrespective of substance ingested. For muscle pain perception, a significant condition by exercise interaction revealed that muscle pain perception was lower in the caffeine condition, irrespective of exercise. With caffeine, pain perception was significantly higher in the deadlift and back squat compared to the bench press. However, with placebo, pain perception was significantly higher for the deadlift and back squat compared to the prone row only.
Therefore, acute caffeine ingestion not only enhances resistance exercise performance to failure but also reduces perception of exertion and muscle pain [086].

The evidence for caffeine's effects on resistance exercise is mixed and has not fully examined the associated psychological and psychophysiological changes. One study examined acute effects of ingesting a caffeine-containing energy drink on repetitions to failure, the rating of perceived exertion (RPE), and the readiness to invest physical effort (RTIPE) and mental effort during resistance exercise to failure. Thirteen resistance-trained men took part in this double-blind, randomized cross-over experimental study whereby they ingested a caffeinated (179 mg) energy drink or placebo solution 60 minutes before completing a bout of resistance exercise comprising bench press, deadlift, prone row, and back squat exercise to failure at an intensity of 60 percent 1-repetition maximum. Experimental conditions were separated by at least 48 hours. Participants completed significantly greater repetitions to failure, irrespective of exercise, in the energy drink condition. Rating of perceived exertion was significantly higher in the placebo condition and was significantly higher during lower-body exercises compared with upper-body exercises irrespective of the substance ingested. Readiness to invest mental effort was greater with the energy drink condition, irrespective of time. A significant time × substance interaction for RTIPE indicated that RTIPE increased for both placebo and energy drink conditions preingestion to pre-exercise, but the magnitude of increase was greater with the energy drink condition compared with placebo. This resulted in higher RTIPE postexercise for the energy drink condition. These results suggest that acute ingestion of a caffeine-containing energy drink can enhance resistance exercise performance to failure and positively enhance psychophysiological factors related to exertion in trained men [087].

**Effects of caffeine on sprint**

One study examined the effects of 6 mg/kg caffeine ingestion in team-sport players (n=10) on repeated-sprint running performance (5 sets of 6 x 20 m) and reaction times, 60 min after caffeine or placebo ingestion. Best single sprint and total set sprint times, blood lactate and simple and choice reaction times were measured. Total sprint times across sets 1, 3 and 5 (departure every 25 s) were significantly faster after caffeine than placebo. Similarly, total sprint times across sets 2 and 4 (departure every 60 s), were significantly faster after caffeine than placebo. Significantly higher blood lactates were recorded in caffeine compared to placebo after set 3 and set 5. There were no significant effects on simple or choice reaktion time, although effect sizes suggested improved post-exercise times after caffeine. It was concluded that caffeine ingestion 60 min prior to exercise can enhance repeated sprint running performance and is not detrimental to reaction times [088].

Using a randomized double-blind research design, 21 physically active men ingested a gelatin capsule containing either caffeine (5 mg per kg body mass) or placebo (maltodextrin) 1 h before completing an indoor multiple sprint running trial (12 x 30 m; repeated at 35 second intervals). Venous blood samples were drawn to evaluate plasma caffeine and primary metabolite concentrations. Sprint times were recorded via twin-beam photocells, and earlobe blood samples were drawn to evaluate pretest and posttest lactate concentrations. Relative to placebo, caffeine supplementation resulted in a 0.06 second (1.4 %) reduction in fastest sprint time (95 % confidence interval 0.04 to 0.09 s), which corresponded with a 1.2 percent increase in fatigue (95 % confidence interval 0.3 to 2.2%). Caffeine supplementation also resulted in a 3.4 beat per minute increase in mean heart rate (95 % confidence interval 0.1 to 6.6) and elevations in pretest (+0.7 mmol per L; 95 % confidence interval 0.1 to1.3) and posttest (+1.8 mmol per L; 95 % confidence interval 0.3 to 3.2) blood lactate concentrations. It was concluded that although the effect of recovery duration on caffeine-induced responses to multiple sprint work requires further investigation, the results of the study showed that caffeine has ergogenic properties with the potential to benefit performance in both single and multiple sprint sports [089].
Caffeine can be a powerful ergogenic aid for the performance of prolonged, submaximal exercise. Little evidence, however, supports an ergogenic effect of caffeine on intermittent-sprint performance. Hence, one study was conducted to examine the effects of acute caffeine ingestion on prolonged intermittent-sprint performance. Using a double-blind, placebo-controlled design, 10 male team-sport athletes (amateur level) completed two exercise trials, separated by 7 d, 60 min after ingestion of either 6 mg/kg caffeine or placebo. The exercise trial was performed on a front-access cycle ergometer and consisted of 2 x 36-min halves, each composed of 18 x 4-s sprints with 2-min active recovery at 35 percent \( \text{VO}_{2\text{peak}} \) between each sprint. Urinary caffeine levels were measured after exercise. The total amount of sprint work performed during the caffeine trial was 8.5 percent greater than that performed during the placebo trial in the first half, and was 7.6 percent greater in the second half. Similarly, the mean peak power score achieved during sprints in the caffeine trial was 7.0 percent greater than that achieved during the placebo trial in the first half, and was 6.6 percent greater in the second half. Urinary caffeine levels following the caffeine trial ranged from 3.5 to 9.1 microg/mL. The study revealed that acute caffeine ingestion can significantly enhance performance of prolonged, intermittent-sprint ability in competitive, male, team-sport athletes [090].

**Effect on caffeine on repeated anaerobe performance**

One study investigated the effects of caffeine on repeated, anaerobic exercise using a double-blind, randomized, crossover design. Seventeen subjects (five female) underwent cognitive (reaction time, number recall) and blood (glucose, potassium, catecholamines, lactate) testing before and after consuming caffeine (6 mg/kg), placebo, or nothing (control). An exercise test (two 60 s maximal cycling bouts) was conducted 90 min after caffeine/placebo consumption. Plasma caffeine concentrations significantly increased after caffeine ingestion. However, there were no positive effects on cognitive or blood parameters except a significant decrease in plasma potassium concentrations at rest. Potentially negative effects of caffeine included significantly higher blood lactate compared to control and significantly slower time to peak power in exercise bout 2 compared to control and placebo. Caffeine had no significant effect on peak power, work output, RPE, or peak heart rate. In conclusion, caffeine had no ergogenic effect on repeated, maximal cycling bouts and may be detrimental to anaerobic performance [091].

**Dose effects of caffeine on acute hormonal responses to resistance exercise**

The purpose of one study was to examine the dose effects of caffeine on acute hormonal responses to resistance exercise (RE). Twelve university males who regularly performed RE participated in this study. Subjects performed one repetition maximum (1RM) test and four treatments in a counterbalanced order: high dose (HD, 6 mg/kg), medium dose (MD, 4 mg/kg), low dose (LD, 2 mg/kg), and placebo (PLA). Subjects ingested caffeine 1 hour before RE and then performed RE (2 exercises, 3 sets of 10 repetitions at 75 % of 1RM). Blood samples were collected before caffeine intake (pre-60), immediately before RE (pre-exe), and 0, 15, 30 min post RE (P0, P15, and P30, respectively) for analysis of serum testosterone, cortisol, insulin, glucose, lactate, and free fatty acid (FFA). Each experiment was separated by 7 days. Statistical analysis of two-way analysis of variance with repeated measures was applied. The concentrations of FFA (pre-exe) were significantly elevated following the HD, MD, and LD ingestions of caffeine. The concentrations of testosterone (P0, P15, and P30) and cortisol (pre-exe, P0, P15, and P30) at HD were significantly increased. However, the responses of insulin (P0 and P15) at HD and MD were significantly decreased. The results of this study indicate that high doses of caffeine increase the responses of testosterone and cortisol. Moreover, moderate and high doses of caffeine attenuate the insulin responses [092].
A meta-analysis

The primary aim of one review was to critically examine studies that have tested caffeine's ability to augment performance during exercise dependent on nonoxidative metabolism such as sprinting, team sports, and resistance training. A review of the literature revealed 29 studies that measured alterations in short-term performance after caffeine ingestion. Each study was critically analyzed using the Physiotherapy Evidence Database (PEDro) scale. The mean PEDro score was 7.76 ± 0.87. Eleven of 17 studies revealed significant improvements in team sports exercise and power-based sports with caffeine ingestion, yet these effects were more common in elite athletes who do not regularly ingest caffeine. Six of 11 studies revealed significant benefits of caffeine for resistance training. Some studies show decreased performance with caffeine ingestion when repeated bouts are completed. The exact mechanism explaining the ergogenic effect of caffeine for short-term exercise is unknown [093].

Effect of caffeine on endurance

Although there are a vast number of studies quantifying caffeine's effects, many research studies measure endurance performance using a time-to-exhaustion test (subjects exercise at a fixed intensity to volitional exhaustion). Time-to-exhaustion as a performance measure is not ideal because of the high degree of measurement variability between and within subjects. Also, one must state that in modern endurance sports there is none in which individuals win by going a longer distance or for a longer amount of time than their competitors. Measuring performance with a time-trial test (set distance or time with best effort) has high reproducibility and is more applicable to sport. Therefore, the purpose of one review was to critically and objectively evaluate studies that have examined the effect of caffeine on time-trial endurance (>5 minutes) performance. A literature search revealed 21 studies with a total of 33 identifiable caffeine treatments that measured endurance performance with a time-trial component. The mean improvement in performance with caffeine ingestion was 3.2 ± 4.3 percent; however, this improvement was highly variable between studies. The high degree of variability may be dependent on a number of factors including ingestion timing, ingestion mode/vehicle, and subject habituation. Further research should seek to identify individual factors that mediate the large range of improvements observed with caffeine ingestion. The authors concluded that caffeine ingestion can be an effective ergogenic aid for endurance athletes when taken before and/or during exercise in moderate quantities (3-6 mg/kg body mass). Abstaining from caffeine at least 7 days before use will give the greatest chance of optimizing the ergogenic effect [094].

Most of the studies looking at caffeine in improving exercise or athletic performance of focused on endurance, submaximal exercise activities such as running and cycling. In these situations, caffeine has generally been shown to improve or sustain exercise performance, typically through an increase in the duration of the exercise or a decreased perception of exertion. In cycling, caffeine has been shown to increase time to exhaustion at 85 percent VO2max and decrease times to finish a fixed period of activity. Increased times to exhaustion have been seen in running as well as decreased times to run set distances. Other benefits on exercise that have been discovered are improved tennis performance and decreased 1500-meter swim times [012].

Effect of caffeine intake on endurance performance and metabolism

Many studies have reported an enhancement of prolonged, submaximal exercise after caffeine ingestion. The mechanism(s) proposed to explain these benefits includes an
increased utilization of plasma free fatty acids (FFA) and/or intramuscular triacylglycerol, which acts to reduce the rate of muscle glycogenolysis, as well as favorable changes in central nervous system (CNS) cues and/or neuromuscular function. In the majority of these studies the “performance” protocol used was a test of exercise “capacity” (i.e. the time to exhaustion at a fixed submaximal power output). Furthermore, in some of these studies, subjects exercised after an overnight fast and usually with the intake of water (or no fluid) during the exercise task. Such conditions fail to simulate the nature of a sporting event and to represent the ideal nutritional preparation for endurance exercise. One study that simulated the conditions of real-life athletic competition reported enhancement of performance of a 1-h cycling time trial (TT) when caffeine was ingested in conjunction with a carbohydrate (CHO)-electrolyte drink. In that study, caffeine was ingested before and during the TT, in contrast to the typical research protocols in which a single dose of caffeine is ingested 60 min before an exercise task. Caffeine intake during sporting events has become more popular and practical since the advent of specialized foods such as sports gels that contain both CHO and caffeine. We have also observed a widespread practice in endurance sports in which competitors drink defizzed Coca-Cola during the latter stages of an event, in replacement of their earlier use of a CHO-electrolyte drink. Testimonials from athletes indicate that they believe that the intake of Coca-Cola late in the event provides an ergogenic benefit due to the intake of caffeine, despite the caffeine concentration in cola drinks (65 mg per typical 500-ml serving) being substantially less than the caffeine doses associated with ergogenic benefits in laboratory research protocols (4-9 mg/kg body mass (BM); 280–630 mg). Competitive athletes completed two studies of 2-h steady-state (SS) cycling at 70 percent peak \( \text{O}_2 \) uptake followed by 7 kJ/kg time trial (TT) with carbohydrate (CHO) intake before (2 g/kg) and during (6 % CHO drink) exercise. In Study A, 12 subjects received either 6 mg/kg caffeine 1 h preexercise (Precaf), 6 x 1 mg/kg caffeine every 20 min throughout SS (Durcaf), 2 x 5 ml/kg Coca-Cola between 100 and 120 min SS and during TT (Coke), or placebo. Improvements in TT were as follows: Precaf, 3.4 percent, Durcaf, 3.1 percent and Coke, 3.1 percent. In Study B, eight subjects received 3 x 5 ml/kg of different cola drinks during the last 40 min of SS and TT: decaffeinated, 6 percent CHO (control); caffeinated, 6 percent CHO; decaffeinated, 11 percent CHO; and caffeinated, 11 percent CHO (Coke). Coke enhanced TT by 3.3 percent, with all trials showing 2.2 percent TT enhancement due to caffeine. Overall, 1) 6 mg/kg caffeine enhanced TT performance independent of timing of intake and 2) replacing sports drink with Coca-Cola during the latter stages of exercise was equally effective in enhancing endurance performance, primarily due to low intake of caffeine (approximately 1.5 mg/kg) [095].

Effects of caffeine on short-endurance performance after limitation of sleep

One study aimed to determine whether caffeine ingestion would increase the workload voluntarily chosen by athletes in a limited-sleep state. In a double-blind, crossover study, 16 professional rugby players ingested either a placebo or 4 mg/kg caffeine 1 hr before exercise. Athletes classified themselves into nondeprived (8 hr+) or sleep-deprived states (6 hr or less). Exercise comprised 4 sets of bench press, squats, and bent rows at 85 percent 1-repetition maximum. Athletes were asked to perform as many repetitions on each set as possible without failure. Saliva was collected before administration of placebo or caffeine and again before and immediately after exercise and assayed for testosterone and cortisol. Sleep deprivation produced a very large decrease in total load. Caffeine ingestion in the nondeprived state resulted in a moderate increase in total load, with a larger effect in the sleep-deprived state, resulting in total load similar to those observed in the nondeprived placebo condition. Eight of the 16 athletes were identified as caffeine responders. Baseline testosterone was higher and cortisol trended lower in non-sleep-deprived athletes. Changes in hormones from predose to preexercise correlated to individual workload responses to caffeine. Testosterone response to exercise increased with caffeine compared with placebo, as did cortisol response. It was concluded that caffeine increased voluntary workload in professional athletes, even more so under conditions of self-reported limited sleep. Caffeine
may prove worthwhile when athletes are tired, especially in those identified as responders [096].

**Pre-exercise caffeinated-coffee ingestion on endurance performance**

Endurance athletes commonly ingest caffeine as a means to enhance training intensity and competitive performance. A widely-used source of caffeine is coffee, however conflicting evidence exists regarding the efficacy of coffee in improving endurance performance. In this context, the aims of one evidence-based review were three-fold: 1) to evaluate the effects of pre-exercise coffee on endurance performance, 2) to evaluate the effects of coffee on perceived exertion during endurance performance, and 3) to translate the research into usable information for athletes to make an informed decision regarding the intake of caffeine via coffee as a potential ergogenic aid. Searches of three major databases were performed using terms caffeine, and coffee, or coffee-caffeine, and endurance, or aerobic. Included studies (n=9) evaluated the effects of caffeinated coffee on human subjects, provided the caffeine dose administered, administered caffeine ≥45 minutes before testing, and included a measure of endurance performance (e.g. time trial). Significant improvements in endurance performance were observed in five of nine studies, which were on average 24.2 percent over controls for time to exhaustion trials, and 3.1 percent for time to completion trials. Three of six studies found that coffee reduced perceived exertion during performance measures significantly more than control conditions. Based on the reviewed studies there is moderate evidence supporting the use of coffee as an ergogenic aid to improve performance in endurance cycling and running. Coffee providing 3-8.1 mg/kg (1.36-3.68 mg/lb) of caffeine may be used as a safe alternative to anhydrous caffeine to improve endurance performance [097].

**Repeated caffeine ingestion on repeated exhaustive exercise endurance**

The purpose of one study was to examine the effect of repeated doses of caffeine on repeated exercise endurance. Nine male caffeine users performed exercise rides (ER) to exhaustion at 80 percent VO$_{2\text{max}}$ after ingesting a placebo, 5 mg/kg of caffeine, or 2.5 mg/kg of caffeine 1 h before the ER. Two ER were performed weekly on the same day once in the morning (AM) and 5 h later in the afternoon (PM). There were four treatments containing either caffeine or placebo, i.e., trial A representing 5 mg/kg caffeine in the AM and 2.5 mg/kg caffeine in the PM; trial B, which was placebo in both AM and PM; trial C representing 5 mg/kg caffeine in the AM and placebo in the PM; and trial D representing a placebo in the AM and 5 mg/kg caffeine in the PM. The order of the treatment trials was double blind and randomized. Caffeine ingestion significantly increased exercise time to exhaustion in the AM. This effect was maintained in the PM and greater than placebo regardless of whether redosing or placebo followed the initial morning dose. Caffeine dosing in the PM also increased ER after placebo trial D in the AM. It was concluded that redosing with caffeine after exhaustive exercise in the AM was not necessary to maintain the ergogenic effect of the drug during subsequent exercise 6 h later [098].

**Maximally caffeine stimulated muscle decreased endurance**

The use of caffeine as an ergogenic aid to promote endurance has been widely studied, with human literature showing the greatest benefit during submaximal muscle activities. Recent evidence suggests that the acute treatment of skeletal muscle with physiological concentrations of caffeine (70 microM maximum) will directly potentiate force production. The aims of the present study were: firstly, to assess the effects of a physiological concentration (70 microM) of caffeine on endurance in maximally activated mouse soleus (relatively slow) muscle; and secondly, to examine whether endurance changes when muscle is activated submaximally during caffeine treatment. Maximally stimulated soleus muscle treated with 70
microM caffeine resulted in a significant (18 %) decrease in endurance. In contrast, at a submaximal stimulation frequency, caffeine treatment significantly prolonged endurance (by 19 %). Findings are activation-dependent such that, during high frequency stimulation, caffeine accelerates fatigue, whereas, during low frequency stimulation, caffeine delays fatigue [099].

**Effect of caffeine in hot and humid conditions during endurance exercise**

Athletes in many southern countries need to perform in a hot and humid climate. Chronic supplementation of caffeine on endurance performance have been studied extensively in different populations. However, concurrent research on the effects of acute supplementation of caffeine on cardiorespiratory responses during endurance. Nine heat adapted recreational Malaysian male runners who were nonusers of caffeine (24 + 13 mg per day) were recruited in a placebo-controlled double-blind randomized study. Caffeine (5 mg per kg of body weight) or placebo was ingested in the form of a capsule one hour prior to the running exercise trial at 70 per cent of VO$_{2\text{max}}$ on a motorised treadmill in a heat-controlled laboratory (31 degrees C, 70 % relative humidity). Subjects drank 3 ml of cool water per kg of body weight every 20 min during the running trials to avoid the adverse effects of dehydration. Heart rate, core body temperature and rate of perceived exertion (RPE) were recorded at intervals of 10 min, while oxygen consumption was measured at intervals of 20 min. Running time to exhaustion was significantly higher in the caffeine trial compared to the placebo trial. Heart rate, core body temperature, oxygen uptake and RPE did not show any significant variation between the trials but it increased significantly during exercise from their respective resting values in both trials. The study showed that ingestion of 5 mg of caffeine per kg of body weight improved the endurance running performance but did not impose any significant effect on other individual cardiorespiratory parameters of heat-acclimated recreational runners in hot and humid conditions [100].

It has been demonstrated that caffeine supplementation improved exercise endurance by about 20 percent and significantly reduced the perception of exertion whilst cycling at 18 and 35°C, compared to a placebo. Since no effects were observed on indicators of peripheral metabolic stress, it was concluded that the action was central and, furthermore, since there was no effect on the release of prolactin, it was concluded that caffeine may be acting on central pathways other than those in the hypothalamus which are sensitive to temperature. There is a wealth of literature describing the effects of caffeine on exercise performance [101].

One double-blind experiment examined the effects of a caffeinated sports drink during prolonged cycling in a warm environment. Sixteen highly trained cyclists completed 3 trials: placebo, carbohydrate-electrolyte sports drink (CES), and caffeinated sports drink (CES+CAF). Subjects cycled for 135 min, alternating between 60 percent and 75 percent VO$_{2\text{max}}$ every 15 min for the first 120 min, followed by a 15-min performance ride. Maximal voluntary (MVC) and electrically evoked contractile properties of the knee extensors were measured before and after cycling. Work completed during the performance ride was 15-23 percent greater for CES+CAF than for the other beverages. Ratings of perceived exertion were lower with CES+CAF than with placebo and CES. After cycling, the MVC strength loss was two-thirds less for CES+CAF than for the other beverages (5 % vs 15 %). Data from the interpolated-twitch technique indicated that attenuated strength loss with CES+CAF was explained by reduced intrinsic muscle fatigue [102].

**Impact on diuresis**

Caffeine is regarded as a diuretic despite evidence that hydration is not impaired with habitual ingestion. The purpose of one study was to determine whether a caffeinated sports drink impairs fluid delivery and hydration during exercise in warm, humid conditions (29 degrees C, 60 % relative humidity). Sixteen cyclists completed 3 trials: placebo (P),
carbohydrate-electrolyte (CE), and caffeinated (195 mg/L) sports drink (CAF+CE). Subjects cycled for 120 min at 60-75 percent VO2max followed by 15 min of maximal-effort cycling. Heart rate and rectal temperature were similar until the final 15 min, when these responses and exercise intensity were higher with CAF+CE than with CE and P. Sweat rate, urine output, plasma-volume losses, serum electrolytes, and blood deuterium-oxide accumulation were not different. Serum osmolality was higher with CAF+CE vs. P but not CE. The authors conclude that CAF+CE appears as rapidly in blood as CE and maintains hydration and sustains cardiovascular and thermoregulatory function as well as CE during exercise in a warm, humid environment [103].

To investigate the effects of caffeine ingestion on thermoregulation and fluid-electrolyte losses during prolonged exercise in the heat seven endurance-trained (VO2max 61 + 8 mL/kg.min) heat-acclimated cyclists pedaled for 120 min at 63 percent VO2max in a hot-dry environment (36 degrees C; 29 % humidity) on six occasions: 1) without rehydration (NF); 2) rehydrating 97% of sweat losses with water (WAT); 3) rehydrating the same volume with a 6% carbohydrate-electrolytes solution (CES); or combining these treatments with the ingestion of 6 mg caffeine/kg body weight 45 min before exercise, that is, 4) CAFF + NF; 5) CAFF + WAT; and 6) CAFF + CES. Without fluid replacement (NF and CAFF + NF), final rectal temperature reached 39.4 + 0.1 degrees C, whereas it remained at 38.7 + 0.1 degrees C during WAT (CES and CAFF + WAT. Caffeine did not alter heat production, forearm skin blood flow, or sweat rate. However, CAFF + carbohydrate-electrolytes solution tended to elevate rectal temperature above CES alone (38.9 + 0.1 degrees C vs 38.6 + 0.1 degrees C). Caffeine ingestion increased sweat losses of sodium, chloride, and potassium (approximately 14 %) and enlarged significantly urine flow (28 %). The authors concluded that caffeine ingested alone or in combination with water or a sports drink was not thermogenic or impaired heat dissipation. Caffeine increased urine flow and sweat electrolyte excretion, but these effects are not enough to affect dehydration or blood electrolyte levels when exercising for 120 min in a hot environment [104].

No effect of caffeine on endurance after nonselective beta-adrenergic blockade

One study was designed to test the hypothesis that combined administration of propranolol and caffeine (Pr+C) would increase endurance performance compared with the administration of propranolol alone (Pr) if caffeine would be able to increase plasma free fatty acid (FFA) availability and/or lower plasma potassium concentration compared with propranolol administration alone. Fifteen volunteers participated in the double-blind placebo-controlled randomized cross-over study. An endurance exercise test until exhaustion was performed after ingestion of placebo (Pl), 80-mg propranolol (Pr), and 80-mg propranolol plus 5 mg/kg caffeine (Pr+C). Endurance time (± SD) was 79.3 ± 20.4 min in the Pl trial, 22.6 ± 10.8 min in the Pr trial and 31.2 ± 17.2 min in the Pr+C trial. The difference between the Pr and Pr+C trials just failed to reach statistical significance. Plasma FFA concentration and plasma potassium concentrations were similar in the Pr and Pr+C trials, but differed significantly from the Pl trial. Thus, although there was a clear tendency for an improved performance in the Pr+C trial compared to the Pr trial, this improvement was not associated with increased plasma FFA concentration and/or reduced plasma potassium concentration in the Pr+C compared to the Pr trial. These results do not support the hypothesis that caffeine improves endurance performance by stimulating lipolysis or lowering plasma potassium concentration [105].

Effects of caffeine on strength

To determine the oral dose of caffeine needed to increase muscle force and power output during all-out single multi-joint movements 13 resistance-trained men, underwent a battery of
muscle strength and power tests in a randomized, double-blind, cross-over design, under four different conditions: placebo ingestion or caffeine ingestion at three different doses (3, 6, and 9 mg/kg bodyweight. The muscle strength and power tests consisted in the measurement of bar displacement velocity and muscle power output during free-weight full-squat and bench press exercises against 4 incremental loads (25 %, 50 %, 75 % and 90 % 1RM). Caffeine side-effects were evaluated at the end of each trial and 24 h later. Mean propulsive velocity at light loads (25 %–50 % 1RM) increased significantly above placebo for all caffeine doses (5.4–8.5 %). Caffeine in the dose 9 mg/kg bw was needed to enhance bench press velocity and full squat power at the heaviest load (90 % 1RM) and cycling peak power output (6.8–11.7 %). However, the 9 mg dosage drastically increased the frequency of the adverse side-effects (15–62 %). It was concluded that the ergogenic dose of caffeine required to enhance neuromuscular performance during a single all-out contraction depends on the magnitude of load used. A dose of 3 mg/kg is enough to improve high velocity muscle actions against low loads, whereas a higher caffeine dose (9 mg/kg) is necessary against high loads, despite the appearance of adverse side-effects [080].

The purpose of one study was to examine the effects of caffeine on strength and muscle activation of the elbow flexors. Thirteen recreationally active male volunteers came to the laboratory four times. Visit one served as a familiarization visit. During visits two through four, subjects ingested a randomly assigned drink, with or without caffeine (0, 5, or 10 mg/kg of body mass), and performed three maximal isometric muscle actions of the elbow flexors sixty minutes after ingestion. Maximal strength and rate of torque development (RTD) were recorded. Electromyographic (EMG) and mechanomyographic (MMG) amplitude and frequency, and electromechanical delay (EMD) and phonomechanical delay (PMD) were measured from the biceps brachii. The results indicated that the ingestion of 0 (placebo), 5 or 10 mg/kg of body mass of caffeine did not significantly influence peak torque, RTD, normalized EMG amplitude or frequency, normalized MMG amplitude, or EMD and PMD. Normalized MMG frequency was significantly lower following ingestion of five mg·kg of body mass of caffeine compared to the placebo trial. This was most likely an isolated finding as MMG frequency was the only variable to have a significant difference across all trials. The results suggested that ingestion of either five or ten mg·kg of body mass of caffeine does not provide an ergogenic effect for the elbow flexors during isometric muscle actions [106].

Isometric maximal force

Studies show caffeine affects isometric maximal force and offers introductory evidence for enhanced muscle endurance for lower body musculature. However, isokinetic peak torque, one-repetition maximum and muscular endurance for upper body musculature are less clear. Since relatively few studies exist with resistance training, a definite conclusion cannot be reached on the extent caffeine affects performance [036].

Isolated skeletal muscle experiments with caffeine

Caffeine is an increasingly popular nutritional supplement due to the legal, significant improvements in sporting performance that it has been documented to elicit, with minimal side effects. Therefore, the effects of caffeine on human performance continue to be a popular area of research as we strive to improve our understanding of this drug and make more precise recommendations for its use in sport. Although variations in exercise intensity seems to affect its ergogenic benefits, it is largely thought that caffeine can induce significant improvements in endurance, power and strength-based activities. There are a number of limitations to testing caffeine-induced effects on human performance that can be better controlled when investigating its effects on isolated muscles under in vitro conditions. The hydrophobic nature of caffeine results in a post-digestion distribution to all tissues of the body making it difficult to accurately quantify its key mechanism of action. This review considers
the contribution of evidence from isolated muscle studies to our understating of the direct effects of caffeine on muscle during human performance. The body of in vitro evidence presented suggests that caffeine can directly potentiate skeletal muscle force, work and power, which may be important contributors to the performance-enhancing effects seen in humans [107].

*Effects on torque and muscle activity during resistance exercise men*

It was examined the effect of caffeine ingestion on muscle torque production and muscle activity at different contraction speeds in trained men. Ten men (22 ± 1 years) volunteered to participate. A double-blind, randomized cross-over design was used. Sixty minutes post ingestion of caffeine (6 mg/kg) or placebo, participants completed 6 repetitions of isokinetic knee extension at 3 angular velocities (30°/s, 150°/s, and 300°/s) from which peak torque was determined. Electromyographic activity of the vastus medialis was also collected. Repeated measures ANOVA indicated that muscle torque production was significantly higher with caffeine compared to placebo. A significant substance by velocity interaction for muscle activity indicated significantly higher vastus medialis muscle activity in the presence of caffeine vs. placebo, and this difference was amplified as angular velocity increased. It was concluded that acute caffeine ingestion improves muscle performance and increases muscle activity during short-duration maximal dynamic contractions [108].

*Caffeine potentiates low frequency skeletal muscle force*

Caffeine is a methylxanthine derivative that has been used for centuries due to its putative ergogenic (work enhancement) effects. Carefully controlled studies have demonstrated an ergogenic effect of caffeine in endurance exercise performance. One of the mechanisms of action that may explain this ergogenic effect is an increase in free fatty acid (FFA) oxidation and a subsequent sparing of muscle glycogen. Caffeine likely exerts these effects through competitive antagonism of adenosine receptors at physiological concentrations. However, there have been several studies that have raised doubts that an ergogenic effect of caffeine was due to the aforementioned metabolic effects. For example, one study found that a low dose of caffeine (3 mg/kg body wt) improved exercise capacity yet did not alter catecholamine or FFA/glycerol concentration in young men. A study in tetraplegic patients found that caffeine ingestion improved exercise performance but did not affect the respiratory exchange ratio (RER) and had minimal effects on catecholamines. Another study found that caffeine ingestion improved exercise capacity yet did not alter RER in young, habitual caffeine consumers in spite of a 2- and 4-day caffeine withdrawal. Together, these data cast doubts on the theory that the ergogenic effects of caffeine are mediated solely by enhanced FFA oxidation and raise speculation that the ergogenic effect of caffeine is mediated at the level of the skeletal muscle [044].

There is substantive evidence that caffeine may also facilitate neuromuscular function at the level of the sarcoplasmic reticulum (SR). In supraphysiological concentrations, caffeine potentiated the release of calcium from the SR and may have induced contracture in vitro. The potentiation of muscle contractile force has also been demonstrated at concentrations that are attainable with ergogenic doses of caffeine in humans. Studies performed in vitro have demonstrated that caffeine directly potentiated calcium release from the ryanodine receptor and that this was not occurring via adenosine antagonism [044].

Studies in humans have demonstrated a potentiation of submaximal skeletal muscle contraction force with caffeine doses ranging from 4 to 7 mg/kg body wt. However, our laboratory has reported that caffeine (6 mg/kg body wt) did not potentiate electrically elicited twitch torque or maximal voluntary contractile force in six habitual caffeine-consuming men. Confounding the latter study was the fact that maximal voluntary contraction strength (MVC)
and twitch measurements are not likely to be sensitive or specific enough to detect a potentiation of calcium release during fatigue. It would also be predicted that the greatest effect of caffeine on skeletal muscle would occur during low frequency electrical stimulation in which the locus of fatigue is thought to be at the level of calcium release from the SR and not at maximal intensities in which the locus of fatigue is proximal and analogous to high stimulation frequencies. The lack of an effect of caffeine on MVC torque or at high stimulation frequencies is consistent with the practical observation that caffeine does not appear to enhance high-intensity exercise performance [044].

**Effects on resistance training**

One study examined the placebo effect of caffeine on number of repetitions, rating of perceived exertion (RPE), blood pressure (BP), and peak heart rate (PHR) during resistance-training exercise with repetitions performed to volitional failure. Following determination of 1-rep maximum in single-leg leg extension, 15 males performed reps to failure at 60 percent 1-RM in 3 conditions: control, perceived caffeine condition, and perceived placebo condition presented in a randomized order. Participants were informed they would ingest 250 mL of solution that contained either 3 mg/kg body weight caffeine or 3 mg/kg body weight placebo 1 h before each exercise trial. A deceptive protocol was employed and subjects consumed a placebo solution in both conditions. During each condition, total reps, RPE for the active muscle and overall body, and PHR were recorded. Subjects completed 2 more repetitions when they perceived they had ingested caffeine. RPE was significantly lower in the perceived caffeine and control conditions and RPE for the active muscle was significantly higher across all conditions compared with RPE for the overall body. No substantial differences were evident in PHR across conditions. Results of this study are similar to studies of actual caffeine ingestion. However, the perception of consuming a substance that purportedly enhances performance is sufficient enough to enable individuals to complete a greater number of reps to failure during short-term resistance exercise [109].

The purpose of one study was to evaluate the effects of caffeine ingestion before a resistance exercise session on markers of muscle damage (CK, LDH, ALT, AST) and leukocyte levels. Fifteen soccer athletes completed two resistance exercise sessions that differed only in the ingestion of caffeine or a placebo pre-workout. CK concentration increased significantly following the caffeine session and the placebo session, with no significant differences between sessions. Similarly, LDH concentration increased significantly following the caffeine session and the placebo session, with no significant differences between sessions. Both sessions resulted in significant increases in the total leukocyte count, neutrophils, lymphocytes, and monocytes, with no significant differences between sessions. It was concluded that ingestion of caffeine at 4.5 mg/kg did not augment markers of muscle damage or leukocyte levels above that which occurs through resistance exercise alone [110].

The primary aim of yet another study was to determine the efficacy of acute caffeine intake to enhance intense resistance training performance. Fourteen resistance-trained men (age and body mass = 23 ± 1 years and 83 ± 13 kg, respectively) who regularly consumed caffeine ingested caffeine (6 mg·kg) or placebo 1 hour before completion of 4 sets of barbell bench press, leg press, bilateral row, and barbell shoulder press to fatigue at 70-80 percent 1-repetition maximum. Two minutes of rest was allotted between sets. Saliva samples were obtained to assess caffeine concentration. The number of repetitions completed per set and total weight lifted was recorded as indices of performance. Compared to placebo, there was a small but significant effect of acute caffeine intake on repetitions completed for the leg press but not for upper-body exercise. Total weight lifted across sets was similar with caffeine vs placebo yet there were 9 “responders” to caffeine, represented by a meaningful increase in total weight lifted with caffeine versus placebo. Any ergogenic effect of caffeine on performance of fatiguing, total-body resistance training appears to be of limited practical
Significance. Additional research is merited to elucidate interindivudual differences in caffeine-mediated improvements [111].

**Strength and endurance**

Multiple studies corroborate the ergogenic properties of caffeine (CAF) for endurance performance, yet fewer investigations document the efficacy of acute caffeine intake for intense, short-term exercise. The aim of one study was to determine the ergogenic potential of caffeine during testing of muscular strength and endurance. Twenty-two resistance-trained men ingested CAF (6 mg/kg) or placebo (PL) 1 h pre-exercise in a randomized, double-blind crossover design. They refrained from caffeine intake and strenuous exercise 48 and 24 h, respectively, pre-visit. Initially, resting heart rate and blood pressure were obtained followed by one-repetition maximum (1-RM) testing on the barbell bench press and leg press. Upon determination of 1-RM, participants completed repetitions to failure at 60 percent 1-RM. Heart rate, blood pressure, and rating of perceived exertion (RPE) were measured after the final repetition. Compared to PL, there was no effect of caffeine on muscular strength, as 1-RM bench press and leg press were similar. Total weight lifted during the 60 percent 1-RM trial was 11 and 12 percent higher for the bench press and leg press with caffeine compared to placebo, yet did not reach significance. RPE was similar at the end of resistance exercise with CAF versus placebo. Acute caffeine intake does not significantly alter muscular strength or endurance during intense bench press or leg press exercise, yet the practical importance of the increased muscular endurance remains to be explored [112].

**Effects of multi-task performance**

The purpose of one study was to examine the acute effects of a caffeine-containing supplement on upper- and lower-body strength and muscular endurance as well as anaerobic capabilities. Thirty-seven resistance-trained men (mean age: 21 years) volunteered to participate in this study. On the first laboratory visit, the subjects performed 2 Wingate Anaerobic Tests (WAnTs) to determine peak power (PP) and mean power (MP), as well as tests for 1 repetition maximum (1RM), dynamic constant external resistance strength, and muscular endurance (TOTV; total volume of weight lifted during an endurance test with 80 % of the 1RM) on the bilateral leg extension (LE) and free-weight bench press (BP) exercises. Following a minimum of 48 hours of rest, the subjects returned to the laboratory for the second testing session and were randomly assigned to 1 of 2 groups: a supplement group (SUPP; n=17), which ingested a caffeine-containing supplement, or a placebo group (PLAC; n=20), which ingested a cellulose placebo. One hour after ingesting either the caffeine-containing supplement or the placebo, the subjects performed 2 WAnTs and were tested for 1RM strength and muscular endurance on the LE and BP exercises. The results indicated that there was a significant increase in BP 1RM for the SUPP group, but not for the PLAC group. The caffeine-containing supplement had no effect, however, on LE 1RM, LE TOTV, BP TOTV, PP, and MP. Thus, the caffeine-containing supplement may be an effective supplement for increasing upper-body strength and, therefore, could be useful for competitive and recreational athletes who perform resistance training [113].

**Neuromuscular and perceptual factors**

Caffeine improves endurance exercise performance, but its ergogenic mechanism(s) remain unclear. This investigation sought to examine the effects of caffeine on perceptual and physiological responses to endurance exercise. Two experiments were performed. In Study A, fourteen participants were tested. Maximal voluntary strength (MVC) and motor-unit recruitment (%ACT) of the knee extensors and elbow flexors were tested prior to, 60-min following ingestion of a 5 mg/kg dose of caffeine or placebo, and following completion of 40-minutes of exercise (30-min of submaximal leg or arm cycling followed by 10-min performance time-trial). Muscle pain, RPE, and cardiorespiratory variables were assessed throughout. To determine the effects of caffeine on muscle pain and RPE during high-
intensity exercise a second study (Study B) was performed. Twelve participants exercised at 95 percent of their gas-exchange threshold (GET) and at 70 percent of the difference between their GET and VO2 peak following caffeine and placebo ingestion. Compared to placebo caffeine improved MVC (6.3 %) and %ACT (5.5 %) in the knee extensors, but not the elbow flexors and reduced muscle pain and RPE during both submaximal cycling modalities. Caffeine ingestion improved time-trial performance during leg (4.9 ± 6.5 %), but not arm crank cycling (2.1 ± 8.2 %), but the effect on pain and RPE was eliminated. Caffeine ingestion had no effect on pain or RPE during cycling at 95 percent GET. The results suggest augmented strength and motor-unit recruitment, rather than reductions in pain and effort may underlie caffeine’s ergogenic effect on endurance exercise [107].

Effect on delayed-onset muscle soreness

One double-blind, placebo-controlled, repeated-measures experiment examined the effects of a 5 mg/kg body weight dose of caffeine on delayed-onset muscle pain intensity and force loss in response to 64 eccentric actions of the dominant quadriceps induced by electrical stimulation. Low caffeine-consuming college-aged females (n=9) ingested caffeine or placebo 24 and 48 hours following electrically stimulated eccentric exercise of the quadriceps. One hour after ingestion, maximal voluntary isometric contractions (MVIC) and submaximal voluntary eccentric actions were used to determine force loss during activation of damaged quadriceps and whether caffeine attenuates muscle pain intensity. Pain intensity was measured using a 0 to 100 visual analog scale. Caffeine produced a large (12.7 raw visual analog scale, VAS, units), statistically significant hypoalgesia during the MVIC. The reduction in pain scores during submaximal voluntary eccentric movements was smaller as was the increase in MVIC force. Thus, eccentric exercise occurs when skeletal muscles produce force while being lengthened. For example, the biceps brachii muscles act eccentrically when a cup of coffee is lowered from the mouth to a tabletop. This experiment found that caffeine (equal to approximately 2 cups of brewed coffee) could produce a large reduction in pain resulting from eccentric exercise-induced, delayed-onset muscle injury. This finding may improve the quality of life of individuals who experience skeletal muscle pain after engaging in unaccustomed, eccentrically biased exercise [114].

Effects of caffeine on skill performance

Popular use of caffeine is often at high concentrations (4-9 mg/kg) on the basis that these are more efficacious, but the proof of this is low with individual variability and consumption habits being the more dominant factors. While the ability of acute caffeine to address cognitive related sleep deficits is reasonably established, it is only recently that creatine has demonstrated similar properties. It has been suggested that sleep deprivation is associated with an acute reduction in high energy phosphates that in turn produces some degree of cognitive processing deficit. If sleep deprivation is associated with an energy deficit then errors in performance are perhaps more likely to occur when concentration demands are high and/or for prolonged periods of repeated task execution. Some evidence suggests that it is tasks of this nature that are most affected by acute sleep deprivation. Sleep deprivation is not uncommon around competition in sport particularly with the frequent demands of international travel. Assessing its effects on performance is however difficult, especially in team sports where multiple physical and skill components are involved. While overt physical components such as power don’t appear affected by acute deprivation a few studies do however suggest acute deprivation can affect certain sport skill and physical performance. Caffeine, for example, has been shown to improve both mood and mental function following sleep deprivation. The psychostimulant effects of caffeine appear to be related to the pre and post synaptic brakes that adenosine imposes on dopaminergic neurotransmission by acting on different adenosine receptor heteromers, although numerous mechanisms are likely to be
involved. It is not known how much mood and other cognitive function, particularly motivation on repeat skill tasks, interact. The absorption of caffeine in plasma following consumption has been estimated at between 30 and 90 min with half life of several hours. Effective doses of caffeine (and their dose response nature) remain contentious in literature possibly reflecting larger inter-subject variability in responses and different sensitivities of various physical and behavioural expressions. It was thus investigated the effects of sleep deprivation with or without acute supplementation of caffeine or creatine on the execution of a repeated rugby passing skill. Ten elite rugby players completed 10 trials on a simple rugby passing skill test (20 repeats per trial), following a period of familiarisation. The players had between 7-9 h sleep on 5 of these trials and between 3-5 h sleep (deprivation) on the other 5. At a time of 1.5 h before each trial, they undertook administration of either: placebo tablets, 50 or 100 mg/kg creatine, 1 or 5 mg/kg caffeine. Saliva was collected before each trial and assayed for salivary free cortisol and testosterone. Sleep deprivation with placebo application resulted in a significant fall in skill performance accuracy on both the dominant and non-dominant passing sides. No fall in skill performance was seen with caffeine doses of 1 or 5 mg/kg, and the two doses were not significantly different in effect. Similarly, no deficit was seen with creatine administration at 50 or 100 mg/kg and the performance effects were not significantly different. Salivary testosterone was not affected by sleep deprivation, but trended higher with the 100 mg/kg creatine dose, compared to the placebo treatment. Salivary cortisol was significantly elevated with the 5 mg/kg dose of caffeine versus placebo. Thus, acute sleep deprivation affects performance of a simple repeat skill in elite athletes and this was ameliorated by a single dose of either caffeine or creatine. At the doses and administration time of caffeine use in this study there was, however, no evidence of an effect in non-sleep deprived subjects. Acute creatine use may help to alleviate decrements in skill performance in situations of sleep deprivation, such as transmeridian travel, and caffeine at low doses appears as efficacious as higher doses, at alleviating sleep deprivation deficits in athletes with a history of low caffeine use. Both options are without the side effects of higher dose caffeine use [115].

**Effect on athletic agility**

Caffeine has been shown to improve sprint time, anaerobic power, and reaction time, all integral aspects of agility. The purpose of this study was to determine whether an acute caffeine dose would enhance agility and anaerobic power. Sixteen subjects participated in a randomized, double-blind experiment and performed the proagility run and the 30-second Wingate test 60 minutes after ingestion of caffeine (6 mg/kg) or placebo. No significant change was observed in the proagility run after caffeine ingestion compared with placebo. Also, no significant change was observed in peak power, mean power, or percent power decrease. Agility is an integral component of athletic skill and any reasonable method for enhancing agility would benefit active individuals. However, results from this study indicate that a 6 mg/kg dose of caffeine does not impact agility as measured by the proagility run test or power output as measured by the 30-second Wingate test in recreationally active young adult males who are not habituated to caffeine [116].

**Effects of performance after chronic use of caffeine**

The purpose of one study was to examine the effects of daily administration of a supplement that contained caffeine in conjunction with 8 weeks of aerobic training on VO$_{2\text{peak}}$, time to running exhaustion at 90 percent VO$_{2\text{peak}}$, body weight, and body composition. Thirty-six college students (14 men and 22 women, age 22 years) volunteered for this investigation and were randomized into either a placebo (n=18) or supplement group (n=18). The subjects ingested 1 dose (3 pills = 201 mg of caffeine) of the placebo or supplement per day during the study period. In addition, the subjects performed treadmill running for 45 minutes at 75
percent of the heart rate at VO\textsubscript{2peak}, three times per week for 8 weeks. All subjects were tested pretraining and posttraining for VO\textsubscript{2peak}, time to running exhaustion (TRE) at 90 percent VO\textsubscript{2peak}, body weight (BW), percentage body fat (%FAT), fat weight (FW), and fat-free weight (FFW). The results indicated that there were equivalent training-induced increases in VO\textsubscript{2peak} and TRE for the supplement and placebo groups, but no changes in BW, %FAT, FW, or FFW for either group. These findings indicated that chronic use of the caffeine-containing supplement in the present study, in conjunction with aerobic training, provided no ergogenic effects as measured by VO\textsubscript{2peak} and TRE, and the supplement was of no benefit for altering body weight or body composition [117].

Effects of caffeine after a withdrawal period

In one study, it was investigated the impact of a controlled 4-day caffeine withdrawal period on the effect of an acute caffeine dose on endurance exercise performance. Twelve well-trained and familiarized male cyclists, who were caffeine consumers (from coffee and a range of other sources), were recruited for the study. A double-blind placebo-controlled cross-over design was employed, involving four experimental trials. Participants abstained from dietary caffeine sources for 4 days before the trials and ingested capsules (one in the morning and one in the afternoon) containing either placebo or caffeine (1.5 mg/kg body weight/day). On day 5, capsules containing placebo or caffeine (3 mg/kg body weight) were ingested 90 min before completing a time trial, equivalent to one hour of cycling at 75 percent peak sustainable power output. Hence the study was designed to incorporate placebo-placebo, placebo-caffeine, caffeine-placebo, and caffeine-caffeine conditions. Performance time was significantly improved after acute caffeine ingestion by 1:49 ± 1:41 min (3.0 %) following a withdrawal period (placebo-placebo vs placebo-caffeine), and by 2:07 ± 1:28 min (3.6 %) following the non-withdrawal period (caffeine-placebo vs caffeine-caffeine). No significant difference was detected between the two acute caffeine trials (placebo-caffeine vs caffeine-caffeine). Average heart rate throughout exercise was significantly higher following acute caffeine administration compared with placebo. No differences were observed in ratings of perceived exertion between trials. A 3 mg/kg dose of caffeine thus significantly improves exercise performance irrespective of whether a 4-day withdrawal period is imposed on habitual caffeine users [118].

It has been traditional in caffeine research or in actual competition use to withdraw people from caffeine use for 24-48 h prior to the study or event (i.e. remove their habituation to repeated use). However, there does not seem to be a consistent difference in the performance effects of caffeine between regular users and non-users of caffeine, or as a result of withdrawal from regular caffeine use. Rather there may be several disadvantages to avoiding or withdrawing caffeine prior to a performance trial. Caffeine withdrawal can be associated with side effects such as headaches and fatigue. In fact, it has been suggested that the benefits of caffeine seen in controlled studies may be overstated, and may actually be explained as the reversal of adverse withdrawal symptoms rather than an ergogenic effect of caffeine per se. It can also increase the risk, with subsequent caffeine intake, of the negative effects often seen with large caffeine doses (irritability, tremor, heart rate increases) [002].
EFFECT OF CAFFEINE IN DIFFERENT SPORTS

Running

The aim of one study was to assess the effect of caffeine ingestion on 8 km run performance using an ecologically valid test protocol. A randomized double-blind crossover study was conducted involving eight male distance runners. The participants ran an 8 km race 1 h after ingesting a placebo capsule, a caffeine capsule (3 mg/kg body mass) or no supplement. Heart rate was recorded at 5 s intervals throughout the race. Blood lactate concentration and ratings of perceived exertion were recorded after exercise. A repeated-measures analysis of variance (ANOVA) identified a significant treatment effect for 8 km performance time; caffeine resulted in a mean improvement of 23.8 s in 8 km performance time (1.2 % improvement). In addition, a two-way (time x condition) repeated-measures ANOVA identified a significantly higher blood lactate concentration 3 min after exercise during the caffeine trial. It was concluded that ingestion of 3 mg/kg body mass of caffeine can improve absolute 8 km run performance in an ecologically valid race setting [100].

The purpose of one study was to investigate if caffeine ingestion improves 5-km time-trial performance in well-trained and recreational runners. Using a double-blind placebo-controlled design, 15 well-trained and 15 recreational runners completed two randomized 5-km time-trials, after ingestion of either 5 mg/kg of caffeine or a placebo. Caffeine ingestion significantly improved 5-km running performance in both the well-trained and recreational runners. In comparison to the placebo trial, the caffeine trial resulted in 1.1 percent (90 % confidence interval 0.4 to 1.6) and 1.0 percent (90 % confidence interval 0.2 to 2.0 %) faster times for the well-trained and recreational runners. Reliability testing of the recreational runners indicated a test-retest error of measurement of 1.4 percent. It was concluded that caffeine ingestion is likely to produce small but significant gains in 5-km running performance for both well-trained and recreational runners [119].

Caffeine and ephedrine on 10-km run performance

The ingestion of either caffeine (C) or ephedrine (E) has been shown to improve performance during high-intensity aerobic activity lasting 10-20 min, with an additive effect being found when the combination (C + E) was ingested. It was the purpose of this study to determine if the addition of E to C would improve performance in activity lasting longer than 20 min. One and one half hours after ingesting a placebo (P), C (4 mg/kg), E (0.8 mg/kg), or C + E, 12 subjects performed a 10-km run while wearing a helmet and backpack weighing 11 kg. The trials were performed in a climatic suite at 12-13 degrees C, on a treadmill where the speed was regulated by the subject. VO₂, VCO₂, Ve, heart rate (HR), and rating of perceived exertion (RPE) were measured during the run at 15 and 30 min, and again when the individual reached 9 km. Blood was sampled at 15 and 30 min and again at the end of the run and assayed for lactate, glucose, and catecholamines. Run times (mean ± SD), in minutes, were for C (46.0 ± 2.8), E (45.5 ± 2.9), C + E (45.7 ± 3.3), and P (46.8 ± 3.2). The run times for the E trials (E and C + E) were significantly reduced compared with the non-E trials (C and P). Pace was increased for the E trials compared with the non-E trials over the last 5 km of the run. VO₂ was not affected by drug ingestion. HR was elevated for the ephedrine trials (E and C + E). RPE remained similar for all trials. Caffeine increased the epinephrine and norepinephrine response associated with exercise and also increased blood lactate, glucose, and glycerol levels. Ephedrine reduced the epinephrine response but increased dopamine and FFA levels. It was concluded that the previously seen additive nature of E and C was not evident in this study, with the primary ergogenic effect being attributed to E [120].
Iron-man

One study assessed the knowledge, prevalence, and quantity of caffeine use by athletes competing at the 2005 Ironman Triathlon World Championships. Caffeine-related questionnaires were self-administered to 140 (105 male and 35 female, 40 + 11 years) athletes representing 16 countries. Fifty of these athletes further consented to immediate post-race blood samples for analysis of plasma caffeine and paraxanthine using high-performance liquid chromatography (HPLC). Seventy-two percent of 70 athletes correctly identified caffeine as being an unrestricted substance in triathlon. The majority of athletes (89%) were planning on using a caffeinated substance immediately prior to or throughout the race. Cola drinks (78%), caffeinated gels (42%), coffee (usually pre-race) (37%), energy drinks (13%), and NoDoz tablets (9%) were the most popular caffeinated choices. Mean + standard deviation post race plasma caffeine and paraxanthine levels were 22 + 20 micromol/L and 9 + 6 micromol/L, respectively. Seven athletes (14%) finished with plasma caffeine levels > 40 micromol/L. Plasma values from elite athletes did not differ from age group competitors. Despite the prevalence of its consumption and the training experience of this athletic group, over one quarter of athletes remained either confused or uninformed about caffeine's legality. Levels of plasma caffeine taken immediately post race indicated that athletes typically finish with quantities of caffeine that have been shown to improve endurance performance (i.e. approximately 20 micromol/L or a dose of + 3 mg/kg body weight) [121].

Biking

The primary aim of one study was to determine the repeatability of caffeine's ergogenic effects on cycling performance. It was hypothesized that improvements in performance would be similar when caffeine was ingested on 2 separate days. Nine endurance-trained men and women (mean age and maximal oxygen uptake, 27 years and 58 mL/kg/min) initially completed two familiarization trials. During 3 subsequent sessions separated by at least 48 hours, the subjects completed a 10-km cycling time trial preceded by ingestion of a drink containing caffeine (5 mg/kg) or placebo. Treatments were ingested using a randomized, single-blind, crossover design, and the subjects were deceived as to the specific content of all drinks. During exercise, heart rate, rating of perceived exertion, and time were recorded every 1.6 km. Repeated-measures analysis of variance was used to compare the differences in variables across distance and treatment. In both caffeine trials, caffeine increased, cycling performance by 1.6 and 1.9 percent versus placebo, and 7 of 9 subjects revealed improved performance. The mean performance improvement in the caffeine trials was similar across days. Heart rate during exercise was higher with caffeine versus placebo, although the rating of perceived exertion was similar. Data reveal that caffeine's ergogenic effects on cycling performance are repeatable across days, yet some individuals did not exhibit improved performance with caffeine [122].

To investigate whether coinciding peak serum caffeine concentration with the onset of exercise enhances subsequent endurance performance it was performed a randomized, placebo-controlled, double-blind crossover study, with 14 male trained cyclists and triathletes who consumed 6 mg/kg caffeine or a placebo either 1h (C(1h)) prior to completing a 40 km time trial or when the start of exercise coincided with individual peak serum caffeine concentrations (C(peak)). C(peak) was determined from a separate “caffeine profiling” session that involved monitoring caffeine concentrations in the blood every 30 min over a 4h period. Following caffeine ingestion, peak serum caffeine occurred 120 min in 12 participants and 150 min in 2 participants. Time to complete the 40 km time trial was significantly faster (2.0 %) in C(1h) compared to placebo. No statistically significant improvement in performance was noted in the C(peak) trial versus placebo (1.1 %). Whilst no differences in
metabolic markers were found between C(peak) and placebo conditions, plasma concentrations of glucose, norepinephrine and epinephrine were higher in the C(1h) trial 6 min post-exercise versus placebo. Thus, in contrast to coinciding peak serum caffeine concentration with exercise onset, caffeine consumed 60 min prior to exercise resulted in significant improvements in 40 km time trial performance. The ergogenic effect of caffeine was not found to be related to peak caffeine concentration in the blood at the onset of endurance exercise [123].

There were little published data in relation to the effects of caffeine upon cycling performance, speed and power in trained cyclists, especially during cycling of approximately 60 s duration. To address this, eight trained cyclists performed a 1 km time-trial on an electronically braked cycle ergometer under three conditions: after ingestion of 5 mg caffeine per kg bodyweight, after ingestion of a placebo, or a control condition. The three time-trials were performed in a randomized order and performance time, mean speed, mean power and peak power were determined. Caffeine ingestion resulted in improved performance time. This change represented a 3.1 percent improvement compared with the placebo condition. Mean speed was also significantly higher in the caffeine than placebo and control conditions. Mean power increased after caffeine ingestion. Peak power also increased from 864 + 107 W (placebo) and 830 + 87 W (control) to 940 + 83 W after caffeine ingestion. These results provide support for previous research that found improved performance after caffeine ingestion during short-duration high-intensity exercise. The magnitude of the improvements observed in our study could be due to our use of sport-specific ergometry, a tablet form and trained participants [124].

The purpose of one work was to determine the effects of caffeine on high intensity time trial cycling performance in well-trained subjects. Six male cyclists undertook three 1-h performances, control, placebo and caffeine, on a Velotron cycle ergometer conducted in a double-blind, random fashion. Subjects rested for 60 min and were then given caffeine or placebo in a dose of 6 mg/kg body mass and then commenced exercise after another 60 min of rest. Before ingestion, 60 min postingestion, and at the end of the test, finger-prick blood samples were analyzed for lactate. The cyclists rode significantly further in the caffeine trial (28.0 + 1.3 km) than they did in the control performance (26.3 + 1.5 km) or placebo (26.4 + 1.5 km trials). No differences were seen in heart rate data throughout the tests. Blood lactate levels were significantly higher at the end of the trials than either at rest or postingestion, but there were no differences between the three trial groups. The authors concluded that on the basis of the data, it was concluded that performance was improved with the use of a caffeine supplement [125].

The purpose of one experiment was to learn whether low doses of caffeine have ergogenic, perceptual, and metabolic effects during cycling. To determine the effects of 1, 2, and 3 mg/kg caffeine on cycling performance, differentiated ratings of perceived exertion (D-RPE), quadriceps pain intensity, and metabolic responses to cycling exercise, 13 cyclists exercised on a stationary ergometer for 15 min at 80 percent VO2 peak performance ride 60 min after ingesting caffeine or placebo. Work done (kJ/kg) during the performance ride was used as a measure of performance. D-RPE, pain ratings, and expired-gas data were obtained every 3 min, and blood lactate concentrations were obtained at 15 and 30 min. Compared with placebo, caffeine doses of 2 and 3 mg/kg increased performance by 4 percent (95% confidence interval 1.0-6.8 %) and 3 percent (95% confidence interval -0.4 % to 6.8 %), respectively. These effects were ergogenic, on average, but varied considerably in magnitude among individual cyclists. There were no effects of caffeine on D-RPE or pain throughout the cycling task. Selected metabolic variables were affected by caffeine, consistent with its known actions. The authors conclude that caffeine preparations of 2 and 3 mg/kg enhanced performance, but future work should aim to explain the considerable interindividual variability of the drug's ergogenic properties [126].
The purpose of another study was to determine if improved supramaximal exercise performance in trained cyclists following caffeine ingestion was associated with enhanced O\textsubscript{2} uptake (VO\textsubscript{2} kinetics), increased anaerobic energy provision (accumulated O\textsubscript{2}-AO\textsubscript{2}-deficit), or a reduction in the accumulation of metabolites (for example, K+) associated with muscular fatigue. Six highly trained male cyclists (VO\textsubscript{2peak} 68 ± 8 mL/kg/min) performed supramaximal (120 % VO\textsubscript{2peak}) exercise bouts to exhaustion on an electronically braked cycle ergometer, following double-blind and randomized ingestion of caffeine/placebo (5 mg/kg). Time to exhaustion (TE), VO\textsubscript{2} kinetics, AO\textsubscript{2} deficit, blood lactate, plasma potassium, caffeine and paraxanthine concentrations were measured. Caffeine ingestion elicited significant increases in TE and AO\textsubscript{2} deficit (7 %). In contrast, no changes were observed in AO\textsubscript{2} deficit at isotime, VO\textsubscript{2} kinetics, blood lactate at exhaustion or peak potassium following caffeine ingestion. However, potassium was significantly reduced (13 %) during warm-up cycling immediately prior to the onset of the supramaximal bout for the caffeine trials, compared with placebo. It appears that caffeine ingestion is beneficial to supramaximal cycling performance in highly trained men. The reduced plasma potassium during submaximal warm-up cycling may prolong the time taken to reach critical potassium at exhaustion, thus delaying fatigue. Considering caffeine ingestion did not change VO\textsubscript{2} kinetics or isotime AO\textsubscript{2} deficit, increases in absolute AO\textsubscript{2} deficit may be a consequence of prolonged TE, rather than causal [127].

Caffeine is thought to act as a central stimulant and to have effects on physical, cognitive, and psychomotor functioning. Twenty-four well-trained cyclists consumed the products (a performance bar containing 45 g of carbohydrate and 100 mg of caffeine, an isocaloric noncaffeine performance bar, or 300 mL of placebo beverage) immediately before performing a 2.5-h exercise at 60 percent VO\textsubscript{2max}, followed by a time to exhaustion trial at 75 percent VO\textsubscript{2max}. Additional products were taken after 55 and 115 min of exercise. Cognitive function measures were performed before exercise and while cycling after 70 and 140 min of exercise and again 5 min after completing the time to exhaustion ride. Participants were significantly faster after caffeine when compared with carbohydrate on both the computerized complex information processing tests, particularly after 140 min and after the time to exhaustion ride. On the beverage trial, performance was significantly slower than after both other treatments. There were no speed-accuracy tradeoffs. Time to exhaustion was significantly longer after caffeine consumption compared with both carbohydrates and beverage trials, and time to exhaustion was longer after carbohydrates than after beverages. No differences were found in the ratings of perceived exertion, mean heart rate, and relative exercise intensity (% VO\textsubscript{2max}). The authors concluded that caffeine in a performance bar can significantly improve endurance performance and complex cognitive ability during and after exercise. These effects may be salient for sports performance in which concentration plays a major role [128].

The purpose of one study was to investigate the effects of caffeine ingestion on the performance of an intermittent sprint cycling test (ISCT) with different rest intervals. Fourteen males with team sport experience consumed 6 mg/kg of caffeine or a placebo 60 min prior to completing two sets of an ISCT with 4-min rest intervals. Each set consisted of 12 × 4-s sprints with 20- or 90-s active recovery intervals at 60-70 rpm. Blood lactate was collected at baseline and immediately following the completion of six sprints in each set. At 20-s recovery intervals, peak power and total work were not significantly different between conditions during the ISCT; but caffeine reduced 6 percent effort for mean power in Sprint 10 of the later stage, as well as an increased fatigue index and elevated blood lactate levels during the ISCT. At 90-s recovery intervals, peak power, mean power, and total work under caffeine conditions were significantly higher than under placebo conditions during the ISCT, but no differences were apparent in fatigue index and blood lactate levels. In conclusion, caffeine ingestion may be ergolytic, affecting performance and fatigue development in the later stage during a prolonged and intermittent sprint test with a short recovery interval. However, caffeine produces an ergogenic effect in the initial stage of an intermittent sprint performance.
Caffeine has been reported to alter perceptions of exertion, muscle pain, and mood, yet the majority of existing data were obtained in resting volunteers or during steady-state exercise. The primary aim of one study was to examine the effects of caffeine on rating of perceived exertion (RPE) and perceptions of leg pain, arousal, and pleasure/displeasure during a simulated cycling time trial. Endurance-trained (n=8, VO$_{2\text{max}}$ 58 ± 4 mL/kg/min) and active (n=8) men initially completed two familiarization trials separated by at least 48 h. Over the next three trials, they completed a 10 km time trial preceded by ingestion of drinks containing caffeine (5 mg/kg ingested on 2 separate days) or placebo. Treatments were ingested using a single-blind, crossover design, and participants were deceived as to the content of all drinks. During exercise, RPE (6-20 scale), leg pain (0-10 scale), arousal (Felt Arousal Scale), and pleasure/displeasure (Feeling Scale) were recorded using various categorical scales. Repeated measures analysis of variance was used to assess differences in all variables across time and treatments, with fitness level used as a between-subjects variable. Pleasure/displeasure was altered with caffeine compared to placebo, although leg pain, RPE, and arousal were similar across treatments. Caffeine increased cycling performance by 0.3-2.0 percent versus placebo, with no effect of fitness level. Only in trained men; however, was there a significant caffeine-mediated improvement in cycling performance, which was consequent with diminished mood in trained and improved mood in active individuals.

Both caffeine (CAF) and pseudoephedrine (PSE) are proposed to be central nervous system stimulants. However, during competition, CAF is a permitted substance, whereas PSE is a banned substance at urinary levels >150 microg/L. As a result, one study aimed to compare the effect of CAF versus PSE use on cycling time trial (TT) performance to explore whether the legal stimulant was any less ergogenic than the banned substance. Here, 10 well-trained male cyclists and/or triathletes were recruited for participation. All athletes were required to attend the laboratory on four separate occasions, inclusive of a familiarisation trial and three experimental trials which required participants to complete a simulated 40 km (1200 kJ) cycling TT, after the ingestion of either 200 mg CAF, 180 mg PSE or a non-nutritive placebo (PLA). The results showed that the total time taken and the mean power produced during each TT was not significantly different between trials, despite a 1.3 percent faster overall time (about 57 sec) after CAF consumption. Interestingly, the time taken to complete the second 50 percent of the TT was significantly faster in CAF as compared to PSE (by 99 sec), with magnitude based inferences suggesting a 91 percent beneficial effect of CAF during the second half of the TT. This investigation further confirms the ergogenic benefits of CAF use during TT performances, and further suggests this legal CNS stimulant has a better influence than a supra-therapeutic dose of PSE.

The aims of one study were to evaluate the effects of caffeine supplementation on sprint cycling performance and to determine if there was a dose-response effect. Using a randomized, double-blind, placebo-controlled design, 17 well-trained men (age: 24) completed 7 maximal 10-second sprint trials on an electromagnetically braked cycle ergometer. Apart from trial 1 (familiarization), all the trials involved subjects ingesting a gelatine capsule containing either caffeine or placebo (maltodextrin) 1 hour before each sprint. To examine dose-response effects, caffeine doses of 2, 4, 6, 8, and 10 mg/kg bm were used. There were no significant differences in baseline measures of plasma caffeine concentration before each trial. There was, however, a significant supplement × time interaction, with larger caffeine doses producing higher postsupplementation plasma caffeine levels. In comparison with placebo, caffeine had no significant effect on peak power, mean power, or time to peak power. There was also no significant effect of supplementation on prettrial blood lactate, but there was a significant time effect, with blood lactate reducing over the 50 minute postsupplementation rest period from 1.29 ± 0.36 to 1.06 ± 0.33 mmol/L. The results of this study show that caffeine supplementation has no effect on short-duration sprint cycling performance, irrespective of the dosage used.
The objective of another study was to analyze the effect of caffeine ingestion on the performance and physiological variables associated with fatigue in 20-km cycling time trials. In a double-blind placebo-controlled crossover study, 13 male cyclists were randomized into 2 groups and received caffeine (CAF) capsules (6 mg/kg) or placebo (PLA) 60 min before performing 20-km time trials. Distance, speed, power, rpm, rating of perceived exertion (RPE), electromyography (EMG) of the quadriceps muscles and heart rate (HR) were continuously measured during the tests. In addition, BRUMS questionnaire was applied before and after the tests. Significant interactions were found in power and speed, which were significantly higher at the end of the test (final 2 km) after CAF condition. A main effect of time was observed for RPE and HR, which increased linearly until the end of exercise in both conditions. The time taken to complete the test was similar in both conditions (PLA = 2191 ± 158 s vs CAF = 2181 ± 194 s). No significant differences between CAF and PLA conditions were identified for speed, power, rpm, RPE, EMG, HR, and BRUMS. The results suggest that caffeine intake 60 min before 20-km time trials has no effect on the performance or physiological responses of cyclists [133].

The aim of one study was to determine the effects of caffeine ingestion on a “preloaded” protocol that involved cycling for 2 min at a constant rate of 100 percent maximal power output immediately followed by a 1-min “all-out” effort. Eleven male cyclists completed a ramp test to measure maximal power output. On two other occasions, the participants ingested caffeine (5 mg/kg) or placebo in a randomized, double-blind procedure. All tests were conducted on the participants’ own bicycles using a Kingcycle test rig. Ratings of perceived exertion (RPE; 6-20 Borg scale) were lower in the caffeine trial by approximately 1 RPE point at 30, 60 and 120 s during the constant rate phase of the preloaded test. The mean power output during the all-out effort was significantly increased following caffeine ingestion compared with placebo. Blood lactate concentration 4, 5 and 6 min after exercise was also significantly higher by approximately 1 mmol/L in the caffeine trial. These results suggest that high-intensity cycling performance can be increased following moderate caffeine ingestion and that this improvement may be related to a reduction in RPE and an elevation in blood lactate concentration [134].

**Caffeine in 100-km cycling time-trial performance**

One study analyzed the effect of caffeine ingestion on performance during a repeated-measures, 100-km, laboratory cycling time trial that included bouts of 1- and 4-km high intensity epochs (HIE). Eight highly trained cyclists participated in 3 separate trials’ placebo ingestion before exercise with a placebo carbohydrate solution and placebo tablets during exercise (Pl), or placebo ingestion before exercise with a 7 percent carbohydrate drink and placebo tablets during exercise (Cho), or caffeine tablet ingestion before and during exercise with 7 percent carbohydrate (Caf). Placebo (twice) or 6 mg/kg caffeine was ingested 60 min prior to starting 1 of the 3 cycling trials, during which subjects ingested either additional placebos or a caffeine maintenance dose of 0.33 mg/kg every 15 min to trial completion. The 100-km time trial consisted of five 1-km HIE after 10, 32, 52, 72, and 99 km, as well as four 4-km HIE after 20, 40, 60, and 80 km. Subjects were instructed to complete the time trial and all HIE as fast as possible. Plasma (caffeine) was significantly higher during Caf. Average power, HIE time to completion, and 100-km time to completion were not different between trials. Mean heart rates during both the 1-km HIE and 4-km HIE was higher in Caf than in the other groups. No significant differences were found between groups for either EMG amplitude (IEMG) or mean power frequency spectrum (MPFS). IEMG activity and performance were not different between groups but were both higher in the 1-km HIE, indicating the absence of peripheral fatigue and the presence of a centrally-regulated pacing strategy that is not altered by caffeine ingestion. Caffeine may be without ergogenic benefit during endurance exercise in which the athlete begins exercise with a defined, predetermined goal measured as speed or distance [135].
Caffeine affects time to exhaustion and substrate oxidation during cycling

The ergogenic effects of caffeine on endurance performance are now well established. A wide variety of mechanisms have been proposed to explain such effects in the human body, which ranges from increased reliance on fat metabolism, attenuation of the rate of muscle glycogenolysis and alterations in central neurotransmitters or neuromuscular function. However, measurements of substrate utilization by indirect calorimetry during whole-body exercises occasionally fails to support the theory of enhanced fat oxidation, leading to the notion that caffeine ingestion has minimal effects on the metabolism in working muscles. In the majority of studies, a protocol of exercise tolerance at a given percentage of maximal oxygen uptake ($VO_{2\text{max}}$) was used, which has been shown to have similar sensitivity to that of time-trials for changes in endurance. However, despite being the most widely used exercise intensity index, a given percentage of $VO_{2\text{max}}$ is possibly not the best functional definition. This is because the parameters that discriminate between selected ranges or clusters of similar metabolic response characteristics (i.e. lactate threshold, maximal lactate steady state (MLSS), and $VO_{2\text{max}}$) have highly variable relationships among each other in different individuals. In other words, assigning exercise intensities based on percentage of $VO_{2\text{max}}$ could actually lead participants to undergo distinct exercise intensity domains, yielding markedly different physiological strain characteristics. Thus, merging such responses from different participants into a single average could be misleading with respect to inferences about the effect of caffeine intake on metabolism. On the other hand, the blood lactate response during exercise is recognized as a better predictor of endurance performance than $VO_{2\text{max}}$. Furthermore, the blood lactate response is a widely used tool for estimating relative exercise intensity and the metabolic responses at submaximal exercise intensities. MLSS represents the highest intensity that can be performed in the absence of progressively increasing in blood lactate concentrations (BLC), which means that the oxidative energy metabolism accounts for the energy provision in active muscles. Indeed, MLSS does not indicate only a given workload but rather an exercise intensity above which metabolism changes qualitatively; the transition from aerobic to partly anaerobic metabolism as indicated by continuing net lactate increase. Additionally, exercise tolerance at MLSS has shown a large negative correlation with the percentage of the energy derived from carbohydrates. This latter result is consistent with the notion that MLSS is highly dependent on carbohydrates metabolism. Therefore, in comparison to a given exercise intensity related to $VO_{2\text{max}}$, exercising to exhaustion at the intensity corresponding to MLSS appears as a more individualized strategy to assess effects of caffeine under a given metabolic situation during submaximal exercise. Since carbohydrate combustion has proven decisive for exercise tolerance at MLSS workload, some sparing of the endogenous carbohydrate stores by an increased reliance on fat oxidation may help explain the ergogenic effects of caffeine intake on exercise tolerance. One study analyzed the effects of caffeine intake on whole-body substrate metabolism and exercise tolerance during cycling by using a more individualized intensity for merging the subjects into homogeneous metabolic responses (the workload associated with the maximal lactate steady state-MLSS). MLSS was firstly determined in eight active males (25 ± 4 years, 176 ± 7 cm, 77 ± 11 kg) using from two to four constant-load tests of 30 min. On two following occasions, participants performed a test until exhaustion at the MLSS workload 1 h after taking either 6 mg/kg of body mass of caffeine or placebo (dextrose), in a randomized, double-blinded manner. Respiratory exchange ratio was calculated from gas exchange measurements. There was an improvement of 23 percent in time to exhaustion at MLSS workload following caffeine ingestion (95 % confidence limits of ±10.3 percent), which was accompanied by decrease in respiratory exchange ratio ($p = 0.001$). These results reinforce findings indicating that sparing of the endogenous carbohydrate stores could be one of the several physiological effects of caffeine during submaximal performance around 1 h [136].
Cross-country skiing

Caffeine (CAF) improves performance of both short and long duration in running and cycling where performance relies on power output, and endurance capacity of leg muscles. No studies have so far tested effects of CAF while using the double poling (DP) technique in cross-country skiing (XCS). When DP arm muscles provide the speed generating force, and therefore play an important role to performance outcome. The metabolism of arm muscles differs from that of leg muscles. Thus, results from studies on leg muscles and CAF may not be directly applicable to exercises while DP in XCS. The purpose of our study was therefore to investigate effects of CAF on exercise performance in DP. Ten highly trained male cross-country skiers performed a placebo (PLA) and CAF trial using a randomized, double-blinded, cross-over design. Performance was assessed by time to complete an 8 km cross country DP performance test (C-PT). CAF (6 mg/kg) or PLA was ingested 75 min before the C-PT. Results: CAF ingestion significantly reduced times to complete the 8 km C-PT. The subjects maintained higher speed and heart rate throughout the C-PT, and lactate was higher immediately after the C-PT with CAF exposure compared to PLA. Subjects reported lower rating of perceived exertion at submaximal intensities during CAF compared to PLA, although heart rate was similar. Conclusion: CAF intake enhances endurance performance in an 8 km C-PT where arm muscles limit performance. CAF ingestion allowed the participants to exercise with a higher heart rate, and work intensity, possibly by reducing perception of effort or facilitating motor unit recruitment [137].

Rowing

To determine whether a dose-response relationship exists between caffeine and 2000-m rowing performance in a randomized, placebo-controlled, double-blind crossover study, 10 competitive male rowers consumed 2, 4, or 6 mg/kg caffeine or a placebo 60 min before completing a 2000-m time trial on a rowing ergometer. The trials were preceded by a 24-h standardized diet (including a light preexercise meal of 2 g/kg carbohydrates), and subjects were tested preexercise for hydration, caffeine abstinence, and blood glucose concentrations. Time trial performance was not significantly different across the three caffeine doses or placebo. After the three caffeine trials, postexercise plasma glucose and lactate concentrations were higher compared with the placebo trial. Plasma caffeine concentrations after 60 min of ingestion were lower than the values reported previously by others following the same dose, and there was considerable interindividual variation in plasma caffeine concentrations in response to the various caffeine doses. It was concluded that the large interindividual response to the caffeine doses suggests that individual characteristics need to be considered when administering caffeine for performance enhancement. In addition, preexercise feeding may significantly affect plasma caffeine concentrations and the potential for caffeine to improve performance [138].

One study examined the ergogenic effects in a 6 min maximal performance test (PT) on 12 elite rowers: 6 open-weight and 6 light-weight following supplementation with caffeine (CAF), sodium bicarbonate (SB), and the combination of both, in a double-blind randomized placebo (PLA) controlled design. PT was executed on 4 occasions, on separate days within a week, and in a non-fasted state, with standardized training being performed the day before PT. Protocols were as follows: (i) CAF, 3 mg/kg, 45 min prior to PT + calcium as SB-PLA; (ii) SB, 0.3 g/kg, 75 min prior to PT + dextrose as CAF-PLA; (iii) CAF + SB; and (iv) PLA; CAF-PLA + SB-PLA. The total distance in the CAF (1878 ± 97 m) and CAF + SB (1877 ± 97 m) was longer than in the PLA (1865 ± 104 m) and SB (1860 ± 96 m). The mean power in CAF (400 ± 58 W) and CAF + SB (400 ± 58 W) was higher than the PLA (393 ± 61 W) and SB (389 ± 57 W). In CAF and CAF + SB, power was higher relative to PLA in the last half (4-6
min) of PT. Trials with CAF were more effective in light-weight rowers than in open-weight rowers. No difference between interventions was observed for readiness and stomach comfort before PT and perceived exertion during PT. The study demonstrates that caffeine ingestion does improve performance in elite rowing. In contrast sodium bicarbonate does not appear to be ergogenic, but it does not abolish the ergogenic effect of caffeine [139].

Enhancement of 2000-m rowing performance after caffeine ingestion
To investigate the effect of caffeine ingestion on short-term endurance performance in competitive rowers in a randomized double-blind crossover study, eight competitive oarsmen performed three familiarization trials of a 2000-m rowing test on an air-braked ergometer, followed by three experimental trials at 3- to 7-d intervals, each 1 h after ingesting caffeine (6 or 9 mg/kg body mass) or placebo. Trials were preceded by a standardized warm-up. Urinary caffeine concentration was similar before ingestion (approximately 1 mg/L) but rose to 6.2 ± 3.6 and 14.5 ± 7.0 mg/L for the low and high caffeine doses, respectively. Plasma free fatty acid concentration before exercise was higher after caffeine ingestion than after placebo. Respiratory exchange ratio during the warm-up was also substantially lower with caffeine than with placebo. Subjects could not distinguish between treatments before or after the exercise test. Both doses of caffeine had a similar ergogenic effect relative to placebo: performance time decreased by a mean of 1.2 percent (95 % likely range 0.4 to 1.9 %); the corresponding increase in mean power was 2.7 percent. Performance time showed some evidence of individual differences in the effect of caffeine. It was concluded that ingestion of 6 or 9 mg/kg of caffeine produces a worthwhile enhancement of short-term endurance performance in a controlled laboratory setting [140].

Eight competitive oarswomen (age, 22) performed three simulated 2,000-m time trials on a rowing ergometer. The trials, which were preceded by a 24-hour dietary and training control and 72 hours of caffeine abstinence, were conducted 1 hour after ingesting caffeine (6 or 9 mg/kg body mass) or placebo. Plasma free fatty acid concentrations before exercise were higher with caffeine than placebo (0.67 ± 0.34 vs 0.72 ± 0.36 vs 0.30 ± 0.10 mM for 6 and 9 mg/kg caffeine and placebo, respectively). Performance time improved 0.7 percent (95 % confidence interval 0 to 1.5 %) with 6 mg/kg caffeine and 1.3 percent (95 % confidence interval 0.5 to 2.0%) with 9 mg/kg caffeine. The first 500 m of the 2,000 m was faster with the higher caffeine dose compared with placebo or the lower dose (1.53 ± 0.52 vs 1.55 ± 0.62 and 1.56 ± 0.43 min). It was concluded that caffeine produces a worthwhile enhancement of performance in a controlled laboratory setting, primarily by improving the first 500 m of a 2,000-m row [141].

Football
One study examined the effect of caffeine supplementation on match activities and development of fatigue during a football match. In a randomised, double-blind cross-over design, two experimental football games separated by 7 days were organised between the junior teams of two professional football clubs (18 years old). The players ingested either a capsule of 6 mg/g/b.w. caffeine or placebo (dextrose) 65 min prior to the matches. Match activities were assessed using the ZXY match analysis system, and a Yo-Yo intermittent recovery test-level 2 (Yo-Yo IR2) was conducted immediately post-game. Heart rate was monitored throughout the game, and blood samples were obtained at baseline, half-time and after the game. There were no differences between caffeine and placebo regarding total distance covered (10,062 ± 916 vs 9854 ± 901 m), high-intensity running (557 ± 178 vs 642 ± 240 m), sprinting distance (109 ± 58 vs 112 ± 69 m) or acceleration counts (123 ± 31 vs 126 ± 24). In both trials, players displayed lower values in total distance and acceleration counts in the last 15 min compared to all other 15-min periods of the matches. Post-game Yo-Yo IR2 performance was not different between game trials (caffeine: 829 ± 322 m;
placebo $819 \pm 289$ m). In conclusion, oral caffeine administration does not appear to have an ergogenic effect in young football players during match play \cite{142}.

There is little information about the effects of caffeine intake on female team-sport performance. The aim of this study was to investigate the effectiveness of a caffeine-containing energy drink to improve physical performance in female soccer players during a simulated game. A double-blind, placebo controlled and randomized experimental design was used in this investigation. In two different sessions, 18 women soccer players ingested 3 mg of caffeine/kg in the form of an energy drink or an identical drink with no caffeine content (placebo). After 60 min, they performed a countermovement jump (CMJ) and a 7 \times 30 m sprint test followed by a simulated soccer match (2 \times 40 min). Individual running distance and speed were measured using GPS devices. In comparison to the placebo drink, the ingestion of the caffeinated energy drink increased the CMJ height ($26.6 \pm 4.0$ vs $27.4 \pm 3.8$ cm) and the average peak running speed during the sprint test ($24.2 \pm 1.6$ vs $24.5 \pm 1.7$ km/h). During the simulated match, the energy drink increased the total running distance ($6,631 \pm 1,618$ vs $7,087 \pm 1,501$ m), the number of sprints bouts ($16 \pm 9$ vs $21 \pm 13$) and the running distance covered at >18 km/h ($161 \pm 99$ vs $216 \pm 103$ m). The ingestion of the energy drink did not affect the prevalence of negative side effects after the game. An energy drink with a dose equivalent to 3 mg of caffeine/kg might be an effective ergogenic aid to improve physical performance in female soccer players \cite{143}.

The use of nutritional ergogenic aids in team sports such as soccer is now commonplace. Aligned with the primary aim of soccer, which is to score more goals than the opposition within the allotted time, the quality of performance of technical actions (i.e. skills) executed during soccer-specific exercise is likely to determine success. However, when seeking to maintain soccer skill performance, information about the efficacy of nutritional interventions is lacking and factors which might modulate the efficacy of such strategies are unclear. One review aimed (i) to systematically evaluate the current research that examines the efficacy of nutritional interventions on soccer skills, and (ii) to provide a qualitative commentary on factors that have the potential to modulate the efficacy of such strategies. Relevant databases (PubMed and SPORTDiscus) were searched up to and including 1 July, 2013 for studies that investigated the efficacy of acute nutritional interventions on soccer skill performances. Overall, 279 records were retrieved. Articles were sequentially excluded from the review based on specific criteria, being: (A) articles that did not report outcomes directly relating to skilled performances in soccer, (B) articles that examined the influence of interventions that were not nutritional in origin and/or were nutritional in origin but provided >3 hours before skill testing commenced, (C) articles that were review papers, and (D) post-acceptance withdrawal of articles methods from database. Articles were independently assessed for the quality of the methods employed based upon the Physiotherapy Evidence Database (PEDro) scale. Records achieving a minimum PEDro score of 5 out of 10 were included in this review. Qualitative appraisal of 13 articles was performed after the application of exclusion criteria and quality assurance processes. The majority (n=8) of articles examined the influence of carbohydrates on technical performance whereas fewer studies investigated the influence of caffeine ingestion (n=2) and fluid provision (n=3).

Findings were reported for a total of 171 participants and all but one of the included articles used cross-over study designs. Most participants (94 %) were male, highly trained (reported maximal aerobic capacity range 50-59 mL/kg/min) and exercised in temperate environments (reported temperature range 13-25 °C). Six of the eight studies reported that carbohydrates, consumed in the form of a 6-8 percent solution of glucose, sucrose or maltodextrin at rates of 30-60 g/h, enhanced at least one aspect of skilled performance over the duration of exercise (75-90 min). Although some evidence exists to support the consumption of caffeine (6 mg/kg body mass) and prescribed fluid to preserve skills performed during soccer-specific exercise, findings from the small number of included studies were inconsistent. The findings from this systematic review suggest that nutritional interventions, which provide carbohydrate, caffeine and fluid, have potential to preserve skills performed under conditions that induce soccer-
specific fatigue. The weight of current evidence supports the consumption of carbohydrate, but is less conclusive with respect to caffeine and fluid provision. It is likely that the efficacy of a nutritional intervention will be modulated by factors including the dose consumed, the mode of administration, individual responsiveness to the intervention and interactions with other physiological changes occurring during soccer-specific exercise. Consequently, these factors should be considered when using carbohydrates, caffeine and fluid provision to maintain skilled performances in soccer. Future research should seek to optimise the nutritional strategies employed to maintain technical performance throughout match-play [144].

Rugby

The aim of one study was to determine the effects of a caffeine-containing energy drink on physical performance during a rugby sevens competition. A second purpose was to investigate the post-competition urinary caffeine concentration derived from the energy drink intake. On two non-consecutive days of a friendly tournament, 16 women from the Spanish National rugby team (mean age and body mass 23 ± 2 years and 66 ± 7 kg) ingested 3 mg of caffeine per kg of body mass in the form of an energy drink (Fure®) or the same drink without caffeine (placebo). After 60 min for caffeine absorption, participants performed a 15-s maximal jump test, a 6 × 30 m sprint test, and then played three rugby sevens games against another national team. Individual running pace and instantaneous speed during the games were assessed using global positioning satellite devices. Urine samples were obtained pre and post-competition. In comparison to the placebo, the ingestion of the energy drink significantly increased muscle power output during the jump series, running pace during the games and pace at sprint velocity. However, the energy drink did not affect maximal running speed during the repeated sprint test. The ingestion of the energy drink resulted in a higher post-competition urine caffeine concentration than the placebo (3.3 ± 0.7 vs 0.2 ± 0.1 microg/mL). In summary, 3 mg/kg of caffeine in the form of a commercially available energy drink considerably enhanced physical performance during a women's rugby sevens competition [145].

The purpose of one study was to investigate the effectiveness of a caffeine-containing energy drink in enhancing rugby players' physical performance during a simulated match. A second purpose was to determine the urinary caffeine excretion derived from the energy drink intake. In a randomized and counterbalanced order, 26 elite rugby players played 2 simulated rugby games (2 × 30 min) 60 min after ingesting 3 mg of caffeine per kilogram of body mass in the form of an energy drink (Fure®) or the same drink without caffeine (placebo). During the matches, the individual running distance and the instantaneous speed were measured, and the number of running actions above 20 km/h (i.e. sprints) were determined, using global positioning system devices. The number of impacts above 5 g during the matches was determined by accelerometry. The ingestion of the energy drink, compared with the placebo, increased the total distance covered during the match, the running distance covered at more than 20 km/h, and the number of sprints. The ingestion of the energy drink also resulted in a greater overall number of impacts and a higher postexercise urine caffeine concentration. The use of an energy drink with a caffeine dose equivalent to 3 mg/kg considerably enhanced the movement patterns of rugby players during a simulated match [146].

Investigation of various exercise parameters in situations devised to simulate the repeated bouts of exercise required in rugby, a highintensity team sport. Subjects were given either placebo or a moderate dose of caffeine (6 mg/kg) that previously has been shown to demonstrate ergogenic effects in submaximal exercise situations. Participants were then put through a series of 14 exercise circuits divided into two 40-minute halves. A 10-minute rest period occurred between the two halves. The design was intended to simulate the conditions
of an actual rugby game with a first half, halftime, and second half. Subjects taking caffeine showed improvement in a variety of skill tasks including sprint tasks, power tasks, and passing accuracy tasks [012].

Caffeine enhances performance of single bouts of endurance exercise, but its effects on repeated bouts typical of those in high-intensity team sports are unclear. To investigate effects of caffeine in a performance test simulating physical and skill demands of a rugby union game it was performed a study with double-blind, randomized, crossover design in which nine competitive male rugby players ingested either caffeine (6 mg/kg body mass) or placebo (dextrose) 70 min before performing a rugby test. Each test consisted of seven circuits in each of two 40-min halves with a 10-min half-time rest. Each circuit included stations for measurement of sprint time (two straight-line and three agility sprints), power generation in two consecutive drives, and accuracy for passing balls rapidly. Interstitial fluid was sampled transdermally by electrosonophoresis before ingestion of caffeine or placebo and then before testing, at half-time, and immediately after testing; samples were assayed chromatographically for caffeine and epinephrine concentrations. The effects of caffeine on mean performance over all 14 circuits were: sprint speeds, 0.5 percent through 2.9 percent; first-drive power, 5.0 percent; second-drive power, -1.2 percent; and passing accuracy, 9.6 percent. The enhancements were mediated partly through a reduction of fatigue that developed throughout the test and partly by enhanced performance for some measures from the first circuit. Caffeine produced a 51 percent increase in mean epinephrine concentration; correlations between individual changes in epinephrine concentration and changes in performance were mostly unclear, but there were some strong positive correlations with sprint speeds and a strong negative correlation with passing accuracy. It was concluded that caffeine is likely to produce substantial enhancement of several aspects of high-intensity team-sport performance [147].

Field hockey

One study examined the impact of caffeine ingestion on field hockey skill performance following high-intensity fatigue. Thirteen male hockey players (mean age 21 years) performed hockey sprint dribble and ball handling tests at rest and after a bout of total body fatigue (90 % maximal capacity) following caffeine (5 mg/kg) or placebo ingestion. Sprint dribble times were slower postfatigue compared with rest but were significantly faster postfatigue with caffeine compared with postfatigue with placebo ingestion. Ball handling scores were higher at rest compared with postfatigue, but scores postfatigue were higher following caffeine than placebo ingestion. Rating of perceived exhaustion (RPE) was lower and readiness to invest physical and mental effort were significantly higher in the caffeine condition. Caffeine ingestion may therefore be effective in offsetting decrements in skilled performance associated with fatigue [148].

The aim of one investigation was to determine the efficacy of a caffeine-containing energy drink to improve physical performance of elite field hockey players during a game. On two days separated by a week, 13 elite field hockey players (age and body mass=23 ± 4 years and 76 ± 6 kg) ingested 3 mg of caffeine per kg of body mass in the form of an energy drink or the same drink without caffeine (placebo drink). After sixty minutes for caffeine absorption, participants played a simulated field hockey game (2 × 25 min). Individual running pace and instantaneous speed during the game were assessed using GPS devices. The total number of accelerations/decelerations was determined by accelerometry. When compared to the placebo drink, the caffeinated energy drink did not modify the total distance covered during the game (6035 ± 451 vs 6055 ± 499 m, respectively), average heart rate (155 ± 13 vs 158 ± 18 bpm) or the number of accelerations/decelerations (697 ± 285 vs 618 ± 221 number). However, the caffeinated energy drink reduced the distance covered at moderate intensity (793 ± 135 vs 712 ± 116) while it increased the distance covered at high intensity running
(303 ± 67 vs 358 ± 117 m) and sprinting (85 ± 41 vs 117 ± 55 m). Elite field hockey players can benefit from ingesting caffeinated energy drinks because these beverages increase the running distance covered at high-intensity and sprinting. Increased running distance at high-speed might represent a meaningful advantage for field hockey performance [149].

**Basketball**

The aim of one study was to investigate the effectiveness of a caffeine-containing energy drink to enhance physical and match performance in elite badminton players. Sixteen male and elite badminton players (25.4 ± 7.3 year; 71.8 ± 7.9 kg) participated in a double-blind, placebo-controlled and randomised experiment. On two different sessions, badminton players ingested 3 mg of caffeine per kg of body mass in the form of an energy drink or the same drink without caffeine (placebo). After 60 min, participants performed the following tests: handgrip maximal force production, smash jump without and with shuttlecock, squat jump, countermovement jump and the agility T-test. Later, a 45-min simulated badminton match was played. Players’ number of impacts and heart rate was measured during the match. The ingestion of the caffeinated energy drink increased squat jump height (34.5 ± 4.7 vs 36.4 ± 4.3 cm), squat jump peak power, countermovement jump height (37.7 ± 4.5 vs 39.5 ± 5.1 cm) and countermovement jump peak power. In addition, an increased number of total impacts was found during the badminton match (7395 ± 1594 vs 7707 ± 2033 impacts). In conclusion, the results show that the use of caffeine-containing energy drink may be an effective nutritional aid to increase jump performance and activity patterns during game in elite badminton players [150].

One study aimed at investigating the effects of a commercially available energy drink on shooting precision, jump performance and endurance capacity in young basketball players. Sixteen young basketball players (first division of a junior national league; 14.9 ± 0.8 years; 73.4 ± 12.4 kg; 182.3 ± 6.5 cm) volunteered to participate in the research. They ingested either (a) an energy drink that contained 3 mg of caffeine per kg of body weight or (b) a placebo energy drink with the same appearance and taste. After 60 min for caffeine absorption, they performed free throw shooting and three-point shooting tests. After that, participants performed a maximal countermovement jump (CMJ), a repeated maximal jumps test for 15 s (RJ-15), and the Yo-Yo intermittent recovery test level 1 (Yo-Yo IR1). Urine samples were obtained before and 30 min after testing. In comparison to the placebo, the ingestion of the caffeinated energy drink did not affect precision during the free throws (Caffeine 70.7 ± 11.8 % vs placebo 70.3 ± 11.0 %), the three-point shooting test (39.9 ± 11.8 vs 39.1 ± 12.8 %) or the distance covered in the Yo-Yo IR1 (2,000 ± 706 vs 1,925 ± 702 m). However, the energy drink significantly increased jump height during the CMJ (38.3 ± 4.4 vs 37.5 ± 4.4 cm) mean jump height during the RJ-15 (30.2 ± 3.6 vs 28.8 ± 3.4 cm) and the excretion of urinary caffeine (1.2 ± 0.7 vs 0.1 ± 0.1 microg/mL). The intake of a caffeine-containing energy drink (3 mg/kg body weight) increased jump performance although it did not affect basketball shooting precision [151].

One study investigated whether performance enhancement from caffeine described by other researchers transfers to male basketball players. The effects of caffeine ingestion were studied in a maximal-effort test on a treadmill that was followed by a vertical-jump test. Five elite-level male basketball players completed a graded treadmill test that measured maximal oxygen uptake, blood lactate profiles, respiratory exchange ratio, and rating of perceived exertion at each 3-minute stage. After a 15-minute warm-down, the subjects performed 10 vertical rebound jumps. Each subject completed the test twice – once with a 3 mg/kg of body weight dose of caffeine and once with a placebo, with the dosage administered 60 minutes before commencement of exercise. The test was thus administered according to a double-blind protocol. No substantial trends were found between caffeine and control trials,
regardless of trial order. The study showed that the specified dosage had negligible effects on the players’ power and endurance performance and had no efficacy as an ergogenic aid for male basketball players [152].

Volleyball

There were no scientific data about the effects of caffeine intake on volleyball performance. The aim of this study was to investigate the effect of a caffeine-containing energy drink to enhance physical performance in male volleyball players. A double-blind, placebo-controlled, randomized experimental design was used. In 2 different sessions separated by 1 week, 15 college volleyball players ingested 3 mg of caffeine per kg of body mass in the form of an energy drink or the same drink without caffeine (placebo). After 60 min, participants performed volleyball-specific tests: standing spike test, maximal squat jump (SJ), maximal countermovement jump (CMJ), 15-s rebound jump test (15RJ), and agility T-test. Later, a simulated volleyball match was played and recorded. In comparison with the placebo drink, the ingestion of the caffeinated energy drink increased ball velocity in the spike test and the mean jump height in SJ, CMJ and 15RJ. The time to complete the agility test was significantly reduced with the caffeinated energy drink. In addition, players performed successful volleyball actions more frequently with the ingestion of the caffeinated energy drink than with the placebo drink during the simulated game. A caffeine-containing energy drink, with a dose equivalent to 3 mg of caffeine per kg body mass, might be an effective ergogenic aid to improve physical performance and accuracy in male volleyball players [153].

The objective of one study is to determine the effects of a caffeine-containing energy drink on female volleyball players’ performance. Thirteen elite female volleyball players ingested 3 mg/kg of caffeine with an energy drink or the same drink without caffeine (placebo drink) in a double-blind and randomized study. Then, participants performed the following: standing spike, jumping spike, spike jump, blocking jump, squat jump, countermovement jump, manual dynamometry, and the agility t-test. A simulated volleyball game was played, videotaped, and notated afterward. In comparison to the placebo drink, the ingestion of the caffeinated energy drink increased the ball velocity in the standing spike and in the jumping spike and the jump height in the squat jump, countermovement jump, spike jump, and block jump. Furthermore, the caffeinated energy drink decreased the time needed to complete the agility t-test. During the game, the volleyball actions categorized as successful were more frequent with the caffeinated energy drink, whereas imprecise actions decreased when compared with the placebo drink. It was concluded that commercially available energy drinks can significantly improve physical performance in female volleyball players. Increased physical performance led to improved accuracy during an actual volleyball match [154].

Tennis

The aim of one study was to investigate the effectiveness of a caffeinated energy drink to enhance physical performance in elite junior tennis players. In 2 different sessions separated by 1 week, 14 young (16 ± 1 years) elite-level tennis players ingested 3 mg caffeine per kg body mass in the form of an energy drink or the same drink without caffeine (placebo). After 60 min, participants performed a handgrip-strength test, a maximal-velocity serving test, and an 8 × 15-m sprint test and then played a simulated singles match (best of 3 sets). Instantaneous running speed during the matches was assessed using global positioning (GPS) devices. Furthermore, the matches were videotaped and notated afterward. In comparison with the placebo drink, the ingestion of the caffeinated energy drink increased handgrip force by 4.2 ± 7.2 percent in both hands, the running pace at high intensity, and the number of sprints during the simulated match. There was a tendency for increased maximal
running velocity during the sprint test and higher percentage of points won on service with the caffeinated energy drink in comparison with the placebo drink. The energy drink did not improve ball velocity during the serving test. The preexercise ingestion of caffeinated energy drinks was effective to enhance some aspects of physical performance of elite junior tennis players [155].

**Badminton**

The aim of one study was to investigate the effectiveness of a caffeine-containing energy drink to enhance physical and match performance in elite badminton players. Sixteen male and elite badminton players (25.4 ± 7.3 year; 71.8 ± 7.9 kg) participated in a double-blind, placebo-controlled and randomised experiment. On two different sessions, badminton players ingested 3 mg of caffeine per kg of body mass in the form of an energy drink or the same drink without caffeine (placebo). After 60 min, participants performed the following tests: handgrip maximal force production, smash jump without and with shuttlecock, squat jump, countermovement jump and the agility T-test. Later, a 45-min simulated badminton match was played. Players' number of impacts and heart rate was measured during the match. The ingestion of the caffeinated energy drink increased squat jump height (34.5 ± 4.7 vs. 36.4 ± 4.3 cm), squat jump peak power, countermovement jump height (37.7 ± 4.5 vs. 39.5 ± 5.1 cm) and countermovement jump peak power. In addition, an increased number of total impacts was found during the badminton match (7395 ± 1594 vs 7707 ± 2033 impacts). In conclusion, the results show that the use of caffeine-containing energy drink may be an effective nutritional aid to increase jump performance and activity patterns during game in elite badminton players [156].

**Wrestling**

*Effect of caffeine on upper-body anaerobic performance*

Peak power (PP) and mean power (MP) attained in upper body sprint performance test are considered important factors for competitive success in wrestling. One study aimed to determine whether acute caffeine ingestion would better maintain PP and MP across a simulated competition day in wrestling. In a double-blind, counterbalanced, crossover study, 14 trained wrestlers ingested either placebo or 5 mg/kg caffeine and completed four 6-min upper body intermittent sprint performance tests with 30-min recovery periods between consecutive tests. PP and MP were recorded during and blood lactate concentration was measured before and after each test. Ratings of perceived fatigue (RPF) and exertion (RPE) were recorded before and after each test, respectively. Heart rate (HR) was monitored across the whole testing period. Mean power decreased across four tests in both trials, but the reduction in PP (from 277 ± 35 W to 257 ± 45 W) only occurred in caffeine trial. Both pretest blood lactate concentration and HR were higher in caffeine than in placebo trial in the third and fourth tests. No between-trial differences occurred in RPF or RPE. It was concluded that under simulated competition day conditions mimicking four consecutive wrestling matches, acute caffeine ingestion has a partially detrimental effect on upper body intermittent sprint performance in trained wrestlers. Elevated HR and blood lactate levels observed between tests after caffeine ingestion suggest that caffeine may impair recovery between consecutive maximal efforts [157].

**Jiu-jitsu**

Although caffeine is one of the most commonly used substances in combat sports,
information about its ergogenic effects on these disciplines is very limited. The aim of this investigation was to determine the effectiveness of ingesting a moderate dose of caffeine to enhance overall performance during a simulated Brazilian Jiu-jitsu (BJJ) competition. Fourteen elite BJJ athletes participated in a double-blind, placebo-controlled experimental design. In a random order, the athletes ingested either 3 mg/kg body mass of caffeine or a placebo (cellulose; 0 mg/kg) and performed two simulated BJJ combats (with 20 min rest between them), following official BJJ rules. Specific physical tests such as maximal handgrip dynamometry, maximal height during a countermovement jump, permanence during a maximal static lift test, peak power in a bench press exercise and blood lactate concentration were measured at three specific times: prior to the first combat and immediately after the first and second combat. The combats were video-recorded to analyze fight actions. After the caffeine ingestion, participants spent more time in offensive actions in both combats and revealed higher blood lactate values. Performance in all physical tests carried out before the first combat was enhanced with caffeine, and some improvements remained post-first combat (e.g. maximal static lift test and bench press exercise). After the second combat, the values in all physical tests were similar between caffeine and placebo. Caffeine might be an effective ergogenic aid for improving intensity and physical performance during successive elite BJJ combats [158].

Weight-lifting

The purpose of the present study was to examine the acute effects of a caffeine-containing supplement (SUPP) on 1 repetition maximum (1RM) bench press and leg extension strength, as well as time to exhaustion (TTE), during cycle ergometry at a power output that corresponded to 80 percent of VO$_{2peak}$. The study used a double-blinded, placebo-controlled, crossover design. Twenty-one untrained men were randomly assigned to take either the SUPP or placebo (PLAC) first. The SUPP contained 400 mg of caffeine, 66.7 mg of capsicum extract, 10 mg of bioperine, and 40 mg of niacin, and the PLAC was microcrystalline cellulose. Sixty minutes after taking either the SUPP or PLAC, the subjects were tested for 1RM bench press and leg extension strength, as well as TTE. After 1 week of rest, the subjects ingested the opposite substance (SUPP or PLAC) and were retested for 1RM bench press and leg extension strength, as well as TTE. The results indicated that the SUPP had no effect on 1RM bench press strength, 1RM leg extension strength, or TTE at 80 percent VO$_{2peak}$. These findings did not support the use of the caffeine-containing SUPP in the present study as an ergogenic aid in untrained individuals [159].

Paraplegic and tetraplegic compared to able-bodied individuals

The aim of one study was to investigate the effect of caffeine supplementation on 3 min all-out arm crank exercise performance in paraplegic (P) and tetraplegic (T) compared to able-bodied (AB) participants. A placebo-controlled, randomized, cross-over and double-blind study design was chosen to investigate the differences between caffeine (CAF) and placebo (PLC). In total, 34 healthy, trained participants were tested. Seventeen were AB (median [minimum; maximum]; VO$_{2peak}$: 33.9 mL/min/kg [23.6; 57.6]), 10 were P (VO$_{2peak}$: 34.4 mL/min/kg [19.5; 48.8]) and 7 were T (VO$_{2peak}$: 13.6 mL/min/kg [8.6; 16.3]). All participants performed two 3 min all-out tests on an arm crank ergometer following the ingestion of either PLC or CAF. Power output parameters, plasma caffeine (PC), epinephrine (EPI) and norepinephrine (NOR) concentrations were assessed. CAF significantly increased average power over the first 30 s and 60 s in P, but not in T nor in AB. Peak power was increased in the CAF trial in AB (+46 W) as well as in P (+21 W) but was not significantly different to PLC. PC significantly increased in all groups, whereas EPI showed a significant increase only in AB and in P. NOR increased significantly in AB but did not increase in the other groups.
Caffeine seems to enhance short-duration exercise performance in P. In contrast, T showed a high inter-individual variability and overall no ergogenic effect was detected in this group [160].

**Vertical jump height**

Caffeine ingestion elicits a variety of physiological effects that may be beneficial to maximal-intensity exercise performance, though its effectiveness and physical mechanism of action enhancing ballistic task performance are unclear. The purpose of this study was to examine the effects of caffeine ingestion on vertical jump height and jump execution in Division I collegiate athletes. The study used a single-blind, randomized, crossover design. Athletes (n=25) consumed either caffeine (5 mg/kg) or placebo. After a sixty-minute waiting period athletes performed three squat jumps (SJ) and three countermovement jumps (CMJ) while standing on a force platform. Jump height and execution variables were calculated from mechanography data. In comparison to placebo, caffeine increased SJ height (32.8 ± 6.2 vs 34.5 ± 6.7 cm) and CMJ height (36.4 ± 6.9 vs 37.9 ± 7.4 cm). Peak force and average rate of force development were increased during the CMJ in the caffeine trail compared to the control. Time to half peak force was the only execution variable improved with caffeine during the SJ. It appears that caffeine affects both height and execution of jumping. Our data indicate that the physical mechanism of jump enhancement is increased peak force production and / or rate of force development during jumping depending on technique. The physical mechanism of jump enhancement suggests that the ergogenic effects of caffeine may transfer to other ballistic tasks involving the lower-body musculature in collegiate athletes [161].

**Golf**

To determine the effect of a caffeine-containing supplement on golf specific performance and fatigue during a 36-hole competitive golf tournament 12 male golfers (34.8 ± 13.9 years, 175.9 ± 9.3 cm, 81.23 ± 13.14 kg) with a United States Golf Association (USGA) handicap of 3-10 participated in a double-blind, placebo-controlled, crossover design in which they played an 18-hole round of golf on two consecutive days (36-hole tournament) and were randomly assigned to consume a caffeine-containing supplement (CAF) or placebo (PLA). CAF/PLA was consumed before and after 9 holes during each 18-hole round. Total score, drive distance, fairways and greens in regulation, first putt distance, heart rate, breathing rate, peak trunk acceleration and trunk posture while putting were recorded. Self-perceived ratings of energy, fatigue, alertness and concentration were also recorded. Total score (76.9 ± 8.1 vs 79.4 ± 9.1), greens in regulation (8.6 ± 3.3 vs 6.9 ± 4.6) and drive distance (239.9 ± 33.8 vs 233.2 ± 32.4) were statistically better during the CAF condition compared to PLA. Statistically significant main effects for condition and time occurred for perceived feelings of energy and fatigue. Compared to PLA, CAF reported more energy and less fatigue over the competitive round of golf. There were no substantial differences in heart or breathing rates, peak trunk acceleration or putting posture between conditions or over the round. A moderate dose (1.9 ± 0.3 mg/kg) of caffeine consumed before and during a round of golf improves golf-specific measures of performance and reduces fatigue in skilled golfers [162].

**Effect on sedentary men**

It is not known if ergogenic effects of caffeine ingestion in athletic groups occur in the sedentary. To investigate this, it was used a counterbalanced, double-blind, crossover design to examine the effects of caffeine ingestion (6 mg/kg body-mass) on exercise performance,
substrate utilisation and perceived exertion during 30 minutes of self-paced stationary cycling in sedentary men. Participants performed two trials, one week apart, after ingestion of either caffeine or placebo one hour before exercise. Participants were instructed to cycle as quickly as they could during each trial. External work (J/kg) after caffeine ingestion was greater than after placebo. Further, heart rate, oxygen uptake and energy expenditure during exercise were greater after caffeine ingestion, whereas ratings of perceived exertion and respiratory exchange ratio values did not differ between trials. The ability to do more exercise after caffeine ingestion, without an accompanying increase in effort sensation, could motivate sedentary men to participate in exercise more often and so reduce adverse effects of inactivity on health [148].
**Physiological Effects of Caffeine on the Nervous System**

**Effects of caffeine on the brain**

Caffeine intake results in a decrease in perception of effort, but the cortical substrates of this perceptual effect of caffeine are unknown. The aim of our randomized counterbalanced double-blind crossover study was to investigate the effect of caffeine on the motor-related cortical potential (MRCP) and its relationship with rating of perceived effort (RPE). It was also investigated whether MRCP is associated with the increase in RPE occurring over time during submaximal exercise. Twelve healthy female volunteers performed 100 intermittent isometric knee extensions at 61 ± 5 percent of their maximal torque 1.5 h after either caffeine (6 mg/kg) or placebo ingestion, while RPE, vastus lateralis electromyogram (EMG), and MRCP were recorded. RPE and MRCP amplitude at the vertex during the first contraction epoch (0-1 s) were significantly lower after caffeine ingestion compared with placebo and were significantly higher during the second half of the submaximal intermittent isometric knee-extension protocol compared with the first half. No significant effects of caffeine and time-on-task were found for EMG amplitude and submaximal force output variables. The covariation between MRCP and RPE across both caffeine and time-on-task provides evidence in favor of the theory that perception of effort arises from neurocognitive processing of corollary discharges from premotor and motor areas of the cortex. Caffeine seems to reduce perception of effort through a reduction in the activity of cortical premotor and motor areas necessary to produce a submaximal force, and time-on-task has the opposite effect [163].

Caffeine can improve exercise performance when it is ingested at moderate doses (3-6 mg/kg body mass). Caffeine also has an effect on the central nervous system (CNS), and it is now recognized that most of the performance-enhancing effect of caffeine is accomplished through the antagonism of the adenosine receptors, influencing the dopaminergic and other neurotransmitter systems. Adenosine and dopamine interact in the brain, and this might be one mechanism to explain how the important components of motivation (i.e. vigor, persistence and work output) and higher-order brain processes are involved in motor control. Caffeine maintains a higher dopamine concentration especially in those brain areas linked with "attention". Through this neurochemical interaction, caffeine improves sustained attention, vigilance, and reduces symptoms of fatigue. Other aspects that are localized in the CNS are a reduction in skeletal muscle pain and force sensation, leading to a reduction in perception of effort during exercise and therefore influencing the motivational factors to sustain effort during exercise. Because not all CNS aspects have been examined in detail, one should consider that a placebo effect may also be present. Overall, it appears that the performance-enhancing effects of caffeine reside in the brain, although more research is necessary to reveal the exact mechanisms through which the CNS effect is established [164].

**Effect on morning reduction in neuromuscular performance**

To investigate whether caffeine ingestion counteracts the morning reduction in neuromuscular performance associated with the circadian rhythm pattern 12 highly resistance-trained men underwent a battery of neuromuscular tests under three different conditions; i) morning (10:00 a.m.) with caffeine ingestion (i.e. 3 mg/kg; AM(CAFF) trial); ii) morning (10:00 a.m.) with placebo ingestion (AM(PLAC) trial); and iii) afternoon (18:00 p.m.) with placebo ingestion (PM(PLAC) trial). A randomized, double-blind, crossover, placebo controlled experimental design was used, with all subjects serving as their own controls. The neuromuscular test battery consisted in the measurement of bar displacement velocity during free-weight full-squat (SQ) and bench press (BP) exercises against loads that elicit maximum strength (75 % 1RM load) and muscle power adaptations (1 m/s load). Isometric maximum...
voluntary contraction (MVC(LEG)) and isometric electrically evoked strength of the right knee (EVOK(LEG)) were measured to identify caffeine’s action mechanisms. Steroid hormone levels (serum testosterone, cortisol and growth hormone) were evaluated at the beginning of each trial (PRE). In addition, plasma norepinephrine (NE) and epinephrine were measured PRE and at the end of each trial following a standardized intense (85 % 1RM) 6 repetitions bout of SQ (POST). In the PM(PLAC) trial, dynamic muscle strength and power output were significantly enhanced compared with AM(PLAC) treatment (3.0-7.5 %). During AM(CAFF) trial, muscle strength and power output increased above AM(PLAC) levels (4.6-5.7 %) except for BP velocity with 1 m/s load. During AM(CAFF), EVOK(LEG) and NE (a surrogate of maximal muscle sympathetic nerve activation) were increased above AM(PLAC) trial. These results indicate that caffeine ingestion reverses the morning neuromuscular declines in highly resistance-trained men, raising performance to the levels of the afternoon trial. The electrical stimulation data, along with the NE values, suggest that caffeine increases neuromuscular performance having a direct effect in the muscle [165].

**Relationship between daily caffeine consumption and accuracy of time estimation**

The present study examined the relationship between regular caffeine consumption and time estimation. Sixty participants (aged 18-57 years, mean 24 years) completed a 47 s time estimation exercise and questionnaires related to daily caffeine consumption and perceptions of time. We hypothesized that the effects of caffeine on time estimation would follow a U-shaped pattern such that individuals who reported moderate amounts of daily caffeine would be more accurate in their perceptions of time than would those who reported high amounts of caffeine intake or no daily caffeine consumption. Timing accuracy was computed by dividing participant-reported time by actual time (47 s). Timing accuracy followed a U-shaped curve such that those respondents who reported ‘low’ daily caffeine consumption (< 135 mg/day, n=24) were the most accurate in their time estimates (mean= 44.2 s). Individuals who reported no caffeine (mean= 69.3 s; n=7) or “high” daily caffeine consumption (mean=56.2 s; >135 mg/day, n=28) were less accurate in their time estimates. Findings suggest that “low” daily caffeine consumption may enhance time estimation accuracy above that of “high” or no daily caffeine consumption [166].

**Caffeine lowers threshold for exercise-induced beta-endorphin and cortisol release**

To examine the effect of caffeine ingestion on muscle glycogen utilization and the neuroendocrine axis during exercise, it was studied 20 muscle glycogen-loaded subjects who were given placebo or caffeine (6 mg/kg) in a double blinded fashion 90 min before cycling for 2 h at 65 percent of their maximal oxygen consumption. Exercise-induced glycogen depletion in the thigh muscle was noninvasively measured by means of 13C nuclear magnetic resonance spectroscopy (NMR) spectroscopy, and plasma concentrations of substrates and neuroendocrine hormones, including beta-endorphins, were also assessed. Muscle glycogen content was increased 140 percent above normal values on the caffeine trial day. After cycling for 2 h, caffeine ingestion was associated with a greater increase in plasma lactate, epinephrine, and cortisol levels. However, plasma free fatty acid concentrations increased and muscle glycogen content decreased to the same extent in both groups. At the same time, plasma beta-endorphin levels almost doubled in the caffeine-treated group, whereas no change occurred in the placebo group. It was concluded that caffeine ingestion 90 min before prolonged exercise does not exert a muscle glycogen-sparing effect in athletes with high muscle glycogen content. However, these data suggest that caffeine lowers the threshold for exercise-induced beta-endorphin and cortisol release, which may contribute to the reported benefits of caffeine on exercise endurance [167].
Caffeine in central fatigue

Strong or sustained contractions can fatigue muscles and reduce their capacity to generate maximal voluntary force. This impairment may result not only from reduced force from the muscle but also from reduced output from the spinal motoneuron pool. This is known as “central fatigue.” Demonstration of the suboptimal volitional output from the motoneuron pool is easily achieved using methods that interpolate an extra motor impulse via an external agency, such as a nerve stimulator. If a twitchlike increment in force is obtained with stimulation of the nerve innervating part of the contracting muscles, suboptimal motoneuron output is obvious. However, quantitation of the level of output to the muscle group is less easy. For example, whereas many motor nerves innervate the bulk of synergists in a particular task, they also innervate antagonists (e.g., stimulation of the common peroneal nerve contracts ankle dorsiflexors but also some plantar flexors, stimulation of the femoral nerve activates knee extensors but also two weak knee flexors), and hence the size of the superimposed twitch can be contaminated by unwanted force produced by antagonists, and voluntary activation is spuriously high. As supraspinal fatigue develops with exercise, there are dramatic changes within the motor cortex and also in corticospinal “connectivity” with motoneurons. For example, the silent period in the electromyogram (EMG) after cortical stimulation lengthens (a reflection of intracortical inhibition) and the initial excitatory EMG response (motor evoked potential, MEP) increases during fatiguing contractions, and there are depressions in MEPs and cervicomedullary evoked potentials (a test of corticomotoneuronal function) after exercise. It has been used caffeine ingestion to probe links between force and motor cortical output. It is argued that, if a decrease in “central excitability” causes central fatigue with its associated failure in voluntary activation of the muscle, then caffeine, which increases central excitability (as represented by the size of the MEP), should reduce the fatiguing decline in voluntary force. Sets of repeated knee extensor contractions reduced force by about 35 percent, and performance was measured in two sessions: one with, and one without prior caffeine administration (6 mg/kg). TMS was delivered during weak contractions between exercise sets. Femoral nerve stimulation was applied during and after maximal voluntary contractions (MVCs) to assess changes in the MEP and in voluntary activation. Before fatigue, caffeine increased voluntary activation in brief maximal efforts (by 2-3 %) and increased the baseline MEP during very weak contractions (3 % MVC). During fatiguing exercise, MEP size was elevated by caffeine compared with placebo, whereas maximal voluntary activation and force recovery were unaffected. That is, increased central excitability did not ameliorate the fatiguing-related falls in voluntary activation and voluntary force. Furthermore, after caffeine, the MEP at the end of fatiguing exercise was not decreased compared with control values, so the impairment of voluntary activation seen at this moment is not due to impaired central excitability [168].

Dose-dependent neuromuscular effects

The purpose of one study was to determine the oral dose of caffeine needed to increase muscle force and power output during all-out single multijoint movements. Thirteen resistance-trained men underwent a battery of muscle strength and power tests in a randomized, double-blind, crossover design, under four different conditions: (a) placebo ingestion (PLAC) or with caffeine ingestion at doses of (b) 3 mg/kg body weight (CAFF 3 mg), (c) 6 mg/kg (CAFF 6 mg), and (d) 9 mg/kg (CAFF 9 mg). The muscle strength and power tests consisted in the measurement of bar displacement velocity and muscle power output during free-weight full-squat (SQ) and bench press (BP) exercises against four incremental loads (25 %, 50 %, 75 %, and 90 % one-repetition maximum, 1RM). Cycling peak power output was measured using a 4-s inertial load test. Caffeine side effects were evaluated at the end of each trial and 24 h later. Mean propulsive velocity at light loads (25-50 % 1RM) increased significantly above PLAC for all caffeine doses (5.4-8.5 %). At the medium load (75 % 1RM), CAFF 3 mg did not improve SQ or BP muscle power or BP
velocity. CAFF 9mg was needed to enhance BP velocity and SQ power at the heaviest load (90 % 1RM) and cycling peak power output (6.8-11.7 %). The CAFF 9 mg trial drastically increased the frequency of the adverse side effects (15-62 %). The ergogenic dose of caffeine required to enhance neuromuscular performance during a single all-out contraction depends on the magnitude of load used. A dose of 3 mg/kg is enough to improve high-velocity muscle actions against low loads, whereas a higher caffeine dose (9 mg/kg) is necessary against high loads, despite the appearance of adverse side effects [169].

*Caffeine's ergogenic effects on neuromuscular and perceptual factors*

One investigation sought to examine the effects of caffeine on perceptual and physiological responses to endurance exercise. Two experiments were performed. In study A, 14 participants were tested. Maximal voluntary strength (MVC) and motor-unit recruitment of the knee extensors and elbow flexors were tested before and 60 min after ingestion of a 5-mg/kg dose of caffeine or placebo and after completion of 40 min of exercise (30 min of submaximal leg or arm cycling followed by a 10-min time-trial performance). Muscle pain, RPE, and cardiorespiratory variables were assessed throughout. To determine the effects of caffeine on muscle pain and RPE during high-intensity exercise, a second study (study B) was performed. Twelve participants exercised at 95 percent of their gas exchange threshold (GET) and at 70 percent of the difference between their GET and VO2peak (70 % delta) after caffeine and placebo ingestion. Compared to placebo, caffeine improved MVC (6.3 %) and motor-unit recruitment (5.5 %) in the knee extensors, but not the elbow flexors, and reduced muscle pain and RPE during both submaximal cycling modalities. Caffeine ingestion improved time-trial performance during leg cycling (4.9 % ± 6.5 %), but not arm crank cycling (2.1 % ± 8.2 %), but the effect on pain and RPE was eliminated. Caffeine ingestion had no effect on pain or RPE during cycling at 95 percent GET and motor-unit recruitment. The results suggest that augmented strength and motor-unit recruitment, rather than reductions in pain and effort, may underlie caffeine's ergogenic effect on endurance exercise [170].

*Ratings of perceived exertion*

The purpose of one study was to use the meta-analytic approach to examine the effects of caffeine ingestion on ratings of perceived exertion (RPE). Twenty-one studies with 109 effect sizes (ESs) met the inclusion criteria. Coding incorporated RPE scores obtained both during constant load exercise (n=89) and upon termination of exhausting exercise (n=20). In addition, when reported, the exercise performance ES was also computed (n=16). In comparison to placebo, caffeine reduced RPE during exercise by 5.6 percent, with an equivalent RPE ES of -0.47. These values were significantly greater than RPE obtained at the end of exercise. In addition, caffeine improved exercise performance by 11 percent. Regression analysis revealed that RPE obtained during exercise could account for approximately 29 percent of the variance in the improvement in exercise performance. The results demonstrate that caffeine reduces RPE during exercise and this may partly explain the subsequent ergogenic effects of caffeine on performance [171].

One study examined effects of caffeine on session ratings of perceived exertion (RPE) following 30 min constant-load cycling. Individuals (n=15) of varying aerobic fitness completed a max trial and two 30 min cycling bouts (double-blind, counterbalanced) following ingestion of 6 mL/kg of caffeine or matched placebo. RPE overall, legs and breathing were estimated every 5 min and session RPE was estimated 30 min post-exercise using the OMNI pictorial scale. Session RPE for caffeine and placebo trails were compared using paired t test. Between-trial comparisons of HR, RPE overall, RPE legs and RPE breathing were analyzed using an independent 2 (trial) × 6 (time point) repeated measures analysis of variance (ANOVA) for each dependent variable. Caffeine resulted in a significantly lower
session RPE for caffeine versus placebo. Acute perceptual responses were significantly lower for caffeine for RPE overall (15, 20, 25, and 30 min), RPE breathing (15, 20, 25, and 30 min) and RPE legs (20 and 30 min). Survey responses post-exercise revealed greater feelings of nervousness, tremors, restlessness and stomach distress following caffeine versus placebo. Blunted acute RPE and survey responses suggest participants responded to caffeine ingestion. Caffeine decreased acute RPE during exercise which could partially account for lower session RPE responses. However, decreased session RPE could also reveal a latent analgesic affect of caffeine extending into recovery. Extending the understanding of session RPE could benefit coaches in avoiding overtraining when adjusting training programs [172].

Caffeine containing energy drinks is commonly consumed in the belief that it will enhance the quality of an exercise session and enhance mood. However, studies examining their efficacy are sparse. The aim of this study was to examine the effect of a caffeinated energy drink on leg pain perception, perceived exertion, mood state and readiness to invest effort pre, during and post 60 min cycling exercise. Fourteen active individuals (7 males, 7 females, mean age 24 years), completed two 60 min cycling trials at an intensity of 60 percent VO₂max preceded by ingestion of solutions containing either a caffeinated energy drink or placebo using a double-blind, deceptive, crossover design. During exercise, RPE (6-20 scale), leg pain (0-10 scale), heart rate (HR) and blood lactate (Bla) were recorded. Participants also completed measures of mood state and readiness to invest physical effort (RTIPE) pre- and post-exercise. Repeated measures analysis of variance was used to assess differences in all variables and across time and treatments, with gender used as a between subjects variable. Results indicate that HR was significantly higher from 30 to 60 min and RPE and pain perception were significantly lower from 20 to 60 min in the energy drink condition compared to placebo. Lactate was significantly higher in the last 15 min of the energy drink trial and RTIPE increased significantly more from pre-ingestion to pre-exercise post-ingestion in the energy drink condition compared to placebo. No gender differences were evident. The data revealed positive effects of energy drink ingestion on perception of exertion, leg muscle pain perception and readiness to invest effort during submaximal cycling in active adults [173].

Pre-existent expectancy regarding the effects of the caffeine

One study investigated the impact of pre-existent expectancy regarding the effects of the caffeine load of a drink and the perception of the caffeine content on subjective mood and vigilance performance. Caffeine deprived participants (n=25) were tested in four conditions (within subjects design), using a 2×2 design, with caffeine load and information regarding the caffeine content of the drink. In two sessions, they were given caffeinated coffee and in two were given decaffeinated coffee. Within these two conditions, on one occasion they were given accurate information about the drink and on the other they were given inaccurate information about the drink. Mood and vigilance performance were assessed post ingestion. Caffeine was found to enhance performance, but only when participants were accurately told they were receiving it. When decaffeinated coffee was given, performance was poorer, irrespective of expectancy. However, when caffeine was given, but participants were told it was decaffeinated coffee, performance was as poor as when no caffeine had been administered. There were no easily interpretable effects on mood. The pharmacological effects of caffeine appear to act synergistically with expectancy [174].

Impact of caffeine on pain perception

There is a large body of literature reporting that the perception of pain during moderate and intense exercise is reduced following the ingestion of 5-10 mg/kg bm caffeine in men and women. However, not all studies have reported an attenuation of pain during strenuous or
high-intensity exercise. It should be noted that pain perception was 74 percent higher in the hot versus cool trial and caffeine was able to partially attenuate this [021].

One double-blind, within-subjects experiment examined the effects of acute caffeine ingestion on perceptions of muscle pain following a bout of high-intensity, upper-body resistance exercise to failure. Moderately trained males (n=18) ingested a dose of caffeine (5 mg/kg) or placebo in a randomised and counterbalanced order and 1 hour later completed bench press exercise to failure at an intensity of 60 percent 1 repetition maximum. Repetitions completed was taken as a measure of performance, peak heart rate was determined via heart rate telemetry during the exercise bout, rating of perceived exertion (RPE) and upper body muscle pain was recorded immediately upon failure of the exercise task and peak blood lactate concentration was determined post-exercise. Caffeine resulted in improved repetitions to failure, greater peak blood lactate, and lower RPE compared to placebo. Muscle pain perception was also significantly lower in the caffeine condition compared to placebo. These results support prior studies using aerobic based exercise modes in suggesting that caffeine ingestion can dampen exercise-induced muscle pain. Specifically, caffeine ingestion enhances muscular strength performance and reduces upper body muscle pain perception immediately following a bout of high-intensity resistance exercise to failure [175].

Caffeine has been shown to reduce leg-muscle pain during submaximal cycle ergometry, as well as in response to eccentric exercise. However, less is known about its analgesic properties during non-steady-state, high-intensity exercise. The primary aim of one study was to examine the effect of 2 doses of caffeine on leg pain and rating of perceived exertion (RPE) during repeated bouts of high-intensity exercise. Fifteen active men (age 26 ± 4 year) completed 2 bouts of 40 repetitions of “all-out” knee extension and flexion of the dominant leg at a contraction velocity equal to 180°/s. Before each trial, subjects abstained from caffeine intake and intense exercise for 48 hr. Over 3 days separated by 48 hr, subjects ingested 1 of 3 treatments (5 mg/kg or 2 mg/kg of anhydrous caffeine or placebo) in a randomized, single-blind, counterbalanced, crossover design. Leg-muscle pain and RPE were assessed during and after exercise using established categorical scales. Across all treatments, pain perception was significantly increased during exercise, as well as from bout 1 to 2, yet there was no effect of caffeine on pain perception or RPE. Various measures of muscle function were improved with a 5-mg/kg caffeine dose versus the other treatments. In the 5-mg/kg trial, it is plausible that subjects were able to perform better with similar levels of pain perception and exertion [176].

One experiment examined the effect of a moderate dose of caffeine on quadriceps muscle pain during a bout of high-intensity cycling in low- versus high-caffeine-consuming males. College-age men who were low (< 100 mg/day; n=12) or high (> 400 mg/day; n=13) habitual caffeine consumers ingested caffeine (5 mg/kg body weight) or a placebo in a counterbalanced order and 1 hr later completed 30 min of cycle ergometry at 75-77 percent of peak oxygen consumption. Perceptions of quadriceps muscle pain, as well as oxygen consumption, heart rate, and work rate, were recorded during both bouts of exercise. Caffeine ingestion resulted in a statistically significant and moderate reduction in quadriceps muscle-pain-intensity ratings during the 30-min bout of high-intensity cycle ergometry compared with placebo ingestion in both low and high caffeine consumers. The results suggest that caffeine ingestion is associated with a moderate hypoalgesic effect during high-intensity cycling in college-age men who are low or high habitual caffeine consumers, but future work should consider better defining and differentiating pain and effort when examining the effects of caffeine during acute exercise [177].
**Moderated effect of caffeine on anxiety**

One experiment examined the effect of a moderate dose of caffeine on perceptions of leg-muscle pain during a bout of high-intensity cycling exercise and the role of anxiety sensitivity in the hypoalgesic effect of caffeine on muscle pain during exercise. Sixteen college-age women ingested caffeine (5 mg/kg body weight) or a placebo and 1 hour later completed 30 min of cycling on an ergometer at 80 percent of peak aerobic capacity. The conditions were completed in a counterbalanced order, and perceptions of leg-muscle pain were recorded during the bouts of exercise. Caffeine resulted in a large reduction in leg-muscle pain-intensity ratings compared with placebo, and the reduction in leg-muscle pain-intensity ratings was larger in those with lower anxiety-sensitivity scores than those with higher anxiety-sensitivity scores. The results support that caffeine ingestion has a large effect on reducing leg-muscle pain during high-intensity exercise, but the effect is moderated by anxiety sensitivity [178].

**Psychological effects of caffeine**

Caffeine’s metabolic and performance effects have been widely reported. However, caffeine’s effects on affective states during prolonged exercise are unknown. Therefore, this was examined in one study. Following an overnight fast and in a randomised, double-blind, counterbalanced design, twelve endurance trained male cyclists performed 90 min of exercise at 70 percent of VO$_2$max 1h after ingesting 6 mg/kg body weight of caffeine (CAF) or placebo (PLA). Dimensions of affect and perceived exertion were assessed at regular intervals. During exercise, pleasure ratings were better maintained in the CAF trial compared to the PLA trial with significantly higher ratings at 15, 30 and 75 min. Perceived exertion increased throughout exercise and values, overall, were significantly lower in the CAF trial compared to the PLA trial. Perceived arousal was elevated during exercise but did not differ between trials. Overall, the results suggest that a moderate dose of CAF ingested 1h prior to exercise maintains a more positive subjective experience during prolonged cycling. This observation may partially explain caffeine’s ergogenic effects [179].

One study examined the effect of coffee ingestion on physiological responses and ratings of perceived exertion (RPE) during submaximal endurance exercises by 10 healthy young adults. Participants performed a submaximal endurance cycling exercise corresponding to 60% of maximum oxygen uptake capacity for 60 min. They drank either caffeinated coffee with a caffeine content of 6 mg/kg body mass of each participant (Caf) or a decaffeinated coffee (Dec) 60 min. before starting exercise. Participants participated in the blind design experiment under both conditions at a one-week interval. Oxygen uptake, respiratory exchange ratio, heart rate, RPE, and plasma lactate concentration were measured during the endurance exercise. The RPE under the Caffeinated coffee condition during the last 60 min. of endurance exercise was significantly lower than that in the Decaffeinated coffee condition. However, no significant differences in any physiological response were observed between conditions. Thus, caffeine ingestion 60 min. before starting exercise had an insignificant effect on the physiological responses, except for RPE during submaximal endurance exercises for 60 min. Caffeine ingestion before endurance exercise of relatively low intensity may have a beneficial effect on psychological responses [180].

General Factor of Personality (GFP) research is an emergent field in personality research. One paper uses a theoretical mathematical model to predict the short-term effects of a dose of a stimulant drug on GFP and reports the results of an experiment showing how caffeine achieves this. This study considers the General Factor of Personality Questionnaire (GFPQ) a good psychometric approach to assess GFP. The GFP dynamic mechanism of change is based on the Unique Trait Personality Theory (UTPT). This theory proposes the existence of GFP which occupies the apex of the hierarchy of personality, and extends from an
impulsiveness-and-aggressiveness pole (approach tendency) to an anxiety-and-introversion pole (avoidance tendency). An experiment with 25 volunteers was performed. All the participants completed the GFPQ and the Sensation-Seeking Scale list of adjectives from the trait version of MAACL-R (Multiple Affect Adjective Checklist Revised) on an empty stomach. The participants in the experimental group (20) received 330 mg of caffeine. All the participants filled in a state version form with the sensation-seeking adjectives every 4.5 minutes. This study considers that the Sensation-Seeking Scale list of adjectives from the MAACL-R, available in both trait and state versions, is a good psychometric approach to assess GFP. The results show that GFP is modified by a single dose of caffeine in the direction predicted by the UTPT [181].

Caffeine choices prospectively predicts positive subjective effects d-amphetamine
Individuals vary in their subjective and behavioral response to psychomotor stimulants and these differences may be associated with the likelihood of developing problematic use of these drugs. The present study sought to determine whether individual differences in caffeine choice prospectively predict subjective response to acute doses of caffeine and d-amphetamine. In phase 1, Choosers and Nonchoosers of caffeine were identified using 10 independent choice trials in which subjects repeatedly chose between caffeine (200 mg/70 kg) and placebo. Choosers were defined as those who chose caffeine over placebo on ≥7 of the 10 trials; Nonchoosers were those who chose placebo on ≥7 trials. In Phase 2, Choosers and Nonchoosers were compared in their subjective response to caffeine (100, 200, 400 mg/70 kg) and d-amphetamine (5, 10, 20 mg/70 kg). Of the 22 participants completing the study, 11 met criteria for being a caffeine Chooser and 8 were Nonchoosers. In phase 1, Choosers reported higher ratings of positive (i.e., pleasant) and lower ratings of negative (i.e. unpleasant) effects of caffeine during the sampling sessions. In phase 2, caffeine Choosers reported more positive subjective effects and fewer negative effects of caffeine and d-amphetamine, particularly at the highest doses examined. It was concluded that individual differences in caffeine reinforcement predicted subsequent subjective response to both d-amphetamine and caffeine. This observation may have clinical utility for identifying individuals who are vulnerable to the reinforcing effects of abused psychomotor stimulants [182].

Experimental: performance-enhancing task considerations
Past animal studies of the performance-enhancing properties of stimulant drugs, such as caffeine, may have suffered from a number of procedural and ethical problems. For example, the housing condition of the animals was often not taken into consideration. As well, endurance tests, such as the forced swim task, sometimes involved ethically (and procedurally) questionable interference with natural swimming behaviour. Some of the manipulations, such as attaching a weight to the swimming animal's tail to increase the difficulty of the task and using mortality as a dependent variable, seem grotesque, even unnecessary. In this experiment, the performance-enhancing effects of caffeine in a modified forced swim task and a dominance task were evaluated using male and female rats as subjects (n=60), housed in either enriched or isolated environments. Analysis indicated that rats respond to caffeine as an interactive function of sex, housing, dose, and task characteristics. It was concluded that performance-enhancing properties of stimulant drugs may be the result of a complex interplay of variables, making simple generalizations questionable [183].

Influence of caffeine, cold and exercise on multiple choice reaction time
The effects of caffeine on psychomotor performance have been evaluated under resting conditions and in a thermoneutral environment. The hypothesis was that these effects could be modified by factors enhancing the level of alertness, such as exercise and cold exposure.
The purpose of one study was to follow up changes in the multiple choice reaction time (RT) during exercise at room and low ambient temperatures after caffeine or placebo administered in a double blind manner. Nine soccer players performed multistage, incremental exercise until volitional exhaustion on a bicycle ergometer at 22 degrees C or 4 degrees C, 1 h after ingestion of coffee with caffeine (CAF) or without it (PL). Immediately before exercise and at the end of each workload, RT and blood lactate (LA) were measured. Oxygen uptake (VO₂) and heart rate (HR) were recorded continuously. Blood LA threshold and the workload associated with the shortest RT were determined. During exercise at 22°C, RT was significantly shorter in CAF than in the PL test, while at 4 degrees C there were no differences in RT between CAF and PL trials. Cold exposure did not affect RT either at rest or during exercise. Neither caffeine nor cold exposure influenced the maximal VO₂, the maximal HR and LA threshold. It was concluded that in the thermoneutral environment, caffeine ingestion improved psychomotor performance during exercise, whilst at low ambient temperature this effect was blunted. These findings suggest that the stimulating action of caffeine depends on the level and source of arousal [184].

Effects of caffeine on sleep and arousal

Caffeine’s effect on autonomic nervous activity

The effects of caffeine ingestion on the activities of the autonomic nervous system (ANS) during endurance exercise at low intensity were investigated using a power spectrum analysis of heart rate variability. Placebo or caffeine (300 mg) capsules were randomly administered to the subjects. Each subject ingested the samples 2 h before cycling on an ergometer for 30 min at an intensity corresponding to 40-50 percent of his ventilatory threshold. The electrocardiogram, blood pressure (BP) and gas exchange parameters were monitored during rest and exercise. The results indicated that there were no significant differences in heart rate and systolic blood pressure between the trials. The spectrum integrated values of the low frequency power and total power components in the caffeine trial were significantly greater than in the placebo trial during exercise, which implied that activities of the ANS were augemnted by caffeine. Caffeine also induced enhanced lipid oxidation as shown by the significantly lower respiratory gas exchange ratio and increases in diastolic blood pressure during exercise. The results shed some light upon the relationship between the activity of the ANS, energy metabolism and BP. In conclusion, the results suggest that caffeinated beverages have a potential to be useful supplements to the prescription of exercise for individuals who experience a depressed activity of the ANS. The results also suggest that the experiment protocol used in this study is a sensitive and noninvasive method for evaluating the effects of various foods and nutrients on the activity of the ANS [185].

Effect on sleep

Several studies looking at caffeine use during periods of sleep deprivation have shown a benefit to caffeine administration in terms of alertness and neurocognitive performance. Time to fall asleep on the multiple sleep latency test (MSLT) following periods of sleep deprivation was increased with administration of caffeine. Similarly, performance on a driving simulator following a period of sleep deprivation was found to be improved with caffeine administration [012].

Impaired sleep female athletes using oral contraceptive steroids after coffee

In a randomised, double-blind, placebo-controlled crossover design, 10 females taking monophasic oral contraceptives completed 90 min intermittent treadmill-running 45 min after ingestion of 6 mg/kg body mass anhydrous caffeine or artificial sweetener (placebo). Water
(3 mL/kg every 15 min during exercise. Venous blood samples were taken before, during and after exercise, as well as after sleep (15 h post-ingestion), and levels of caffeine, paraxanthine, theobromine and theophylline were measured using high-performance liquid chromatography. Sleep quality was assessed using the Leeds Sleep Evaluation Questionnaire. Plasma caffeine concentration peaked 100 min after ingestion. Caffeine clearance was 0.95 ± 0.14 mL/min/kg while the elimination half-life of caffeine was 17.63 ± 8.06 h. Paraxanthine and theophylline levels were significantly elevated at 15 h with no significant change in theobromine. Sleep latency and subsequent quality of sleep was impaired following caffeine supplementation but there were no differences between trials for how participants were feeling upon awakening. This is the first controlled study to examine caffeine supplementation on sleep quality in female athletes taking a low-dose monophasic oral contraceptive steroid following an intermittent-exercise running protocol. The data shows that female athletes using monophasic oral contraceptive steroids will have impaired sleep quality following evening caffeine ingestion [186].

**Polysomnographic sleep disturbances**

In the United States, approximately 60 million Americans suffer from sleep disorders and about 22 million Americans report substance dependence or use disorders annually. Sleep disturbances are common consequences of substance use disorders and are likely found in primary care as well as in specialty practices. The aim of this review was to evaluate the effects of the most frequently used substances: nicotine, alcohol, opioids, cocaine, caffeine, and cannabis-have on sleep parameters measured by polysomnography (PSG) and related clinical manifestations. It was used electronic databases such as PubMed and PsycINFO to search for relevant articles. We only included studies that assessed sleep disturbances using polysomnography and reviewed the effects of these substances on six clinically relevant sleep parameters: Total sleep time, sleep onset latency, rapid-eye movement, REM latency, wake after sleep onset, and slow wave sleep. One review indicates that these substances have significant impact on sleep and that their effects differ during intoxication, withdrawal, and chronic use. Many of the substance-induced sleep disturbances overlap with those encountered in sleep disorders, medical, and psychiatric conditions. Sleep difficulties also increase the likelihood of substance use disorder relapse, further emphasizing the need for optimizing treatment interventions in these patients. The review highlights the importance of systematically screening for substance use in patients with sleep disturbances and highlights the need for further research to understand mechanisms underlying substances-induced sleep disturbances and on effective interventions addressing these conditions [187].

**Effects of caffeine on arousal**

Studies indicate that the change from closed to open eyes in a resting condition results in an increase in skin conductance level (SCL) and a global decrease in EEG alpha activity, both indicative of increased arousal. Other studies show that ingestion of caffeine also produces SCL increase and alpha reduction. One study investigated the additivity of the effects of these two independent arousing variables. EEG activity and SCL were recorded from 22 university students during both eyes-closed and eyes-open resting conditions, under the action of both caffeine and placebo, in a counterbalanced randomised double-blind study. SCL increased significantly from eyes-closed to eyes-open conditions, and from placebo to caffeine, with no interaction. Global reductions in EEG alpha amplitude were apparent with opening of the eyes and caffeine ingestion; again, there was no interaction. Caffeine had a larger effect than opening the eyes on SCL, but their relative effect sizes were reversed in alpha. The two dependent measures showed the predicted negative correlation in both eyes-closed placebo and eyes-open caffeine conditions, with the latter substantially reduced relative to the former. It was concluded that caffeine and opening the eyes have additive effects on two measures of arousal, increasing SCL and reducing global EEG alpha. However, the independent variable effects are not equivalent, suggesting that one or both measures reflect additional non-arousal processes. As caffeine is widely used by both
children and adults, knowledge of the additivity of arousal effects of caffeine and opening the eyes is important in controlling participant state in EEG studies [188].

**Effect on alertness**

Caffeine is one of the most widely consumed drugs in the world, taken socially and for its alertness- and performance-promoting actions. Extensive reports assert that caffeine increases alertness and cognitive performance levels and, when taken before exercise, demonstrates ergogenic properties. Caffeine ingestion has been associated with increased performance during endurance submaximal, and acute, high-intensity exercise. The exact mechanism of action for the performance effects of caffeine is unknown, although several physiologically and psychologically based theories exist as to how caffeine achieves increased performance capabilities. One paper outlined the known sites of caffeine activity in the body and discusses these with respect to the effects of caffeine observed during performance assessments [189].

**Maintenance of vigilance on night operations**

One study examined the effects of caffeine (CAF) on vigilance, marksmanship, and run performance during 27 h of sustained wakefulness in Special Forces personnel. There were 31 soldiers who were divided into placebo (PLAC, n=15) and CAF (n=16) groups. A 6.3-km control run was completed on the morning of Day 1. In the evening of Day 2, soldiers performed a control observation and reconnaissance vigilance task (ORVT) in the field. This 90-min task was repeated twice more between 02:00 and 06:00 on Day 3 during an overnight period of sleep deprivation. Marksmanship was assessed before and after the ORVT. PLAC or 200 mg of CAF gum was administered at 01:45, 03:45, and approximately 06:30 on Day 3. A final 6.3-km run commenced within 30 min of receiving the final dose. ORVT was maintained in CAF at control levels of 77 ± 13 percent during the overnight testing. However, values decreased significantly for PLAC from 77 ± 15 percent to 54 ± 29 percent and 51 ± 31 percent during the first and second overnight testing periods, respectively. CAF had no effect on marksmanship but improved 6.3-km run times. Run times slowed for PLAC from approximately 35 min during the control run; the changes in performance were significant between groups. It was concluded that CAF maintained vigilance and improved running performance during an overnight field operation for Special Forces personnel [190].

**Morning coffee**

Coffee is one of the most widely consumed beverages in the world and has a number of potential health benefits. Coffee may influence energy expenditure and energy intake, which in turn may affect body weight. However, the influence of coffee and its constituents – particularly caffeine – on appetite remains largely unexplored. The objective of one study was to examine the impact of coffee consumption (with and without caffeine) on appetite sensations, energy intake, gastric emptying, and plasma glucose between breakfast and lunch meals. In a double-blind, randomised crossover design. Participants (n=12, 9 women) completed 4 trials: placebo (PLA), decaffeinated coffee (DECAF), caffeine (CAF), and caffeine with decaffeinated coffee (COF). Participants were given a standardised breakfast labelled with $^{13}$C-octanoic acid and 225 mL of treatment beverage and a capsule containing either caffeine or placebo. Two hours later, another 225 mL of the treatment beverage and capsule was administered. Four and a half hours after breakfast, participants were given access to an ad libitum meal for determination of energy intake. Between meals, participants provided exhaled breath samples for determination of gastric emptying; venous blood and appetite sensations. Energy intake was not significantly different between the trials. Other than main effects of time, no significant differences were detected for appetite sensations or plasma glucose between treatments. Gastric emptying was not significantly different across
trials. No significant effects of decaffeinated coffee, caffeine or their combination were detected. However, the consumption of caffeine and/or coffee for regulation of energy balance over longer periods of time warrant further investigation [191].

Sleep-related vehicle accidents are prevalent early morning, especially in younger drivers. In two independent studies following a night of either restricted or nil sleep, young experienced drivers drove for 2 hr (0600-0800 h) continuously in an immobile car on an interactive, computer-generated, dull, and monotonous roadway. This exercise followed ingestion (at 0530 h) of 200 mg caffeine (= 2-3 cups coffee) versus placebo, counterbalanced, double blind. Driving incidents (lane drifting), subjective sleepiness, and 4-11 Hz electro-encephalogram (EEG) activity were logged. In Study 1 (sleeping 0000-0500 h), caffeine significantly reduced incidents and subjective sleepiness throughout the 2-hr drive, and EEG power for the second 30-min period. In Study 2 (no sleep), sleepiness affected all measures profoundly, and driving was terminated after 1 hr. Nevertheless, caffeine reduced incidents significantly for the first 30 min and subjective sleepiness for the hour. This caffeine dose, feasibly taken via coffee, effectively reduces early morning driver sleepiness for about 30 min following nil sleep, and for around 2 hr after sleep restriction [192].

**Effect on insomnia, nervousness, and activeness**

The use of caffeine containing energy drinks has dramatically increased in the last few years, especially in the sport context because of its reported ergogenic effect. The ingestion of low to moderate doses of caffeinated energy drinks has been associated with adverse side effects such as insomnia or increased nervousness. The aim of one study was to assess psycho-physiological changes and the prevalence of side effects resulting from the ingestion of 3 mg caffeine/kg body mass in the form of an energy drink. In a double-blind and placebo controlled experimental design, ninety experienced and low-caffeine-consuming athletes (fifty-three male and thirty-seven female) in two different sessions were provided with an energy drink that contained 3 mg/kg of caffeine or the same decaffeinated energy drink (placebo; 0 mg/kg). At 60 min after the ingestion of the energy drink, participants completed a training session. The effects of ingestion of these beverages on psycho-physiological variables during exercise and the rate of adverse side effects were measured using questionnaires. The caffeinated energy drink increased self-perceived muscle power during exercise compared with the placebo beverage (6.4 vs 5.7). Moreover, the energy drink produced a higher prevalence of side effects such as insomnia (31 vs 10), nervousness (13 vs 0) and activeness (17 vs 4) than the placebo energy drink. There were no sex differences in the incidence of side effects. The ingestion of an energy drink with 3 mg/kg of caffeine increased the prevalence of side effects. The presence of these side effects was similar between male and female participants [193].

**Effect on nocturnal sleep**

In athletes, caffeine use is common although its effects on sleep have not been widely studied. This randomised, double-blind, placebo-controlled crossover trial investigated the effects of late-afternoon caffeine and carbohydrate-electrolyte (CEB) co-ingestion on cycling performance and nocturnal sleep. Six male cyclists/triathletes (age 28 years) completed an afternoon training session (TS; cycling 80 min; 65 % VO₂max) followed by a 5 kJ/kg cycling time trial (TT). Caffeine (split dose 2 × 3 mg/kg) or placebo was administered 1 h prior and 40 min into the TS. A 7.4 percent CEB was administered during the TS, followed 30 min after by a standardised evening meal. Participants retired at their usual bedtime and indices of sleep duration and quality were monitored via polysomnography. All participants performed better in the caffeine TT while ratings of perceived exertion and heart rate were lower in the caffeine TS. Caffeine intake induced significant disruptions to a number of sleep indices including increased sleep onset latency and decreased sleep efficiency, rapid eye movement
sleep and total sleep time. The study supports a performance-enhancing effect of caffeine, although athletes (especially those using caffeine for late-afternoon/evening training and competition) should consider its deleterious effects on sleep [194].

**Physical performance during 24 h of active wakefulness**

Reductions in both cognitive and physical performance occur during periods of sleep loss with sustained operations. It was the purpose of this study to examine the effects of caffeine on activities chosen to simulate the physical challenges that might occur during a military scenario involving a period of sleep loss. There were 16 subjects (mean 27 years) who completed a double-blind caffeine and placebo trial involving a control day and sleep period followed by 28 h of sleep deprivation. A 400-mg dose of caffeine was administered at 21:30 followed by subsequent 100-mg doses at 03:00 and 05:00. At 22:00, subjects began a 2-h forced march followed by a sandbag piling task. A treadmill run to exhaustion at 85 percent of maximal aerobic power was performed at 07:00 of the second day of sleep deprivation. Caffeine had no effect on the heart rate or oxygen consumption, but rating of perceived exertion (RPE) was reduced with caffeine during the forced march. Time to complete the sandbag piling task during set 1 was significantly reduced with caffeine compared with placebo but there was no difference during set 2 and RPE was increased. Time to exhaustion was significantly increased 25 percent during the run with caffeine compared with placebo and caffeine maintained performance at control levels. It was concluded that caffeine is an effective strategy to maintain physical performance during an overnight period of sleep loss at levels comparable to the rested state [195].

**Influence on circadian rhythms**

Although caffeine alters sleep in many animals, whether or not it affects mammalian circadian clocks remains unknown. It was found that incubating cultured mammalian cell lines, human osteosarcoma U2OS cells and mouse fibroblast NIH3T3 cells, with caffeine lengthened the period of circadian rhythms. Adding caffeine to ex vivo cultures also lengthened the circadian period in mouse liver explants from Per2::Luciferase reporter gene knockin mice, and caused a phase delay in brain slices containing the suprachiasmatic nucleus, where the central circadian clock in mammals is located. Furthermore, chronic caffeine consumption ad libitum for a week delayed the phase of the mouse liver clock in vivo under 12 h light-dark conditions and lengthened the period of circadian locomotor rhythms in mice under constant darkness. The results showed that caffeine alters circadian clocks in mammalian cells in vitro and in the mouse ex vivo and in vivo [196].
CAFFEINE EFFECTS ON GLUCOSE HOMEOSTASIS

Caffeine is a substance that has been used in our society for generations, primarily for its effects on the central nervous system that causes wakefulness. Caffeine supplementation has become increasingly more popular as an ergogenic aid for athletes and considerable scientific evidence supports its effectiveness. Because of their potential to alter energy metabolism, the effects of coffee and caffeine on glucose metabolism in diabetes have also been studied both epidemiologically and experimentally. Predominantly targeting the adenosine receptors, caffeine causes alterations in glucose homeostasis by decreasing glucose uptake into skeletal muscle, thereby causing elevations in blood glucose concentration. Caffeine intake has also been proposed to increase symptomatic warning signs of hypoglycemia in patients with type 1 diabetes and elevate blood glucose levels in patients with type 2 diabetes. Other effects include potential increases in glucose counter-regulatory hormones such as epinephrine, which can also decrease peripheral glucose disposal. Despite these established physiological effects, increased coffee intake has been associated with reduced risk of developing type 2 diabetes in large-scale epidemiological studies. One review highlighted the known effects of caffeine on glucose homeostasis and diabetes metabolism during rest and exercise [057].

Effect of caffeine on glycogen

*Caffeine’s effect of inhibition of glycogen phosphorylase*

Caffeine reduces fatigue and increases concentration and alertness, and athletes regularly use it as an ergogenic aid. Caffeine-induced increases in performance have been observed in aerobic as well as anaerobic sports. Trained athletes seem to benefit from a moderate dose of 5 mg/kg, however, even lower doses of caffeine (1.0-2.0 mg/kg) may improve performance. Some groups found significantly improved time trial performance or maximal cycling power, most likely related to a greater reliance on fat metabolism and decreased neuromuscular fatigue, respectively. Theophylline, a metabolite of caffeine, seems to be even more effective in doing so. The effect of caffeine on fat oxidation, however, may only be significant during lower exercise intensities and may be blocked at higher intensities. It was found that ingestion of a high dose of caffeine before exercise reduced muscle glycogenolysis in the initial 15 min of exercise by increasing free fatty acid (FFA) levels which inhibits glycolysis and spares glycogen for later use. Caffeine’s effect of inhibition of glycogen phosphorylase has also been shown in vitro as well as its effect on increasing HSL activity. The effect of caffeine on adipose triglyceride lipase has not been studied and warrants investigation. Following caffeine administration prior to and after the onset of cycling, it was found that plasma free fatty acid levels were increased 30 percent compared to placebo. This action might be mediated by inhibition of the enzyme phosphodiesterase, thereby yielding higher levels of cAMP, which has been identified as important molecule for glycogen metabolism and lipolysis. Phosphodiesterase inhibition has been observed only at high concentrations. When direct Fick measurements were applied, it was not found altered CHO or fat metabolism, at least in the monitored leg. Further research is needed to evaluate the effect of caffeine on lipolysis, especially during higher exercise intensities [011].

*Impact on glycogen accumulation*

It was determined the effect of coingestion of caffeine with carbohydrate (CHO) on rates of muscle glycogen resynthesis during recovery from exhaustive exercise in seven trained subjects who completed two experimental trials in a randomized, double-blind crossover design. The evening before an experiment subjects performed intermittent exhaustive cycling and then consumed a low-CHO meal. The next morning subjects rode until volitional fatigue.
On completion of this ride subjects consumed either CHO (4 g/kg body mass) or the same amount of CHO + caffeine (8 mg/kg) during 4 hours of passive recovery. Muscle biopsies and blood samples were taken at regular intervals throughout recovery. Muscle glycogen levels were similar at exhaustion and increased by a similar amount (approximately 80 %) after 1 hour of recovery. After 4 hours of recovery caffeine resulted in higher glycogen accumulation. Accordingly, the overall rate of resynthesis for the 4-hour recovery period was 66 percent higher in caffeine compared with CHO. After 1 hour of recovery plasma caffeine levels had increased to 31 + 11 microM, which was a significant difference, and at the end of the recovery reached 77 + 11 microM with caffeine. Phosphorylation of CaMK(Thr286) was similar after exercise and after 1 hour of recovery, but after 4 hour CaMK(Thr286) phosphorylation was significantly higher in caffeine than CHO. Phosphorylation of AMP-activated protein kinase (AMPK)(Thr172) and Akt(Ser473) was similar for both treatments at all time points. It was provided the first evidence that in trained subjects coingestion of large amounts of caffeine (8 mg/kg) with CHO has an additive effect on rates of postexercise muscle glycogen accumulation compared with consumption of CHO alone [198].

**Higher rates of muscle glycogen accumulation after the co-ingestion of caffeine**

Augmented post-exercise recovery by increased rates of muscle glycogen resynthesis has been observed. It was found higher rates of muscle glycogen accumulation after the co-ingestion of caffeine with CHO during recovery in highly trained subjects. This might, at least in part, be mediated by the activation of AMP-activated protein kinase (AMPK) as it is involved in the translocation of glucose transporter 4 (GLUT4) to the plasma membrane. This mechanism enables the cell to take up glucose from the plasma and store it as glycogen. Not only does caffeine impact endurance, it has also been reported to benefit cognitive function and fine motor skills. While the performance enhancing effects of caffeine in moderate-to-highly trained endurance athletes are quite clear and well documented, its effects on anaerobic, high-intensity tasks are less well investigated. Whereas caffeine supplementation did not yield significant performance increases in a Wingate test in untrained subjects, it was reported that caffeine ingestion of 3 mg/kg could counter reductions in maximum dynamic strength and muscle power output on the morning (2.5-7.0 %) thereby increasing muscle performance to the levels found in the afternoon. Especially with regard to anaerobic performance caffeine’s adenosine receptor blocking effect in the CNS may be important. A possible explanation for the diverging effect of caffeine on anaerobic performance is that caffeine seems to benefit trained athletes who show specific physiological adaptations whereas performance gains in untrained subjects might be lost or masked by a high variability in performance [011].

**Caffeine at low muscle glycogen availability**

Commencing selected workouts with low muscle glycogen availability augments several markers of training adaptation compared with undertaking the same sessions with normal glycogen content. However, low glycogen availability reduces the capacity to perform high-intensity (>85 % of peak aerobic power, VO2peak) endurance exercise. We determined whether a low dose of caffeine could partially rescue the reduction in maximal self-selected power output observed when individuals commenced high-intensity interval training with low (LOW) compared with normal (NORM) glycogen availability. Twelve endurance-trained cyclists/triathletes performed four experimental trials using a double-blind Latin square design. Muscle glycogen content was manipulated via exercise-diet interventions so that two experimental trials were commenced with LOW and two with NORM muscle glycogen availability. Sixty minutes before an experimental trial, subjects ingested a capsule containing anhydrous caffeine (CAFF, 3 mg/kg body mass) or placebo (PLBO). Instantaneous power output was measured throughout high-intensity interval training (8 × 5 min bouts at maximum self-selected intensity with 1 min recovery). There were significant main effects for both preexercise glycogen content and caffeine ingestion on power output. LOW reduced power
output by approximately 8 percent compared with NORM, whereas caffeine increased power output by 2.8 and 3.5 percent for NORM and LOW, respectively. It was concluded that caffeine enhanced power output independently of muscle glycogen concentration but could not fully restore power output to levels commensurate with that when subjects commenced exercise with normal glycogen availability. However, the reported increase in power output does provide a likely performance benefit and may provide a means to further enhance the already augmented training response observed when selected sessions are commenced with reduced muscle glycogen availability [199].

**Caffeine ingestion increases estimated glycolytic metabolism**

The aim of one study was to evaluate the effect of caffeine ingestion on performance and estimated energy system contribution during simulated taekwondo combat and on post-exercise parasympathetic reactivation. Ten taekwondo athletes completed two experimental sessions separated by at least 48 hours. Athletes consumed a capsule containing either caffeine (5 mg/kg) or placebo (cellulose) one hour before the combat simulation (3 rounds of 2 min separated by 1 min passive recovery), in a double-blind, randomized, repeated-measures crossover design. All simulated combat was filmed to quantify the time spent fighting in each round. Lactate concentration and rating of perceived exertion were measured before and after each round, while heart rate (HR) and the estimated contribution of the oxidative (WAER), ATP-PCr (WPCR), and glycolytic (W[La-]) systems were calculated during the combat simulation. Furthermore, parasympathetic reactivation after the combat simulation was evaluated through 1) taking absolute difference between the final HR observed at the end of third round and the HR recorded 60-s after (HRR60s), 2) taking the time constant of HR decay obtained by fitting the 6-min post-exercise HRR into a first-order exponential decay curve (HRR\(\tau\)), or by 3) analyzing the first 30-s via logarithmic regression analysis (T30). Caffeine ingestion increased estimated glycolytic energy contribution in relation to placebo. However, caffeine did not improve performance as measured by attack number or attack time. Similarly, RPE, HR, oxidative and ATP-PCr energy contributions during the combat simulation were unaffected. Furthermore, T30, HRR60s, HRR\(\tau\), and HRRamp were not affected by caffeine ingestion. Caffeine ingestion increased the estimated glycolytic contribution during taekwondo combat simulation, but this did not result in any changes in performance, perceived exertion or parasympathetic reactivation [200].

**Caffeine increase of exogenous carbohydrate oxidation during exercise**

It is well established that carbohydrate (CHO) feeding during prolonged exercise can postpone fatigue and enhance endurance capacity. The benefits of ingesting CHO during exercise have been attributed to the maintenance of plasma glucose concentrations and high rates of CHO oxidation late in exercise when muscle and liver glycogen levels are low. Ingested CHO can be oxidized at rates of up to 1.0 g/min during prolonged exercise. It has been suggested that absorption of glucose in the intestine or output by the liver, regulates glucose appearance into the circulation and they are therefore rate-limiting factors for exogenous CHO oxidation. There is emerging indirect evidence that the sodium-dependent glucose transporter (SGLT1), which is responsible for the intestinal transport of glucose, becomes saturated at high glucose ingestion rates (>1.2 g/min). This would prevent further absorption and thus limit CHO availability to the circulation. Both carbohydrate (CHO) and caffeine have been used as ergogenic aids during exercise. It has been suggested that caffeine increases intestinal glucose absorption, but there are also suggestions that it may decrease muscle glucose uptake. The purpose of one study was to investigate the effect of caffeine on exogenous CHO oxidation. In a randomized crossover design, eight male cyclists (age 27) exercised at 64 percent of maximal oxygen uptake for 120 min on three occasions. During exercise subjects ingested either a 5.8 percent glucose solution (Glu; 48 g/h), glucose
with caffeine (Glu+Caf, 48 g/h + 5 mg/kg/h), or plain water (Wat). The glucose solution contained trace amounts of \([^{13}\text{C}]{\text{U}}\)glucose so that exogenous CHO oxidation could be calculated. CHO and fat oxidation were measured by indirect calorimetry, and \(^{13}\text{C}\) appearance in the expired gases was measured by continuous-flow IRMS. Average exogenous CHO oxidation over the 90- to 120-min period was 26 percent higher in Glu+Caf compared with Glu. Total CHO oxidation rates were higher in the CHO ingestion trials compared with Wat, but they were highest when Glu+Caf was ingested. There was also a trend toward an increased endogenous CHO oxidation with Glu+Caf. In conclusion, compared with glucose alone, 5 mg/kg/h of caffeine coingested with glucose increases exogenous CHO oxidation, possibly as a result of an enhanced intestinal absorption [201].

Caffeine doses of 3-9 mg/kg have been shown to improve exercise time to exhaustion, although there is still considerable debate about the exact mechanism by which caffeine exerts its effect. The performance effects are typically observed when caffeine is ingested 1 h preexercise, but they are also evident when it is ingested during prolonged exercise. It was identified improvements in time trial cycling performance when moderate amounts of caffeine (2.1 and 4.5 mg/kg) were ingested in combination with a 7 percent CHO solution during exercise. Both 2.1 and 4.5 mg/kg of caffeine added to a CHO solution resulted in faster performance times than water placebo or CHO alone. Interestingly, a study in which liquid chromatography with fluorescence labeling was applied to determine intestinal permeability and glucose absorption, caffeine significantly increased intestinal glucose absorption (55). In that study, consumption of small amounts of caffeine and glucose (1.4 mg/kg and 0.5 g/min, respectively) during 90 min cycling at 70 percent of maximum power output (\(\dot{W}_{\text{max}}\)) produced 23 percent greater intestinal glucose absorption compared with glucose or water consumption. Because it has previously been suggested that intestinal absorption is one of the main limiting factor for exogenous CHO oxidation, it was speculated that the ingestion of caffeine could increase the availability of ingested CHO and increase exogenous CHO oxidation during prolonged exercise. Oral and intravenous caffeine administration with glucose ingestion has been shown to induce a rise in blood glucose concentrations and reduce glucose uptake into tissues. Although muscle glucose uptake is not thought to be an important rate-limiting factor for exogenous CHO oxidation, these effects of caffeine on glucose disposal have the potential to reduce exogenous CHO oxidation [201].

Caffeine in combination with carbohydrate supplement

To determine the effects of co-ingesting caffeine (CAF) and carbohydrate (CHO) on high-intensity intermittent sprints (HIS) performance and physiological responses. Twelve active males underwent 4 interventions at least 7 days apart in a randomized, double-blind, placebo-controlled, balanced trial. A meal contained 65 percent CHO was provided 2 h before the HIS test. Participants ingested the placebo (PLA) or CAF (6 mg/kg BW) 1 h before taking an HIS test, and ingested a PLA or CHO solution (0.8 g/kg BW) before undergoing the testing protocol. The HIS protocol comprised ten sets of 5 × 4-s sprints on a cycle ergometer with a 2-min recovery between each set. There was no significant difference between peak power output and mean power output between trials. Compared with PLA, CAF + CHO resulted in a 5.2 percent reduction in total work, corresponding to a 24.7-25.7 percent increase in fatigue at the end stage of the HIS. The administration of CAF + CHO supplementation also resulted in an 11.1 percent increase in blood lactate, and elevated blood glucose concentrations throughout HIS testing compared with PLA. Cortisol concentrations also increased with CAF + CHO intake compared with PLA; however, there was no significant effect of CAF + CHO supplementation on testosterone concentrations. It was concluded that co-ingestion of CAF and CHO did not improve high-intensity sprint cycling performance or reduce fatigue in active males. Moreover, combined CAF and CHO supplementation might facilitate catabolism during prolonged high-intensity intermittent exercise [202].
Carbohydrate (CHO) and caffeine (CAF) both improve endurance performance. To determine by systematic literature review coupled with meta-analysis whether CAF ingested with CHO (CHO+CAF) improves endurance performance more than CHO alone, databases were searched using the keywords caffeine, endurance, exercise, carbohydrate, and performance. Criteria for inclusion were studies that used human subjects performing an endurance-exercise performance task and included both a CHO and CHO+CAF condition. Effect sizes were calculated as the standardized mean difference. Twenty-one studies met the criteria for analysis. Effect sizes for individual studies ranged from -0.08 (trivial effect favoring CHO) to 1.01 (large effect favoring CHO+CAF). The overall ES equaled 0.26 (95% confidence interval 0.15 to 0.38), indicating that CHO+CAF provides a small but significant performance benefit over CHO. Effect size was not significantly related to CAF dose, exercise duration, or performance-assessment method. To determine whether effect size of CHO+CAF versus CHO was different than CAF compared with water (placebo), a subgroup meta-analysis compared 36 CAF versus placebo studies against the 21 CHO+CAF versus CHO studies. The overall effect size for the former group of studies was nearly 2-fold greater than in CHO+CAF versus CHO studies. CHO+CAF ingestion provides a significant but small effect to improve endurance performance compared with CHO alone. However, the magnitude of the performance benefit that CAF provides is less when added to CHO than when added to placebo [203].

The aim of one study was to evaluate the effect of co-ingesting carbohydrate and caffeine (CHO+CAF) in comparison to carbohydrate (CHO) and placebo (PLA), during a reliable soccer-specific test. Eight university-standard soccer players ingested a PLA, a 6.4 percentCHO or 6.4 percent CHO and 160 mg CAF (CHO+CAF) solution on three occasions, in a double-blind randomized cross-over design, with each trial separated by 7 days. The protocol was 90 min in duration, made up of ten 6 min exercise blocks, each followed by soccer-specific skills tests (agility, dribbling, heading and kicking accuracy). Dependant variables (agility, dribbling, heading, kicking accuracy, glucose, lactate, HR and RPE) were analyzed using one-way repeated measures ANOVA. Significant difference was found between CHO+CAF, CHO and PLA for each of the soccer-specific skill tests. Significant improvement was observed in agility time in CHO versus PLA trials, although no significant difference was reported for dribbling, heading and kicking accuracy. Blood glucose and lactate were significantly elevated with CHO+CAF supplementation over PLA, but there was no difference compared to CHO. Blood glucose increased significantly in the CHO trial compared to PLA, with no difference between CHO+CAF and CHO. No significant difference was reported for HR and RPE values across all trial conditions. Skill performance during simulated soccer activity improved with CHO+CAF supplementation in comparison to both CHO and PLA. CHO+CAF co-ingestion had no ergogenic benefit over CHO in the maintenance and availability of blood glucose however, CHO+CAF co-ingestion did allow players to sustain a higher work intensity as opposed to CHO and PLA beverages as shown by elevated blood lactate levels [204].

The aim of one study was to test the hypothesis that adding caffeine to postexercise carbohydrate (CHO) feedings improves subsequent high-intensity interval-running capacity compared with CHO alone. In a repeated-measures design, 6 men performed a glycogen-depleting exercise protocol until volitional exhaustion in the morning. Immediately after and at 1, 2, and 3 hr postexercise, participants consumed 1.2 g/kg body mass CHO of a 15 percent CHO solution, a similar CHO solution but with addition of 8 mg/kg body mass of caffeine (CHO+CAFF), or an equivalent volume of flavored water only (WAT). After the 4-hr recovery period, participants performed the Loughborough Intermittent Shuttle Test (LIST) to volitional exhaustion as a measure of high-intensity interval-running capacity. Average blood glucose values during the 4-hr recovery period were higher in the CHO conditions than in the WAT trial (4.6 ± 0.3 mmol/L), although there was no difference between CHO (6.2 ± 0.8 mmol/L) and CHO+CAFF (6.7 ± 1.0 mmol/L). Exercise capacity during the LIST was significantly longer in the CHO+CAFF trial (48 ± 15 min) than in the CHO (32 ± 15 min) and WAT
conditions (19 ± 6 min). All 6 participants improved performance in CHO+CAFF compared with CHO. The study provides novel data by demonstrating that adding caffeine to postexercise CHO feeding improves subsequent high-intensity interval-running capacity, a finding that may be related to higher rates of postexercise muscle glycogen resynthesis previously observed under similar feeding conditions [205].

The aim of one study was to test the hypothesis that adding caffeine to postexercise carbohydrate (CHO) feedings improves subsequent high-intensity interval-running capacity compared with CHO alone. In a repeated-measures design, 6 men performed a glycogen-depleting exercise protocol until volitional exhaustion in the morning. Immediately after and at 1, 2, and 3 hr postexercise, participants consumed 1.2 g/kg body mass CHO of a 15 percent CHO solution, a similar CHO solution but with addition of 8 mg/kg body mass of caffeine (CHO+CAFF), or an equivalent volume of flavored water only (WAT). After the 4-hr recovery period, participants performed the Loughborough Intermittent Shuttle Test to volitional exhaustion as a measure of high-intensity interval-running capacity. Average blood glucose values during the 4-hr recovery period were higher in the CHO conditions than in the WAT trial (4.6 ± 0.3 mmol/L), although there was no difference between CHO (6.2 ± 0.8 mmol/L) and CHO+CAFF (6.7 ± 1.0 mmol/L). Exercise capacity during the study was significantly longer in the CHO+CAFF trial (48 ± 15 min) than in the CHO (32 ± 15 min) and WAT conditions (19 ± 6 min). All 6 participants improved performance in CHO+CAFF compared with CHO. The study provides novel data by demonstrating that adding caffeine to postexercise CHO feeding improves subsequent high-intensity interval-running capacity, a finding that may be related to higher rates of postexercise muscle glycogen resynthesis previously observed under similar feeding conditions [206].

The importance of endogenous carbohydrate (CHO) availability for high-intensity exercise performance has been well described in the literature. Several studies have shown that performance during high-intensity exercise is impaired when endogenous CHO availability (i.e. muscle and liver glycogen stores) is reduced. For example, it was reported that after three days of a low-CHO diet (about 5 % CHO) the average power output measured during a 30 s Wingate test in healthy men not engaged in any competitive sport was significantly reduced (from 581 ± 7 to 533 ± 7 W) when compared with a normal diet (about 50 % CHO). According to these authors, the reduction in performance (9 %) with low CHO availability was due to a lower contribution of the anaerobic energy system. Similarly, it was found a reduction in the anaerobic work capacity of healthy, non-athletic men when exercise was performed after a muscle-glycogen-depletion protocol compared to a control condition (10.33 ±2. 41 vs 12.83 ± 2.21 kJ, respectively), suggesting that low CHO availability can reduce the anaerobic contribution to total energy expenditure during high-intensity exercise. In addition, reduction in self-selected power output during high-intensity interval training when performed with low endogenous CHO availability has been also reported in well-trained subjects, and it may be associated with a reduction in the anaerobic contribution. While low CHO availability seems to reduce the anaerobic contribution and impair performance during high-intensity exercise, acute ingestion of caffeine seems to have the opposite effect. Taken together, several studies suggest that acute ingestion of caffeine may improve performance during high-intensity exercise via an increase in the anaerobic contribution. The purpose one study was therefore to examine the effects of caffeine ingestion on performance and energy expenditure (anaerobic and aerobic contribution) during a 4 km cycling time trial (TT) performed after a carbohydrate (CHO) availability-lowering exercise protocol. After preliminary and familiarization trials, seven amateur cyclists performed three 4-km cycling TT in a double-blind, randomized and crossover design. The trials were performed either after no previous exercise (CON), or after a CHO availability-lowering exercise protocol (DEP) performed in the previous evening, followed by either placebo (DEP-PLA) or 5 mg/kg of caffeine intake (DEP-CAF) 1 hour before the trial. Performance was reduced (-2.1 %) in DEP-PLA versus CON. However, performance was restored in DEP-CAF (404.6±17.1 s) compared with DEP-PLA, while no differences were found between DEP-CAF and CON. The
anaerobic contribution was increased in DEP-CAF compared with both DEP-PLA and CON, and this was more pronounced in the first 3 km of the trial. Similarly, total anaerobic work was higher in DEP-CAF than in the other conditions. The integrated electromyographic activity, plasma lactate concentration, oxygen uptake, aerobic contribution and total aerobic work were not different between the conditions. The reduction in performance associated with low CHO availability is reversed with caffeine ingestion due to a higher anaerobic contribution, suggesting that caffeine could access an anaerobic "reserve" that is not used under normal conditions [207].

The mechanisms by which caffeine increases the anaerobic contribution and performance during high-intensity exercise is not fully understood, but it has been proposed that caffeine intake would promote an inhibitory action on adenosine receptors, which would increase the activity of the enzyme phosphofructokinase, thereby increasing anaerobic glycolysis. Alternatively, caffeine may act on the central nervous system leading to an increase in motivational drive and neuromuscular excitability, which, in turn, results in a lowered rating of perceived exertion (RPE) for a given workload and improved neuromuscular function, as measured via electromyography activity (EMG). In addition, it has also been suggested that caffeine attenuates muscle sensory signals to the brain and decreases the threshold of activation of motor neurons. All of these central alterations could lead to an ability to produce more work anaerobically [207].

Although several studies have investigated the isolated effects of both CHO availability and caffeine intake on anaerobic contribution and performance, no study has examined whether acute caffeine ingestion could counteract the negative effects of low CHO availability on both the anaerobic contribution and performance. This seems to be particularly important since many athletes perform two training sessions in the same day, or participate in multi-stage event races (e.g. tour de France), where the time to replenish endogenous CHO stores between sessions or races may not be sufficient. Furthermore, most studies with either caffeine or CHO availability have focused on investigating their effects during time-to-exhaustion tests. However, time trials (TT) appear to be more reliable and to have greater external validity compared to constant-workload tests until exhaustion. Furthermore, during a high-intensity TT, where athletes are free to vary power output, anaerobic metabolism seems to exert a decisive effect on both performance and the distribution of work [207].

Effects of caffeine and carbohydrates on hydration status

One study compared the effects of three carbohydrate-hydration strategies on blood glucose concentration, exercise performance and hydration status throughout simulated soccer match-play. A randomized, double-blind and cross-over study design was employed. After familiarization, 14 recreational soccer players completed the soccer match simulation on three separate occasions. Participants consumed equal volumes of 9.6 percent carbohydrate-caffeine-electrolyte (6 mg/kg BW caffeine) solution with carbohydrate-electrolyte gels (H-CHO), 5.6 percent carbohydrate-electrolyte solution with electrolyte gels (CHO) or electrolyte solution and electrolyte gels (PL). Blood samples were taken at rest, immediately before exercise and every 15 min during exercise (first half: 15, 30, 45 min; second half: 60, 75, 90 min). Supplementation influenced blood glucose concentration, however, none of the supplementation regimes were effective in preventing a drop in blood glucose at 60 min. Mean sprint speed was 3 ± 1 percent faster in H-CHO when compared with PL. Supplementation caused a 2.3 ± 0.5 percent increase in plasma osmolality in H-CHO without change in CHO or PL. Similarly, mean sodium concentrations were 2.1 ± 0.4 percent higher in H-CHO when compared with PL. It was concluded that combining high carbohydrate availability with caffeine resulted in improved sprint performance and elevated blood glucose concentrations throughout the first half and at 90 min of exercise; however, this supplementation strategy negatively influenced hydration status when compared with 5.6 percent carbohydrate-electrolyte and electrolyte solutions [208].
CAFFEINE’S EFFECT ON ENERGY EXPENDITURE

PA energy expenditure (PAEE) is the most variable component of Total Energy Expenditure (TEE) and largely due to the balance of sedentary time (SedT) and low intensity physical activity (LIPA). There has been an emergence for seeking an understanding of factors which determine variations in SedT, LIPA, and PAEE. Sedentary behavior and physical activity are relatively resistant to change by experimental dietary treatments and significant body weight changes. Although caffeine (Caf) is by far the most heavily used nutritional agent ingested to promote a sense of vigor/alertness, it is still unknown if Caf is effective in increasing PAEE and physical activity. The aim of one study was to test the hypothesis that 2 daily doses of Caf (as a capsule to blind the treatment and divided equally during breakfast and lunch) increase PAEE and TEE, and it would do so through increasing the frequent and brief bouts of physical activity (1-5 min long) through the day as measured by accelerometry. In 21 low Caf users (<100 mg/day), it was used a double-blind crossover trial with two conditions (4-day each with a 3-day washout period) randomly ordered as 5 mg/kg/day of Caf and maltodextrin as placebo (Plc). Resting energy expenditure (REE) by indirect calorimetry, total energy expenditure (TEE) from doubly labeled water, PAEE calculated as TEE-(REE+0.1TEE), and accelerometry measurements of both LIPA and MVPA were not different between conditions. However, regardless of caffeine or placebo, there were several significant relationships between brief bouts of LIPA and MVPA with PAEE. In conclusion, the double-blind study found that low and moderate vigorous activity as well as the total volume of PAEE in free-living conditions is resistant to dietary caffeine intake that was equivalent to 5 cups of espresso or 7 cups of tea [209].

Effect of caffeine on thermogenesis and lipolysis

The measurement of oxygen consumption (VO2) is the primary index and documented evidence of a person's aerobic metabolism and energy expenditure. Thus, thermogenic claims associated with ephedrine have been supported, as increases in resting VO2 have been observed after both acute and chronic ephedrine ingestion. Similarly, ephedrine and combined ephedrine and caffeine have been observed to partially prevent the usual fall in resting metabolic rate during a calorie-restricted diet. However, the higher metabolic rates observed in these studies were not always associated with weight loss. There is also support for lipolytic claims, as significant increases in both fat oxidation and fat loss have been observed when ephedrine is administered in combination with caffeine. In contrast, however, ephedrine ingestion alone failed to produce such changes. Only clinically obese individuals were used as subjects in these investigations; thus, it is likely that the subjects may have had deficient metabolic rates or fat metabolism or both. Unfortunately, it is common practice for supplement manufacturers to take results from deficiency studies and generalize them to young, healthy, athletic individuals when advertising their products. Those of us in the research community know that this cannot and should not be done [210].

Caffeine as a lipolytic food component

Caffeine is one of the famous ergogenic aids in the athletic field. Caffeine has been known to stimulate lipolysis that spares stored glycogen utilization during moderate intensity exercise. Therefore, we investigated the effects of caffeine ingestion on exercise performance in rats and athletes. Rats were administered the caffeine (6 mg/kg) 1 h prior to the exercise then were run on a treadmill at a speed of 20 m/min. They were decapitated at 0 min, 30 min, 60 min of exercise, and exhausted time point. Human subjects ingested the caffeine (5 mg/kg) 1 h prior to the exercise. They exercised on a cycle ergometer at 60% of their VO2max for 45 min, and then the exercise intensity was increased to 80% of their VO2max until exhaustion. Blood and breathing gas samples were collected and calculated every 10 min during
exercise. Respiratory exchange ratio of the caffeine trial was significantly lower than that of the placebo trial in the athletes' study. Blood free fatty acid (FFA) levels in studies of both rats and athletes were increased by caffeine ingestion during exercise. Blood lactate levels were also increased during exercise in both rats and athletes. Increased FFA and glycerol concentrations reduced glycogen utilization during exercise compared with placebo group in rats. In addition, endurance time to exhaustion was significantly increased by the caffeine ingestion in both rats and athletes. These results suggest that the caffeine ingestion enhanced endurance performance resulting from spare stored glycogen with increasing lipolysis from adipose tissues and fat oxidation during exercise both in rats and in athletes [211].

**Caffeine’s effect on individuals with negative energy balance**

The ingestion of carbohydrate (+CHO) and caffeine (+CAF) during exercise is a commonly used ergogenic practice. Investigations are typically conducted with subjects who are in a rested state after an overnight fast. However, this state of positive energy balance is not achieved during many work and exercise circumstances. The aim of one study was to evaluate the substrate use and performance effects of caffeine and carbohydrate consumed alone and in combination while participants were in negative energy balance. Male participants (n=9) completed 4 trials in random order: -CAF/-CHO, -CAF/+CHO, +CAF/-CHO, and +CAF/+CHO. Diet and exercise were prescribed for 2 days before each trial to ensure negative energy balance. For each trial, before and after 2 h of cycling at 50 percent of maximal watts, a saliva sample and a muscle biopsy (vastus lateralis) were obtained. A simulated 20 km time trial was then performed. The respiratory exchange ratio was higher in +CHO trials and lower in the +CAF/+CHO trial than in the -CAF/+CHO trial. Salivary cortisol response was significantly higher in the +CAF/-CHO trial than in any of the other trials. Muscle glycogen and heart rates were similar in all trials. Performance in the 20 km time trial was significantly better in the -CAF/+CHO trial than in the -CAF/-CHO trial, but the +CAF/+CHO trial was no better than the +CAF/-CHO trial or any of the other trials. When co-ingested with carbohydrate, caffeine increased fat use and decreased nonmuscle glycogen carbohydrate use over carbohydrate alone when participants are in negative energy balance; however, caffeine had no effect on the 20 km cycling time trial performance [212].

**Impact of caffeine on post-exercise oxygen consumption**

This study investigated the effect of acute caffeine (CAF) intake on post-exercise oxygen consumption (EPOC) after intense resistance training. Fourteen strength-trained men (mean ± SD age and mass =23 ± 4 years and 83 ± 13 kg, respectively) who were caffeine users initially completed one-repetition maximum testing (1-RM) of four exercises: bench press, leg press, lat row, and shoulder press. On each of two days separated by one week, they completed four sets of each exercise to fatigue at 70-80 percent 1-RM, which was preceded by ingestion of CAF (6 mg/kg) or placebo. Pre-exercise, indirect calorimetry was used to assess energy expenditure for 35 min; this was repeated for 75 min postexercise while subjects remained seated in a quiet lab. Results revealed that EPOC was significantly higher with CAF (27 ± 4. L) compared to placebo (23 ± 4 L). With CAF ingestion, oxygen uptake was significantly higher from 10 min pre-exercise to 70 min postexercise. Respiratory exchange ratio was significantly different with CAF versus placebo. Caffeine intake increased total energy expenditure by 15 percent, but the additional calories burned was minimal (+27 kcal). Caffeine ingestion in individuals regularly completing rigorous resistance training significantly increases EPOC and energy expenditure pre-and post-exercise, yet the magnitude of this effect is relatively small [213].
Effects of caffeine on performance after a fat meal

One study examined the effects of caffeine, co-ingested with a high fat meal, on perceptual and metabolic responses during incremental (experiment 1) and endurance (experiment 2) exercise performance. Trained participants performed three constant-load cycling tests at approximately 73 percent of maximal oxygen uptake (VO2max) for 30 min at 20 degrees C (experiment 1, n=8) and to the limit of tolerance at 10 degrees C (experiment 2, n=10). The 30 min constant-load exercise in experiment 1 was followed by incremental exercise (15 W/min) to fatigue. Four hours before the first test, the participants consumed a 90 percent carbohydrate meal (control trial); in the remaining two tests, the participants consumed a 90% fat meal with (fat + caffeine trial) and without (fat-only trial) caffeine. Caffeine and placebo were randomly assigned and ingested 1 h before exercise. In both experiments, ratings of perceived leg exertion were significantly lower during the fat + caffeine than fat-only trial. Ratings of perceived breathlessness were significantly lower in experiment 1 and heart rate higher in experiment 2 on the fat + caffeine than fat-only trial. In the two experiments, oxygen uptake, ventilation, concentration on blood glucose, lactate and plasma glycerol were significantly higher on the fat + caffeine than fat-only trial. In experiment 2, concentration of plasma free fatty acids, blood pyruvate and the lactate to pyruvate ratio were significantly higher on the fat + caffeine than fat-only trial. Time to exhaustion during incremental exercise and constant-load exercise was not different between the fat-only and fat + caffeine trials. In conclusion, while a number of metabolic responses were increased during exercise after caffeine ingestion, perception of effort was reduced and this may be attributed to the direct stimulatory effect of caffeine on the central nervous system. However, this caffeine-induced reduction in effort perception did not improve exercise performance [214].

Duration of coffee- and exercise-induced changes in the fatty acid profile

Fatty acids are involved in a multitude of diverse physiological functions, including energy production, lipid biosynthesis, protein modification, regulation of transcription, and intracellular signaling. Furthermore, they have been implicated in pathological conditions, such as insulin resistance, atherosclerosis, and obesity. Although they are usually treated as one entity, it is becoming increasingly apparent in recent years that different fatty acids exhibit distinct functions. For example, they have divergent effects on liver lipoprotein metabolism and on glucose transport into skeletal muscle. Given this, one may assume that changes in the fatty acid profile of plasma may affect the metabolism of several tissues by modifying the composition of the mixture of fatty acids delivered to them. Utilization of blood-borne nonesterified fatty acids (NEFA) in working muscles is important for aerobic ATP resynthesis during prolonged exercise of moderate intensity. Although an increase in the total concentration of plasma NEFA (as a result of augmented lipolysis in adipose tissue) during such efforts is well documented, little is known about the effect of exercise on their percent distribution. Studies have found that exercise changes the percentage of individual plasma NEFA, although there is no consensus on this issue. The most striking finding was an increase in the ratio of unsaturated to saturated (U/S) NEFA in the plasma of athletes and untrained individuals. This change may add to the health benefits of exercise, given the protective role of dietary unsaturated fatty acids against cardiovascular disease and the development of insulin resistance. It is reasonable to think that the magnitude of the effect(s) of this change will depend on its duration; that is, the longer the U/S remains elevated, the higher its impact on human metabolism will probably be. Because our findings and the findings of the relevant studies cited above were based on blood samples taken solely at the end of exercise, we deemed it worthwhile to investigate how far into the recovery period the changes in individual NEFA are extended. Numerous studies have investigated the influence of coffee and caffeine on metabolism, with emphasis on their probable glycogen-sparing
effect as the explanation for the increase in endurance performance caused by their intake. On the basis of measurements of glycerol and NEFA release from adipose tissue, the majority of the relevant studies have shown caffeine to stimulate lipolysis. The vast majority of these studies have measured total NEFA. Prolonged moderate exercise increases the concentration of nonesterified fatty acids and the ratio of unsaturated to saturated (U/S) NEFA in human plasma. One study examined the duration of these effects and compared them with the effects of coffee ingestion. On separate days and in random order, seven men and six women 1) cycled for 1 h, 2) ingested coffee containing 5 mg caffeine/kg body mass, 3) ingested coffee followed by exercise 1 h later, and 4) did nothing. Blood samples were drawn at 0, 1, 2, 4, 8, 12, and 24 h. Serum was analyzed for lactate, glucose, glycerol, individual NEFA, triacylglycerols, total cholesterol, and HDL cholesterol. Exercise elevated the U/S NEFA and the percentage of oleate, while decreasing the percentages of palmitate and stearate, at the end of exercise but not subsequently. Consumption of coffee triggered a lower lipolytic response with no alterations in U/S or percentages of individual NEFA. These findings may prove useful in discovering mechanisms mediating the effects of exercise training on the fatty acid profile of human tissues [215].

Experimental

*Increases in VO$_{2\text{max}}$ and metabolic markers of fat oxidation by caffeine*

It was previously shown that the combination of caffeine, carnitine, and choline supplementation decreased body fat and serum leptin concentration in rats and was attributed to increased fat utilization for energy. As a result, it was hypothesized that the supplements may augment exercise performance including physiological and biochemical indexes. Twenty 7-week-old male Sprague-Dawley rats were given free access to a nonpurified diet with or without supplementation of caffeine, carnitine, and choline at concentrations of 0.1, 5, and 11.5 g/kg diet, respectively. One half of each dietary group was exercised on a motor-driven treadmill for 3 weeks and maximal aerobic power (VO$_{2\text{max}}$) was determined on the 18th day of exercise. Rats were killed 24-hr postexercise, and blood, regional fat pads, and skeletal muscle were collected. The VO$_{2\text{max}}$ was significantly increased in the supplemented/exercised group; however, the respiratory quotient (RQ) was not affected. Postexercised concentrations of serum triglycerides were decreased but beta-hydroxybutyrate, acylcarnitine, and acetylcarnitine were increased in the supplemented animals. The changes in serum metabolites were complemented by the changes in the muscle and urinary metabolites. The magnitude of increase in urinary acylcarnitines (34-45-fold) is a unique effect of this combination of supplements. Cumulative evidence indicates enhanced beta-oxidation of fatty acids without a change in the RQ because acetyl units were excreted in urine as acetylcarnitine and not oxidized to carbon dioxide. For this phenomenon, we propose the term “fatty acid dumping.” It was concluded that supplementation with caffeine, carnitine, and choline augments exercise performance and promotes fatty acid oxidation as well as disposal in urine [216].
IMPACT OF CAFFEINE ON THE HEART

Caffeine’s effect on cardiac blood flow

Caffeine-reduced myocardial blood flow during exercise

Acute ingestion of caffeine usually increases cardiac work; however, caffeine impairs the expected proportional increase in myocardial blood flow to match this increased work of the heart, most notably during exercise. This appears to be mainly due to caffeine’s effect on blocking adenosine-induced vasodilatation in the coronary arteries in normal healthy subjects. One review summarized the available medical literature specifically relating to pure caffeine tablet ingestion and reduced exercise coronary blood flow, and suggests possible mechanisms. Further studies are needed to evaluate this effect for other common caffeine-delivery systems, including coffee, energy beverages, and energy gels, which are often used for exercise performance enhancement, especially in teenagers and young athletes [217].

Caffeine decreased exercise-induced myocardial flow reserve

Caffeine is a widely consumed stimulant, although its cardiovascular safety remains controversial and its effect on myocardial blood flow (MBF) is unknown. It was studied the acute effect of caffeine on myocardial blood flow at rest and exercise in healthy volunteers at normoxia and during acute exposure to simulated altitude.

O-labeled H\textsubscript{2}O and positron emission tomography (PET) were used to measure regional MBF at rest and immediately after supine bicycle exercise in healthy volunteers at normoxia (n=10; mean workload, 175 W) as well as during hypoxia, simulating an altitude of 4,500 m by inhalation of a mixture of 12.5 percent oxygen (n=8; 148 W). Measurements were repeated 50 min after oral ingestion of caffeine (200 mg). Myocardial flow reserve (MFR) was calculated as the ratio of hyperemic to resting MBF. Resting MBF was not affected by caffeine at normoxia, although it was significantly increased at hypoxia. By contrast, exercise-induced hyperemic MBF decreased significantly at normoxia and hypoxia. The MFR decreased by 22 percent at normoxia and by 39 percent at hypoxia. It was concluded that in healthy volunteers, a caffeine dose corresponding to two cups of coffee (200 mg) significantly decreased exercise-induced MFR at normoxia and was even more pronounced during exposure to altitude [218].

Effects of caffeine on linear and nonlinear measures of heart rate variability

Caffeine intake is associated with an increase in heart rate (HR) variability. One study sought to examine the effects of caffeine on HR variability measures before and during progressive exercise in 11 healthy volunteers in a double-blind randomized and counterbalanced placebo-controlled paradigm. As expected, there were significant increases in HR and decreases in HR variability after exercise during both placebo and caffeine conditions; however, pre-exercise caffeine condition was associated with a significant increase of HR variability, especially in the high-frequency range (0.15-0.5 Hz), and also approximate entropy (APEN), which is usually attributed to cardiac vagal function. But during progressive exercise, caffeine intake resulted in a greater decrease of HF power as well as HR APEN. Caffeine also was associated with significantly higher LF power during exercise compared to the placebo condition. These results suggest that caffeine may have different effects on HR variability at rest, compared to exercise. These findings may have implications for patients with cardiac illness and anxiety, depression, and psychotic disorders who use beverages containing excessive caffeine [219].
EFFECT OF CAFFEINE ON RENAL FUNCTIONS

Effect of caffeine on hydration

Acute and chronic caffeine intakes have no impact on hydration status [Maughan RJ, Griffin J. J Hum Nutr Diet 2003; 16: 411-20], although no research has been conducted to analyze the effects using dilution techniques on total-body water (TBW) and its compartments. Therefore, the aim of this study was to investigate the effects of a moderate dose of caffeine on TBW, extracellular water (ECW), and intracellular water (ICW) during a 4-day period in active males. Thirty men, nonsmokers and low caffeine users (<100 mg/day), aged 20-39 years, participated in this double-blind, randomized, crossover trial. The study included 2 conditions (5 mg/kg/day of caffeine and placebo (malt-dextrin)) of 4 days each, with a 3-day washout period. TBW and ECW were assessed by deuterium oxide and sodium bromide dilution, respectively, whereas ICW was calculated as TBW minus ECW. Body composition was assessed by dual-energy X-ray absorptiometry. Physical activity was assessed by accelerometry and water intake was assessed by dietary records. Repeated-measures analysis of variance (ANOVA) was used to test main effects. No changes in TBW, ECW, or ICW and no interaction between the randomly assigned order of treatment and time were observed. TBW, ECW, and ICW were unrelated to fat-free mass, water ingestion, and PA. These findings indicate that a moderate caffeine dose, equivalent to approximately 5 espresso cups of coffee or 7 servings of tea, does not alter TBW and fluid distribution in healthy men, regardless of body composition, PA, or daily water ingestion [220].

Caffeine and related methylxanthine compounds are recognized as having a diuretic action, and consumers are often advised to avoid beverages containing these compounds in situations where fluid balance may be compromised. The aim of this review is to evaluate the available literature concerning the effect of caffeine ingestion on fluid balance and to formulate targeted and evidence-based advice on caffeinated beverages in the context of optimum hydration. A literature search was performed using the Medline database of articles published in the medical and scientific literature for the period of January 1966-March 2002. Subject headings and key words used in this search were: tea, coffee, caffeine, diuresis, fluid balance and water-electrolyte balance. A secondary search was performed using the bibliographies of publications identified in the initial search. The available literature suggests that acute ingestion of caffeine in large doses (at least 250-300 mg, equivalent to the amount found in 2-3 cups of coffee or 5-8 cups of tea) results in a short-term stimulation of urine output in individuals who have been deprived of caffeine for a period of days or weeks. A profound tolerance to the diuretic and other effects of caffeine develops, however, and the actions are much diminished in individuals who regularly consume tea or coffee. Doses of caffeine equivalent to the amount normally found in standard servings of tea, coffee and carbonated soft drinks appear to have no diuretic action. The most ecologically valid of the published studies offers no support for the suggestion that consumption of caffeine-containing beverages as part of a normal lifestyle leads to fluid loss in excess of the volume ingested or is associated with poor hydration status. Therefore, there would appear to be no clear basis for refraining from caffeine containing drinks in situations where fluid balance might be compromised [221].

Diuretic effects

Maintenance of fluid balance is essential to sustain human life. Water intake balances fluid losses to achieve adequate hydration of bodily tissues. Although there are widespread guidelines in scientific literature and media for achieving optimal hydration status and about the effects that various caffeinated beverages may have on fluid balance, there is no clear consensus about how much fluid an individual should consume. One study found total daily
fluid intake observed in healthy adults varied from 0.4-4.3 L/day. However, published guidelines range from 1.5 L/day to 3.7 L/day for adult males. It has been suggested that caffeinated beverages should not be included in daily fluid requirement guidelines and that a glass of water should be consumed with every cup of coffee or tea to ensure hydration is maintained. It is often suggested that coffee causes dehydration and its consumption should be avoided or significantly reduced to maintain fluid balance. It is estimated that 1.6 billion cups of coffee are consumed worldwide every day, thus it is of interest to know whether coffee contributes to daily fluid requirement, or whether it causes low-level chronic dehydration. In the present study, our aim was to directly compare the effects of a moderate intake of coffee in caffeine-habituated adults against equal amounts of water across a wide range of hydration markers, including the gold standard TBW measure. The aim of one study was to directly compare the effects of coffee consumption against water ingestion across a range of validated hydration assessment techniques. In a counterbalanced cross-over design, 50 male coffee drinkers (habitually consuming 3-6 cups per day) participated in two trials, each lasting three consecutive days. In addition to controlled physical activity, food and fluid intake, participants consumed either 4×200 mL of coffee containing 4 mg/kg caffeine (C) or water (W). Total body water (TBW) was calculated pre- and post-trial via ingestion of Deuterium Oxide. Urinary and haematological hydration markers were recorded daily in addition to nude body mass measurement (BM). Plasma was analysed for caffeine to confirm compliance. There were no significant changes in TBW from beginning to end of either trial and no differences between trials (51.5 ± 1.4 vs 51.4 ± 1.3 kg, for C and W, respectively). No differences were observed between trials across any haematological markers or in 24 h urine volume (2409 ± 660 vs 2428 ± 669 mL, for C and W, respectively). USG, osmolality or creatinine. Mean urinary Na+ excretion was higher in C than W. No significant differences in BM were found between conditions, although a small progressive daily fall was observed within both trials (0.4 ± 0.5 kg). The data show that there were no significant differences across a wide range of haematological and urinary markers of hydration status between trials. These data suggest that coffee, when consumed in moderation by caffeine habituated males provides similar hydrating qualities to water [222].

**Body fluid-electrolyte balance and exercise performance**

Recreational enthusiasts and athletes often are advised to abstain from consuming caffeinated beverages (CB). The dual purposes of one review were to (a) critique controlled investigations regarding the effects of caffeine on dehydration and exercise performance, and (b) ascertain whether abstaining from CB is scientifically and physiologically justifiable. The literature indicates that caffeine consumption stimulates a mild diuresis similar to water, but there is no evidence of a fluid-electrolyte imbalance that is detrimental to exercise performance or health. Investigations comparing caffeine (100-680 mg) to water or placebo seldom found a statistical difference in urine volume. In the 10 studies reviewed, consumption of a CB resulted in 0-84 percent retention of the initial volume ingested, whereas consumption of water resulted in 0-81 percent retention. Further, tolerance to caffeine reduces the likelihood that a detrimental fluid-electrolyte imbalance will occur. The scientific literature suggests that athletes and recreational enthusiasts will not incur detrimental fluid-electrolyte imbalances if they consume CB in moderation and eat a typical U.S. diet. Sedentary members of the general public should be a less risk than athletes because their fluid losses via sweating are smaller [223].

**Effect on urea formation**

It was investigated the effects of caffeine on the ammonia and amino acid metabolism of elite soccer players. In a double-blind randomized study, athletes (n=19) received 5 mg/kg caffeine or lactose (LEX, control) and performed 45 min of intermittent exercise followed by an intermittent recovery test (Yo-Yo IR2) until exhaustion. The caffeine-supplemented
athletes were divided into two groups (CEx and SCEx) depending on their serum caffeine levels (<900 % and >10,000 %, respectively). Data were analyzed by ANOVA and Tukey post hoc test. Caffeine supplementation did not significantly affect the performance. Exercise changed the blood concentrations of several amino acids and increased the serum concentrations of ammonia, glucose, lactate, and insulin. The LEx group showed an exercise-induced increase in valine (>29 %), which was inhibited by caffeine. Higher serum caffeine levels abolished the exercise-induced increase (24 %-27 %) in glutamine but did not affect the exercise-induced increase in alanine (110 %-160 %) and glutamate (42 %-61 %). In response to exercise, the SCEx subjects did not exhibit an increase in uremia and showed a significantly lower increase in their serum arginine (15 %), citrulline (16 %), and ornithine concentrations. The data suggest that caffeine might decrease systemic urea by decreasing the glutamine serum concentration, which decreases the transportation of ammonia to the liver and thus urea synthesis [224].
IMPACT OF CAFFEINE ON IMMUNOLOGICAL FACTORS

Impact on the inflammatory response

The objective of one study was to determine the effects of caffeine supplementation on the inflammatory response (IL-6 and IL-10 levels and leukocyte numbers) induced by a 15-km run competition and to examine the effect of caffeine supplementation on the energetic metabolites as well as on the exercise-induced oxidative stress. A double-blinded study of supplementation with caffeine was performed. Athletes participating in the study (n=33) completed a 15 km run competition. Before competition, athletes took 6 mg /kg body weight of caffeine (caffeine group, n=17) or a placebo (placebo group, n=16). Blood samples were taken before and after competition (immediately and after 2-h recovery). Leukocyte numbers were determined in blood. Concentrations of oxidative stress markers, antioxidants, interleukins (IL-6 and IL-10), caffeine, adrenaline, and energetic metabolites were measured in plasma or serum. Caffeine supplementation induced higher increases in circulating total leukocytes and neutrophils, with significant differences between groups after recovery. Adrenaline, glucose, and lactate levels increased after exercise, with higher increases in the caffeine group. Exercise induced significant increases in IL-6 and IL-10 plasma levels, with higher increases in the caffeine group. Caffeine supplementation induced higher increases in oxidative stress markers after the competition. In conclusion, caffeine supplementation induced higher increases in IL-6 levels, as well as for the increased lactate levels. Furthermore, caffeine seems to enhance oxidative stress induced by exercise [225].

The levels of circulatory inflammatory markers, including interleukin (IL) IL-1beta, IL-6, tumor necrosis factor-alpha (TNF-alpha) and interferon (INF-gamma), are known to increase associated to aging. Caffeine has been reported to produce many beneficial effects for health. Exercise is considered to be a safe medicine to attenuate inflammation and cellular senescence. The purpose of the present study was to investigate the effects of a moderate-intensity swimming exercise (3 % of body weight, 20 min per day, 4 weeks) and sub-chronic supplementation with caffeine (30 mg/kg, 4 weeks) on the serum cytokine levels in middle-aged (18 months) Wistar rats. The effects of swimming exercise and caffeine on oxidative stress in muscle and liver of middle-aged rats were also investigated. The two-way ANOVA of pro-inflammatory cytokine levels demonstrated a significant exercise x caffeine interaction for IL-1beta, IL-6, and INF-gamma. The two-way ANOVA of TNF-alpha levels revealed a significant exercise x caffeine interaction. Swimming exercise and caffeine supplementation increased the ratio of reduced glutathione/oxidized glutathione in the rat liver and gastrocnemius muscle. Hepatic and renal markers of damage were not modified. In conclusion, a moderate-intensity swimming exercise protocol and caffeine supplementation induced positive adaptations in modulating cytokine levels without causing oxidative stress in muscle and liver of middle-aged rats [226].

Effect of caffeine ingestion on lymphocyte counts

Caffeine ingestion is associated with increases in the concentration of plasma epinephrine and epinephrine is associated with alterations in immune cell trafficking and function following intensive exercise. Therefore, the purpose of this study was to investigate the effect of caffeine ingestion on plasma epinephrine concentration, lymphocyte counts and subset activation in vivo, as measured by the expression the CD69 surface antigen, before and after intensive cycling. On two occasions, following an overnight fast and 60 h abstention from caffeine containing foods and drinks, eight endurance trained males cycled for 90 min at 70 percent VO2max 60 min after ingesting caffeine (6 mg/kg body mass; CAF) or placebo (PLA).
Venous blood samples were collected at pre-treatment, pre-exercise, post-exercise and 1 h post-exercise. Plasma epinephrine concentrations were significantly higher in CAF compared with PLA at pre-exercise and immediately post-exercise. Compared with pre-treatment, numbers of CD4(+) and CD8(+) cells decreased by 54% and 55%, respectively, in CAF at 1 h post-exercise but did not significantly differ in PLA. Compared with PLA, in CAF the percentage of CD4(+)CD69(+) cells was 5-fold higher at post-exercise and 5.5-fold higher at 1 h post-exercise. Compared with PLA, in CAF the percentage of CD8(+)CD69(+) cells was 2-fold higher at pre-exercise and 1.7-fold higher at post-exercise. These findings suggest that caffeine ingestion is associated with alterations in lymphocyte subset trafficking and expression of CD69 in vivo following prolonged, intensive exercise [227].

Effect on NK cells

One study investigated the effect of a high and low dose of caffeine on antigen-stimulated natural killer (NK) cell (CD3-CD56+) activation after prolonged, strenuous cycling, as assessed by the early-activation molecule CD69. In a randomized crossover design, 12 healthy male endurance-trained cyclists cycled for 90 min at 70 percent VO2peak 60 min after ingesting either 0 (PLA), 2 (2CAF), or 6 (6CAF) mg/kg body mass of caffeine. Whole blood was stimulated with Pediacel (5 in 1) vaccine. A high dose of caffeine (6CAF) significantly increased the number of CD3-CD56+ cells in the circulation immediately postexercise compared with PLA. For both 2CAF and 6CAF, the geometric mean fluorescence intensity (GMFI) of CD69+ expression on unstimulated CD3-CD56+ cells was significantly higher than with PLA. When cells were stimulated with antigen, the GMFI of CD69 expression remained significantly higher with 2CAF than with PLA 1 hr postexercise. Although not achieving statistical significance, 6CAF also followed a similar trend when stimulated. There were no differences in GMFI of CD69 expression between 2CAF and 6CAF. These results suggest that a high (6 mg/kg) dose of caffeine was associated with the recruitment of NK cells into the circulation and that both a high and low (2 mg/kg) dose of caffeine increased unstimulated and antigen-stimulated NK-cell activation 1 hr after high-intensity exercise. Furthermore, there does not appear to be a dose-dependent effect of caffeine on NK-cell activation 1 hr after prolonged intensive cycling [228].

Several studies investigating the effect of caffeine on immune function following exercise have used one large bolus dose of caffeine. However, this does not model typical caffeine consumption. Therefore, the purpose of one study was to investigate whether small repeated doses of caffeine ingested throughout the day would elicit a similar response as one large bolus dose ingested 1 h prior to exercise on antigen-stimulated NK cell CD69 expression following strenuous intermittent exercise. In a randomized cross-over design, 15 healthy males completed six 15 min blocks of intermittent running consisting of maximal sprinting interspersed with less intense running and walking. Participants had ingested either 0 (PLA), 2 mg/kg body mass (BM) caffeine on three separate occasions during the day (3 × CAF) or one dose of 6 (1 × CAF) mg/kg BM caffeine, 1 h before exercise. At 1-h post-exercise, the number of antigen-stimulated CD3(-)CD56(+) cells expressing CD69 was lower on 1 × CAF compared with PLA, with values on 1 × CAF at this time point remaining close to pre-supplement. 1 × CAF tended to attenuate the exercise-induced increase in geometric mean fluorescence intensity of CD69 expression on antigen-stimulated CD3(-)CD56(+) cells 1-h post-exercise. These findings suggest that although one large bolus dose of caffeine attenuated the exercise-induced increase in antigen-stimulated NK cell CD69 expression 1 h following strenuous intermittent exercise, this attenuation at no point fell below pre-supplement values and caffeine does not appear to depress NK cell CD69 expression [229].
Immunoendocrine effects

One study investigated the effect of caffeine consumed with and without carbohydrate (CHO) on immunoendocrine responses after exercise. On four occasions, 12 recreational male cyclists cycled for 2 h at 65 percent VO$_{2\text{max}}$. Sixty minutes before exercise, participants ingested 6 mg.kg$^{-1}$ body mass of caffeine (CAF) or placebo (PLA), then during exercise they consumed a 6 percent CHO or placebo (PLA) drink, providing CAF/CHO, PLA/CHO, CAF/PLA, and PLA/PLA conditions. f-MLP-stimulated neutrophil oxidative burst responses were significantly higher after exercise on CAF/CHO and PLA/CHO than PLA/PLA when expressed as a percentage of baseline value. The response on CAF/PLA tended to be higher than PLA/PLA at this point. No significant differences between CAF/CHO, PLA/CHO, and CAF/PLA were observed after exercise; however, only PLA/CHO showed no significant postexercise decline. Coingestion of CAF/CHO significantly attenuated epinephrine and IL-6 responses that occurred after ingestion of CAF alone (CAF/PLA) and significantly attenuated the transient alterations in circulating leukocyte and neutrophil counts. Plasma cortisol concentration was significantly lower on PLA/CHO than CAF/PLA and PLA/PLA after exercise. Perceived exertion during exercise was significantly lower on CAF/CHO than the other three trials. Taken together, this suggests that coinestion of caffeine and CHO has greater influence on immunoendocrine responses than neutrophil functional responses to prolonged exercise [230].
OTHER PHYSIOLOGICAL EFFECTS OF CAFFEINE

Gastrointestinal function during exercise with caffeine

Caffeine is suspected to affect gastrointestinal function. We therefore investigated whether supplementation of a carbohydrate-electrolyte solution (CES) sports drink with 150 mg/L caffeine leads to alterations in gastrointestinal variables compared with a normal CES and water using a standardized rest-exercise-rest protocol. Ten well-trained subjects underwent a rest-cycling-rest protocol three times. Esophageal motility, gastroesophageal reflux, and intragastric pH were measured by use of a transnasal catheter. Orocecal transit time was measured using breath-H$_2$ measurements. A sugar absorption test was applied to determine intestinal permeability and glucose absorption. Gastric emptying was measured via the (13)C-acetate breath test. In the postexercise episode, midesophageal pressure was significantly lower in the CES + caffeine trial compared with the water trial. There were no significant differences between the three drinks for gastric pH and reflux during the preexercise, the cycling, and the postexercise episode, respectively. Gastric emptying, orocecal transit time, and intestinal permeability showed no significant differences between the three trials. However, glucose absorption was significantly increased in the CES + caffeine trial compared with the CES trial. No significant differences in gastroesophageal reflux, gastric pH, or gastrointestinal transit could be observed between the CES, the CES + caffeine, and the water trials. However, intestinal glucose uptake was increased in the CES + caffeine trial [231].

Impact of caffeine on ventilation

The purpose of one project was to determine whether a moderate dosage of caffeine, a common ventilatory stimulant, could augment resting ventilatory responsiveness, exercise ventilation, end-tidal O$_2$ partial pressure (PetO$_2$), and arterial oxyhemoglobin saturation (HbSaO$_2$) in athletes with exercise-induced hypoxemia. Eight highly trained males who demonstrated exercise-induced hypoxemia, ingested in a randomized design a placebo or caffeine (8 mg/kg body wt) 1 hour before testing. Ventilatory responsiveness at rest was assessed via the isocapnic hypoxic and hyperoxic hypercapnic ventilatory responses (HVR and HCVR, respectively). The failure of HbSaO$_2$ to increase at despite an increase in ventilation suggests that mechanisms influencing HbSaO$_2$ other than an inadequate hyperventilatory response may operate to different degrees across individuals as VO$_2$max is approached [232].

The effects of caffeine on exercise performance have been well documented, with most reviews focusing on the metabolic, hormonal, and/or central nervous system effects. However, caffeine's effects on ventilation and pulmonary function are often overlooked. Studies have shown that caffeine is a strong ventilatory stimulant, increasing the sensitivity of the peripheral chemoreceptors in untrained subjects and increasing exercise ventilation at all workloads in highly trained endurance athletes. The consequences of increased exercise ventilation could hold either positive or negative effects for exercise performance. Anti-inflammatory and bronchoprotective effects of caffeine are great enough to consider its efficacy as a possible prophylactic antiasthma treatment. Although an upper urinary concentration limit exists for caffeine with international sports doping control agencies, caffeine's universal accessibility in the marketplace has resulted in its daily use being increasingly more socially acceptable as an ergogenic substance for sport and exercise [233].
Impact on sweating

It was assessed the effect of caffeine on sudomotor activity and sweating sensitivity during physical loading. Both physiological responses could occur due to energy expenditure. Subjects were 13 athletically trained males (22 ± 4 years old, 174 ± 5 cm tall, and weighing 71 ± 5 kg, with maximal oxygen consumption (VO2max) of 54 ± 4 mL/kg/minute). The study involved a within-subject, random, crossover design. Tests were performed following the ingestion of 3 mg/kg caffeine. The physical loading involved running for 30 minutes at 60 percent VO2max (24 ± 0.5°C, 40 ± 3 % relative humidity). Tympanic temperature (TYMP) was significantly higher in the caffeine-consuming group (Caffe-I) at pre-exercise (40 minutes after caffeine intake and immediately before running). Mean body temperature (mTb) was significantly higher in the Caffe-I group at pre- and post-exercise (30 min after start of running). Onset time of localized sweating was significantly shorter in the Caffe-I group, but localized sweat volume and active sweat gland output (per single gland) was significantly higher in the Caffe-I group. Activated sweat gland density was significantly increased in the Caffe-I group on the abdomen and thigh. In conclusion, caffeine ingestion caused not only increases in TYMP and mTb through thermogenesis, but also an increased sweating sensitivity via changes in sudomotor activity [234].

Effect of caffeine on delayed onset muscle soreness

The beneficial effects of caffeine on aerobic activity and resistance training performance are well documented. However, less is known concerning caffeine's potential role in reducing perception of pain and soreness during exercise. In addition, there is no information regarding the effects of caffeine on delayed onset muscle soreness (DOMS). The primary purpose of this study was to examine the effect of caffeine ingestion on muscle soreness, blood enzyme activity, and performance after a bout of elbow flexion/extension exercise. Nine low-caffeine-consuming males were randomly assigned to ingest either caffeine or placebo 1 hour before completing 4 sets of 10 bicep curls on a preacher bench, followed by a fifth set in which subjects completed as many repetitions as possible. Soreness and soreness on palpation intensity were measured using three 0-10 visual analog scales before exercise, and 24, 48, 72, 96, and 120 hours after exercise. After a washout period, subjects crossed over to the other treatment group. Caffeine ingestion resulted in significantly lower levels of soreness on day 2 and day 3 compared with placebo. Total repetitions in the final set of exercise increased with caffeine ingestion compared with placebo. The study demonstrates that caffeine ingestion immediately before an upper-body resistance training out enhances performance. A further beneficial effect of sustained caffeine ingestion in the days after the exercise bout is an attenuation of DOMS. This decreased perception of soreness in the days after a strenuous resistance training workout may allow individuals to increase the number of training sessions in a given time period [235].

Lack of effect on oxidative stress

Coffee has been reported to be rich in antioxidants, with both acute and chronic consumption leading to enhanced blood antioxidant capacity. High-fat feeding is known to result in excess production of reactive oxygen and nitrogen species, promoting a condition of postprandial oxidative stress. It was tested the hypothesis that coffee intake following a high-fat meal would attenuate the typical increase in blood oxidative stress during the acute postprandial period. On 3 different occasions, 16 men and women consumed a high-fat milk shake followed by either 16 ounces of caffeinated or decaffeinated coffee or bottled water. Blood samples were collected before and at 2 and 4 hours following intake of the milk shake and analyzed for triglycerides (TAG), malondialdehyde (MDA), hydrogen peroxide (H2O2), and
Trolox equivalent antioxidant capacity (TEAC). Values for TAG and MDA, as well as for H2O2, increased significantly following milk shake consumption, with values higher at 4 hours compared with 2 hours post consumption for TAG and H2O2. TEAC was unaffected by the milk shake consumption. Coffee had no impact on TAG, MDA, H2O2, or TEAC, with no condition or interaction effects noted for any variable. It was concluded that acute coffee consumption following a high-fat milk shake has no impact on postprandial oxidative stress [236].

Modulation of oxidative stress markers in the liver of trained rats

Caffeine has been widely used in sports competitions due to its ergogenic effects. Most of the studies regarding caffeine and exercise have focused on muscle and plasma adaptations, while the impact on the liver is scarcely described. The aim of one study was to analyze the effects of caffeine and exercise training on oxidative stress markers and injury-related parameters in the liver. Rats were divided into sedentary/saline, sedentary/caffeine, exercise/saline, and exercise/caffeine groups. Exercise groups underwent 4 weeks of swimming training, and caffeine (6 mg/kg, p.o.) was supplemented throughout the training protocol. Injury-related liver parameters were assessed in plasma, while redox status and oxidative stress markers were measured on liver homogenates. Exercise training increased muscle citrate synthase activity in the muscle, while in caffeine decreased its activity in both sedentary and trained rats. Aspartate transaminase levels were increased after training, and caffeine intake suppressed this elevation. Caffeine also diminished alanine transaminase levels in both sedentary and exercised rats. Exercise training induced a significant increase on the activity of the enzymes superoxide dismutase and glutathione peroxidase, as an increase on thiobarbituric acid-reactive substances levels was also reached; caffeine intake blunted these alterations. Caffeine intake also suppressed liver catalase activity in both sedentary and exercise groups. The data suggest that caffeine modified the hepatic responses associated to exercise-induced oxidative stress without affecting the performance, exerting different actions according to the tissue. However, further studies are needed to better understand caffeine's role on liver under exercise training [237].

Caffeine improves performance at high altitude

There is limited research on the physiological effects of caffeine (CAF) ingestion on exercise performance during acute hypoxia. The aim of one study was therefore to test the effect of placebo (PLA) and CAF (4.5 mg/kg) on double poling (DP) performance during acute hypoxia. Thirteen male subelite cross-country skiers were included. Performance was assessed as 1) an 8-km cross-country DP time-trial (C-PT), and 2) time until task failure at a set workload equal to about 90 percent of DP VO2max. Testing was carried out in a hypobaric chamber, at 800 mbar (Pio2: 125 mmHg) corresponding to about 2,000 m above sea level in a randomized double-blinded, placebo-controlled, cross-over design. CAF improved time to task failure from 6.10 ± 1.40 to 7.22 ± 1.30 min and velocity the first 4 km but not overall time usage for the 8-km C-PT. During submaximal exercise subjects reported lower pain in arms and rate of perceived exertion (RPE) following CAF ingestion. Throughout C-PTs similar RPE and pain was shown between treatments. However, higher heart rate was observed during the CAF 8 km and 90 percent C-PT (185 ± 7 vs 181 ± 9) associated with increased ventilation, blood lactate, glucose, adrenaline, decreased pH, and bicarbonate. The present study demonstrates for the first time that CAF ingestion improves DP time to task failure although not consistently time trial performance during acute exposure to altitude. Mechanisms underpinning improvements seem related to reduced pain RPE and increased heart rate during CAF C-PTs [238].
Effect of caffeine on liver during training

Caffeine has been widely used in sports competitions due to its ergogenic effects. Most of the studies regarding caffeine and exercise have focused on muscle and plasma adaptations, while the impact on the liver is scarcely described. The aim of one study was to analyze the effects of caffeine and exercise training on oxidative stress markers and injury-related parameters in the liver. Rats were divided into sedentary/saline, sedentary/caffeine, exercise/saline, and exercise/caffeine groups. Exercise groups underwent 4 weeks of swimming training, and caffeine (6 mg/kg, p.o.) was supplemented throughout the training protocol. Injury-related liver parameters were assessed in plasma, while redox status and oxidative stress markers were measured on liver homogenates. Exercise training increased muscle citrate synthase activity in the muscle, while in caffeine decreased its activity in both sedentary and trained rats. Aspartate transaminase levels were increased after training, and caffeine intake suppressed this elevation. Caffeine also diminished alanine transaminase levels in both sedentary and exercised rats. Exercise training induced a significant increase on the activity of the enzymes superoxide dismutase and glutathione peroxidase, as an increase on thiobarbituric acid-reactive substances levels was also reached; caffeine intake blunted these alterations. Caffeine intake also suppressed liver catalase activity in both sedentary and exercise groups. The data suggest that caffeine modified the hepatic responses associated to exercise-induced oxidative stress without affecting the performance, exerting different actions according to the tissue. However, further studies are needed to better understand caffeine's role on liver under exercise training [237].
POSSIBLE HEALTH-PROMOTING EFFECTS OF CAFFEINE

The health-promoting properties of coffee are according to the literature attributed to its rich phytochemistry, including caffeine, chlorogenic acid, caffeic acid, hydroxyhydroquinone (HHQ), etc. Many research investigations, epidemiological studies, and meta-analyses regarding coffee consumption revealed its inverse correlation with that of diabetes mellitus, various cancer lines, Parkinsonism, and Alzheimer's disease. Moreover, it ameliorates oxidative stress because of its ability to induce mRNA and protein expression, and mediates Nrf2-ARE pathway stimulation. Furthermore, caffeine and its metabolites help in proper cognitive functionality. Coffee lipid fraction containing cafestol and kahweol act as a safeguard against some malignant cells by modulating the detoxifying enzymes [239].

Specific diagnoses

Alzheimer's disease  Human and animal studies show hints of protection. Some preliminary evidence suggests activity against beta-amyloid plaque that may have a causative role in Alzheimer’s.

Parkinson's disease  Studies show a moderate (25 %) decrease in risk for coffee drinkers. The effect is less in women. Research has found evidence of activity in the part of the brain affected by Parkinson’s.

Cancer  Studies suggest a lower risk for some cancers (endometrial, aggressive prostate, estrogen-negative breast), but not others (esophageal). Antioxidant and anti-inflammatory substances could be responsible for possible anticancer activity.

Diabetes  Effects on insulin and blood sugar levels that would promote diabetes seem to be temporary. Regular use is associated with lower risk, and high intake (3-6 cups a day) seems to have a greater effect. Protection may come from increases in the hormone adiponectin and other factors that affect insulin and blood sugar levels.

Myocardial infarction  Coffee drinking increases some factors (homocysteine) associated with higher risk. But moderate consumption (1-3 cups a day) has been linked to a small decrease in risk. The evidence for a possible protective effect is stronger for women.

Stroke  Moderate consumption (3-4 cups a day) is associated with lower risk. But chance of a stroke may increase immediately after intake, particularly among infrequent consumers.

Liver disease  Coffee drinking is associated with lower levels of enzymes that indicate liver damage and inflammation. Coffee may improve response to some treatments for hepatitis C. Findings suggest some protection against liver cancer. Cafestol and kahweol, substances found in unfiltered coffee, may be responsible for liver benefits.
Caffeine in exercise-induced bronchoconstriction

The main aim of one study was to evaluate the comparative and additive effects of caffeine and albuterol (short-acting beta2-agonist) on the severity of EIB (exercise-induced bronchoconstriction). Ten asthmatic subjects with EIB participated in a randomized, double-blind, double-dummy crossover study. One hour before an exercise challenge, each subject was given 0, 3, 6, or 9 mg/kg of caffeine or placebo mixed in a flavored sugar drink. Fifteen minutes before the exercise bout, an inhaler containing either albuterol (180 microg) or placebo was administered to each subject. Pulmonary function tests were conducted pre- and post-exercise. Caffeine at a dose of 6 and 9 mg/kg significantly reduced the mean maximum percentage fall in post-exercise FEV1 compared to the double-placebo and baseline. There was no significant difference in the post-exercise percent fall in FEV1 between albuterol (plus caffeine) and the 9 mg/kg dose of caffeine. Interestingly, there was no significant difference in the post-exercise percentage fall in FEV1 between albuterol (plus caffeine) and albuterol with 3, 6 or 9 mg/kg of caffeine. Similar changes were observed for the post-exercise percentage fall in FVC, FEF (25-75 %) and PEF. These data indicate that moderate (6 mg/kg) to high doses (9 mg/kg) of caffeine provide a significant protective effect against EIB. It is feasible that the negative effects of daily use of short-acting beta2-agonists by asthmatic athletes could be reduced simply by increasing caffeine consumption prior to exercise [240].

Caffeine in diabetics

Caffeine is a substance that has been used in our society for generations, primarily for its effects on the central nervous system that causes wakefulness. Caffeine supplementation has become increasingly more popular as an ergogenic aid for athletes and considerable scientific evidence supports its effectiveness. Because of their potential to alter energy metabolism, the effects of coffee and caffeine on glucose metabolism in diabetes have also been studied both epidemiologically and experimentally. Predominantly targeting the adenosine receptors, caffeine causes alterations in glucose homeostasis by decreasing glucose uptake into skeletal muscle, thereby causing elevations in blood glucose concentration. Caffeine intake has also been proposed to increase symptomatic warning signs of hypoglycemia in patients with type 1 diabetes and elevate blood glucose levels in patients with type 2 diabetes. Other effects include potential increases in glucose counter regulatory hormones such as epinephrine, which can also decrease peripheral glucose disposal. Despite these established physiological effects, increased coffee intake has been associated with reduced risk of developing type 2 diabetes in large-scale epidemiological studies. One review paper highlighted the known effects of caffeine on glucose homeostasis and diabetes metabolism during rest and exercise [241].

Several prospective epidemiologic studies over the past 4 years concluded that ingestion of caffeinated and decaffeinated coffee can reduce the risk of diabetes. This finding is at odds with the results of trials in humans showing that glucose tolerance is reduced shortly after ingestion of caffeine or caffeinated coffee and suggesting that coffee consumption could increase the risk of diabetes. This review discusses epidemiologic and laboratory studies of the effects of coffee and its constituents, with a focus on diabetes risk. Weight loss may be an explanatory factor, because one prospective epidemiologic study found that consumption of coffee was followed by lower diabetes risk but only in participants who had lost weight. A second such study found that both caffeine and coffee intakes were modestly and inversely associated with weight gain. It is possible that caffeine and other constituents of coffee, such as chlorogenic acid and quinides, are involved in causing weight loss. Caffeine and caffeinated coffee have been shown to acutely increase blood pressure and thereby to pose a health threat to persons with cardiovascular disease risk. One short-term study found that
ground decaffeinated coffee did not increase blood pressure. Decaffeinated coffee, therefore, may be the type of coffee that can safely help persons decrease diabetes risk. However, the ability of decaffeinated coffee to achieve these effects is based on a limited number of studies, and the underlying biological mechanisms have yet to be elucidated [242].
POSSIBLE ADVERSE EFFECTS OF CAFFEINE ON HEALTH

When consumed in moderation, caffeine-containing products have an excellent safety profile. Apart from CNS stimulation, moderate caffeine consumption can, in many instances, transiently increase blood pressure and reflexively lower heart rate. Long-term ingestion of caffeine, however, can lead to pharmacologic tolerance of some CNS effects but not necessarily its cardiovascular effects. Excessive amounts of caffeine (>2000 mg) can give rise to significant toxic effects, including nausea, vomiting, tachycardia, severe hypertension, arrhythmia, seizures, and even death; however, individuals sensitive to caffeine may exhibit adverse effects at lower doses. The deleterious aspects of caffeine overconsumption were first recognized in 1833, and up until 1980, reports of the toxic effects of caffeine only occasionally appeared in the medical literature, often in the context of ingestions with other legal (e.g. amphetamine) or illegal (e.g. cocaine) stimulants [001].

Between 1980 and 2013, the number of publications in the medical literature that described adverse effects of caffeine or caffeine-containing products has increased by a factor of 8. An uptick in reports beginning in the 1990s may have been bolstered by passage of the US Dietary Supplement Health and Education Act in 1994. From the figure, it is clear that published accounts of caffeine-related toxic effects took another noticeable upswing in 2000-2001, a trend that has continued to the present, where the number of yearly reports has more than doubled during the 13-year period. This increase was likely in part due to the increased use of Ephedra-containing dietary supplements (almost all of which contained natural caffeine sources) during the period of 2000 until 2004, at which time the US Food and Drug Administration (FDA) banned these products because of tolerability concerns. Since 2005, a proliferation of aggressively promoted Ephedra-free dietary supplements and caffeine-containing energy drinks have inundated the world market and appear to underlie many of the tolerability concerns associated with caffeine [001].

Addiction

The common-sense use of the term addiction is that regular consumption is irresistible and that it creates problems. Caffeine use does not fit this profile. However, caffeine intake does no harm to the individual or to society and its users is not compelled to consume it. Though cessation of regular use may result in symptoms such as headache and lethargy, these are easily and reliably reversed by ingestion of caffeine. Some have argued that continued caffeine use is an attempt to suppress low grade withdrawal symptoms such as sleepiness and lethargy. In some moderate users, this is possible; however, in experimental contexts, the phenomenon is too inconsistent to constitute a reliably valid syndrome [243].

Withdrawal effects

It has been well documented that caffeine produces a withdrawal syndrome with cessation of repeated use. This can occur even with repeated usage at low dosages. Studies have demonstrated that withdrawal symptoms can occur with cessation of caffeine use for a short time period as soon as 3 days after administration in novel users and as soon as 12 hours in habitual users. Common symptoms of caffeine withdrawal include headache, irritability, increased fatigue, drowsiness, decreased alertness, difficulty concentrating, and decreased energy and activity levels. Symptoms can be mild to moderate in severity. Fortunately, withdrawal symptoms are generally short-lived [012].
Cerebral problems

Reported effects at moderate doses include locomotor agitation, tachycardia, diuresis, insomnia, irritability, and increased anxiety [06183] and high doses of caffeine can more regularly cause anxiety, insomnia, and nervousness [06171]. Caffeine intake at very high doses (>500-600 mg or four to seven cups per day) can cause restlessness, tremor and tachycardia [13008]. Severe caffeine toxicity has been linked to seizures [012].

Cardiovascular problems

In the cardiovascular system, caffeine acts to increase heart rate [012].

Especially in the short term, caffeine has negative effects, which include making arteries stiffer, and increasing levels of homocysteine, insulin, and possibly cholesterol. Habitual use may cause some of these effects to wear off [028].

Caffeine’s physiological effects include increased heart rate and output, metabolic rate, and urine production [244]. Severe caffeine toxicity has been linked to arrhythmias [012].

Coffee lipid fraction containing cafestol and kahweol but in higher levels they raise serum cholesterol, posing a possible threat to coronary health, for example, myocardial and cerebral infarction, insomnia, and cardiovascular complications [239].

Caffeine may also increase the incidence of premature ventricular contractions (PVCs). Although these hemodynamic effects are similar despite gender, the underlying mechanism appears to differ slightly when comparing men and women. Men given caffeine show an increase in vascular resistance with no effect on cardiac output. However, women given similar amounts of caffeine show no difference in vascular resistance. There is an increase in stroke volume, which results in an increased cardiac output, which accounts for the hemodynamic changes that are seen. There is speculation that this effect may be due to estrogen effects, but has not been proven [012].

Hypertension

In the cardiovascular system, caffeine acts to increase blood pressure. There is a positive relationship with caffeine consumption (in the form of coffee intake) and elevated systolic blood pressure. The extent of blood pressure elevation appears to depend on the individual’s baseline blood pressure. Studies have shown that individuals with diagnosed hypertension have a greater increase in blood pressure in response to caffeine than do normotensive individuals. These effects are additive to that of other pressor agents, including cigarette smoking and psychologic stress [012].

A meta-analysis

The effect of coffee and caffeine on blood pressure (BP) and cardiovascular disease (CVD) in hypertensive persons is uncertain. The objective of one study was to summarize the evidence on the acute and longer-term effects of caffeine and coffee intake on BP and on the association between habitual coffee consumption and risk of CVD in hypertensive individuals. A systematic review and meta-analysis of publications identified in a PubMed and EMBASE search up to 30 April 2011 was undertaken. Data were extracted from controlled trials on the effect of caffeine or coffee intake on BP change and from cohort studies on the association between habitual coffee consumption and CVD. In 5 trials, the administration of 200-300 mg caffeine produced a mean increase of 8.1 mm Hg (95 % confidence interval 5.7 to 10.6 mm Hg) in systolic BP and of 5.7 mm Hg (95 % confidence
interval: 4.1 to 7.4 mm Hg) in diastolic BP. The increase in BP was observed in the first hour after caffeine intake and lasted ≥3 h. In 3 studies of the longer-term effect (2 weeks) of coffee, no increase in BP was observed after coffee was compared with a caffeine-free diet or was compared with decaffeinated coffee. Last, 7 cohort studies found no evidence of an association between habitual coffee consumption and a higher risk of CVD. It was concluded that in hypertensive individuals, caffeine intake produces an acute increase in BP for ≥3 h. However, current evidence does not support an association between longer-term coffee consumption and increased BP or between habitual coffee consumption and an increased risk of CVD in hypertensive subjects [245].

Core body temperature

Several studies have shown that caffeine can increase core body temperature [012].

Increased diuresis

Although questionable, a potential downside is that caffeine also has diuretic properties which can exert ergolytic effects during prolonged endurance events [011] with a concomitant decrease in body weight has also been demonstrated after administration of caffeine [012].

Respiratory problems

Caffeine also increases respiratory rate. In neonates, caffeine is used as a respiratory stimulant to prevent apneic episodes [012].

Experimental

*Inhibitory respiratory responses to progesterone in newborn rats treated with caffeine*

In premature newborns, recurrent apnoea is systematically treated with caffeine to prevent long-term neurocognitive disorders, but a substantial percentage of apnoea persists particularly in neonates born before 28 weeks of gestation. Progesterone has been proposed as a respiratory stimulant potentially suitable for the treatment of newborn apnoea persistent to caffeine. Accordingly we asked whether acute progesterone administration reduces apnoea frequency in newborn rats treated with caffeine. Surprisingly our results show that in newborn rats treated with caffeine, administration of progesterone inhibits breathing and increases apnoea frequency. Additional experiments showed an enhanced GABAergic inhibitory drive on breathing after caffeine treatment, and that progesterone is converted to allopregnanolone (an allosteric modulator of GABAA receptors) to inhibit breathing. We conclude that combining progesterone and chronic caffeine is not an option in preterm neonates, unless the effects of allopregnanolone can be counteracted. Caffeine is the main treatment for apnoea in preterm neonates, but its interactions with other respiratory stimulants like progesterone are unknown. It was tested the hypothesis that the addition of progesterone to caffeine treatments further stimulates ventilation. Newborn rats were treated with water (control) or caffeine (15 mg/kg) by daily gavage between postnatal day (P)3 and P12. At P4 and P12, we measured apnoea frequency, ventilatory responses and metabolic parameters under both normoxia and hypoxia (12 % O2, 20 min) following an acute administration of either saline or progesterone (4 mg/kg; i.p.). Progesterone injection increased the serum levels of both progesterone and its neuroactive metabolite
allopregnanolone. Progesterone had no effect on ventilation in control rats under normoxia. Progesterone depressed ventilation in P12 caffeine-treated rats under normoxia and hypoxia and increased apnoea frequency in both P4 and P12 rats. Because allopregnanolone is an allosteric modulator of GABAA receptors and caffeine may enhance GABAergic inhibition in newborns, we studied the effects of the GABAA receptor antagonist bicuculline at 0, 1, 2 and 3 mg/kg doses and allopregnanolone (10 mg/kg dose) in P12 rats. In caffeine-treated rats, bicuculline enhanced ventilation, while allopregnanolone decreased ventilation and increased total apnoea time. Progesterone had no effect on ventilation and apnoea frequency in caffeine-treated rats injected with finasteride, which blocks the conversion of progesterone to allopregnanolone. It was concluded that combining progesterone and chronic caffeine therapy is not an option for the treatment of persistent apnoea in preterm neonates, unless the effects of allopregnanolone can be counteracted [246].

Muscle fatigue

Caffeine also affects adenosine receptors and its withdrawal may be accompanied with muscle fatigue and allied problems in those addicted to coffee [239].

Interference with females and female hormones

An array of evidence showed that pregnant women or those with postmenopausal problems should avoid excessive consumption of coffee because of its interference with oral contraceptives or postmenopausal hormones [239].

Caffeine ingestion enhances perceptual responses in females

It was examined the influence of caffeine supplementation on cognitive performance and perceptual responses in female team-game players taking low-dose monophasic oral contraceptives of the same hormonal composition. Ten females (24 ± 4 years; 59.7 ± 3.5 kg body mass; 2-6 training sessions per week) took part in a randomised, double-blind, placebo-controlled crossover-design trial. A 90-min intermittent treadmill-running protocol was completed 60 min following ingestion of a capsule containing either 6 mg/kg anhydrous caffeine or artificial sweetener (placebo). Perceptual responses (ratings of perceived exertion (RPE), feeling scale (FS), felt arousal scale (FAS)), mood (profile of mood states (POMS)) and cognitive performance (Stroop test, choice reaction time (CRT)) were completed before, during and after the exercise protocol, as well as after about 12 h post exercise. Caffeine ingestion significantly enhanced the ratings of pleasure and arousal during the exercise protocol, as well as increased vigour, while there was a tendency for reduced fatigue. Caffeine ingestion showed a tendency to decrease RPE and improve reaction times in the Stroop and CRT tests. Caffeine supplementation showed a positive effect on perceptual parameters by increasing vigour and a tendency to decrease fatigue during intermittent running activity in female games players taking low-dose monophasic oral contraceptive steroids (OCS) [247].

Interference of caffeine with alcohol consumption

Interestingly, caffeine ingestion potentiates the slowed reaction time that is induced by alcohol consumption. Therefore, the popularly held belief that coffee is an “antidote” for alcohol intoxication is false [012].
Effects in children

Both cognitive and physical performance can be viewed as potentially enhanceable, and arguments can be made that enhancement can serve two purposes: gaining an edge or keeping up with others (who may or may not have used performance-enhancing substances). Caffeine, a central nervous system and cardiac stimulant, is frequently used by children for both academic and athletic performance enhancement. In fact, the marketplace contains a plethora of caffeinated products marketed directly to children. One article examines safety and ethical issues associated with the use of caffeine by children and explores the question: Can cognitive performance enhancement be ethically permissible if sports performance enhancement is not? [248].

The increased availability of caffeinated drinks raises questions about the level of caffeine that is appropriate for children, as well as the benefits and risks associated with their consumption. Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, this systematic review evaluates evidence from randomised controlled trials investigating the effects of caffeine on cognition, behaviour, mood and exercise performance in children. Observational studies and expert panel guidelines are also discussed. One hundred and nine studies were found, with 11 randomised controlled trials and 13 observational studies meeting the criteria. High caffeine intakes (e.g. >5 mg/kg body weight/day) were associated with an increased risk of anxiety and withdrawal symptoms. However, smaller amounts were not linked with such effects and may benefit cognitive function and sports performance based on adult studies. The evidence suggests that children and adolescents should limit daily caffeine consumption to 2.5 mg/kg body weight/day, equating to one or two cups of tea or one small cup of coffee. Lower contributors of caffeine, such as tea, may be more appropriate for children because they contribute to daily fluid intakes and provide flavonoids. By contrast, caffeinated soft drinks may be less suitable options for children as a result of their acidity, higher caffeine content, presence of added sugar (in some cases) and absence of bioactive compounds. It was concluded that more studies are needed to determine the intakes that represent a risk and whether there may be benefits for alertness and sports performance with moderate intakes of caffeine [249].

One study investigated effects of low (1 mg/kg), moderate (3 mg/kg) and high (5 mg/kg) doses of caffeine on anaerobic performance in boys. Twenty-six 8-10 year old boys participated in a double-blind, crossover, counter-balanced study. Boys received in random order a placebo (PL) or anhydrous caffeine: 1 (CAF-1), 3 (CAF-3), or 5 (CAF-5) mg caffeine/kg body mass in cherry flavored Sprite®. Sixty minutes following consumption boys performed a static handgrip test and then a 30-sec Wingate test. Maximal grip strength was significantly higher in CAF-5 and CAF-3 vs PL, respectively. Absolute and relative peak power were significantly higher in CAF-3 vs PL, respectively. Mean power was significantly higher in CAF-5 vs PL, respectively. Peak Wingate HR was significantly higher in CAF-5 versus PL, respectively. These findings suggest that in boys CAF-1 did not affect performance. During the Wingate test CAF-3 resulted in higher peak power while CAF-5 increased mean power. The significant increase in peak HR following the Wingate test is likely related to greater mean power generated during CAF-5 [250].
One descriptive cross-sectional study assessed the perceptions, knowledge, and experiences of caffeine use by athletes competing at the 2005 Ironman Triathlon World Championships. Questionnaires were distributed to 140 athletes (105 men and 35 women, 40 ± 11 years old) representing 16 countries during prerace registration. A large proportion (73 %) of these endurance athletes believe that caffeine is ergogenic to their endurance performance, and 84 percent believe it improves their concentration. The most commonly reported positive caffeine experiences related to in-competition use of cola drinks (65 %) and caffeinated gels (24 %). The athletes’ ability to accurately quantify the caffeine content of common food items was limited. The most popular sources of caffeine information were self-experimentation (16 %), fellow athletes (15 %), magazines (13 %), and journal articles (12 %). Over half the athletes (53 %) could not identify an amount of caffeine required to improve their triathlon performance. Mean suggested doses were 3.8 ± 3.0 mg/kg body weight. Few side effects associated with taking caffeine during exercise were reported [251].
COMBINATION OF PHARMACOLOGICAL SUBSTANCES WITH CAFFEINE

Combination with ephedrine

The purpose of one study was to investigate the effects of ingesting caffeine (C), ephedrine (E), and their combination on muscular endurance, using a double-blind, repeated measures design. Ninety minutes after ingesting either C (4 mg/kg), E (0.8 mg/kg), a combination of C+E, or a placebo (P), 13 male subjects performed a weight-training circuit consisting of three supersets (SS), each SS consisting of leg press (at 80 % of 1 RM to exhaustion) followed by bench press (at 70 % 1-RM to exhaustion); 2 min of rest intervened between SS. The trials involving ephedrine ingestion (C+E and E), when compared with the nonephedrine trials (C and P), caused significant increases in the mean number of repetitions completed for both the leg-press and bench-press exercises but only during the first SS. During that first set, the mean number ± SD of repetitions for leg press was 19 ± 8, 16 ± 7, 14 ± 6, and 13 ± 5 for the C+E, E, C, and P trials, respectively. The mean numbers of repetitions for the first set of bench-press exercise were 14 ± 3, 13 ± 3, 12 ± 3, and 12 ± 3 for the C+E, E, C, and P trials, respectively. As a result, the total weight lifted during all three sets was greater for the trials involving ephedrine ingestion. Systolic blood pressure before exercise was significantly increased with both ephedrine treatment trials when compared with the other trials. It was concluded that acute ingestion of caffeine and ephedrine increases muscular endurance during the first set of traditional resistance-training exercise. The performance enhancement was attributed primarily to the effects of E; there was no additive effect of caffeine [252].

Caffeine and ephedrine-related alkaloids recently have been removed from International Olympic Committee banned substances lists, whereas ephedrine itself is now permissible at urinary concentrations less than 10 mug.mL. The changes to the list may contribute to an increased use of caffeine and ephedra as ergogenic aids by athletes. Consequently, It was investigated the effects of ingesting caffeine (C) or a combination of ephedra and caffeine (C + E) on muscular strength and anaerobic power using a double-blind, crossover design. Forty-five minutes after ingesting a glucose placebo (P: 300 mg), C (300 mg) or C + E (300 mg + 60 mg), 9 resistance-trained male participants were tested for maximal strength by bench press (1 repetition maximum) and latissimus dorsi pull down (1 repetition maximum). Subjects also performed repeated repetitions at 80 percent of 1 repetition maximumon both activities until exhaustion. After this test, subjects underwent a 30-second Wingate test to determine peak anaerobic cycling power, mean power, and fatigue index. Although subjects reported increased alertness and enhanced mood after supplementation with caffeine and ephedra, there were no significant differences between any of the treatments in muscle strength, muscle endurance, or peak anaerobic power. The results do not support the contention that supplementation with ephedra or caffeine will enhance either muscle strength or anaerobic exercise performance [253].

Unfortunately, there have been multiple deaths linked to the use of caffeine in combination with ephedra. It is felt that, when used in combination, the potential deadly effects are secondary to ephedra, rather than caffeine. However, the cardiovascular effects of ephedra are likely increased with concomitant stimulant use (e.g. caffeine). In fact, based on this evidence, ephedra was banned by the US Food and Drug Administration in 2004. None of the reported deaths were linked to the use of caffeine alone [012].

Preparations containing caffeine and ephedrine have become increasingly popular among sportspersons in recent years as a means to enhance athletic performance. This is due to a slowly accumulating body of evidence suggesting that combination of the two drugs may be more efficacious than each one alone. Caffeine is a compound with documented ergogenicity in various exercise modalities, while ephedrine and related alkaloids have not been shown, as yet, to result in any significant performance improvements. Caffeine-ephedrine mixtures,
however, have been reported in several instances to confer a greater ergogenic benefit than either drug by itself. Although data are limited and heterogeneous in nature to allow for reaching consensus, the increase in performance is a rather uniform finding as it has been observed during submaximal steady-state aerobic exercise, short- and long-distance running, maximal and supramaximal anaerobic cycling, as well as weight lifting. From the metabolic point of view, combined ingestion of caffeine and ephedrine has been observed to increase blood glucose and lactate concentrations during exercise, whereas qualitatively similar effects on lipid fuels (free fatty acids and glycerol) are less pronounced. In parallel, epinephrine and dopamine concentrations are significantly increased, whereas the effects on norepinephrine are less clear. With respect to pulmonary gas exchange during short-term intense exercise, no physiologically significant effects have been reported following ingestion of caffeine, ephedrine or their combination. Yet, during longer and/or more demanding efforts, some sporadic enhancements have indeed been shown. On the other hand, a relatively consistent cardiovascular manifestation of the latter preparation is an increase in heart rate, in addition to that caused by exercise alone. Finally, evidence to date strongly suggests that caffeine and ephedrine combined are quite effective in decreasing the rating of perceived exertion and this seems to be independent of the type of activity being performed. In general, our knowledge and understanding of the physiological, metabolic and performance-enhancing effects of caffeine-ephedrine mixtures are still in their infancy. Research in this field is probably hampered by sound ethical concerns that preclude administration of potentially hazardous substances to human volunteers. In contrast, while it is certainly true that caffeine and especially ephedrine have been associated with several acute adverse effects on health, athletes do not seem to be concerned with these, as long as they perceive that their performance will improve. In light of the fact that caffeine and ephedra alkaloids, but not ephedrine itself, have been removed from the list of banned substances, their use in sports can be expected to rise considerably in the foreseeable future. Caffeine-ephedra mixtures may thus become one of most popular ergogenic aids in the years to come and while they may indeed prove to be one of the most effective ones, and probably one of the few legal ones, whether they also turn out to be one of the most dangerous ones awaits to be witnessed [254].

Herbal weight loss and athletic performance-enhancing supplements that contain ephedrine and caffeine have been associated with serious adverse health events. It was sought to determine whether ephedrine and caffeine have clinically significant pharmacologic interactions that explain these toxicities. Sixteen healthy adults ingested 25 mg ephedrine, 200 mg caffeine, or both drugs in a randomized, double-blind, placebo-controlled crossover study. Plasma and urine samples were collected over a 24-hour period and analyzed by liquid chromatography-tandem mass spectrometry for ephedrine and caffeine concentrations. Heart rate, blood pressure, and subjective responses were recorded. Serum hormonal and metabolic markers were serially measured during a 3-hour fasting period. Ephedrine plus caffeine increased systolic blood pressure (peak difference, 12 ± 9 mmHg; compared with placebo) and heart rate (peak difference, 6 ± 9 beats/min; compared with placebo) and raised fasting glucose, insulin, free fatty acid, and lactate concentrations. Ephedrine alone increased heart rate and glucose and insulin concentrations but did not affect systolic blood pressure. Caffeine increased systolic blood pressure and plasma free fatty acid and urinary epinephrine concentrations but did not increase heart rate. Compared with ephedrine, caffeine produced more subjective stimulant effects. Clinically significant pharmacokinetic interactions between ephedrine and caffeine were not observed. Women taking oral contraceptives had prolonged caffeine elimination (mean elimination half-life, 9.7 hours versus 5.0 hours in men), but sex differences in pharmacodynamic responses were not seen. It was concluded that the individual effects of ephedrine and caffeine were modest, but the drugs in combination produced significant cardiovascular, metabolic, and hormonal responses. These enhanced effects appear to be a result of pharmacodynamic rather than pharmacokinetic interactions [255].
One paper addresses areas where there is controversy regarding caffeine as an ergogenic aid and also identifies topics that have not been adequately addressed. It is clear that caffeine, in moderate amounts, can be used orally as an ergogenic aid in aerobic activity lasting for more than 1 min. It increases endurance and speed, but not maximal VO$_2$ and related parameters. While there are fewer well-controlled studies for resistance exercise, the literature would suggest similar improvements: increased endurance at submaximal tension and power generated in repeated contractions and no change in maximal ability to produce force. It is likely that theophylline (a related methylxanthine) has similar actions and it has been suggested that the combination of caffeine and sympathomimetics may be a more potent ergogenic aid. The voids in our understanding of caffeine include the dose (what amount is optimal, what vehicle is used to deliver the drug as well as method, pattern, and mode of administration), the potential side effects (particularly in competitive settings), health implications (insulin resistance and if combined with ephedrine, cardiovascular risks) and mechanisms of action. It appears unlikely that increased fat oxidation and glycogen sparing is the prime ergogenic mechanism [256].

It has been suggested that the thermogenic effects of combining ephedrine and caffeine are synergistic (the effect of the 2 drugs combined is greater than their additive effects). Similar to ephedrine, caffeine has been suggested to have stimulating effects on the central nervous system (CNS) and energy metabolism. However, the primary reason for combining the 2 drugs is to potentiate the effects of the ephedrine. Ephedrine exerts its thermogenic effects via catecholamine release. The increased catecholamine release after ephedrine ingestion is subjected to negative feedback systems, which then tend to inhibit catecholamine release and actions. These negative feedback systems include adenosine and prostaglandin release in the synaptic junction and elevated phosphodiesterase enzyme activity, which results in degradation of cyclic adenosine monophosphate (cAMP). Caffeine interferes with this negative feedback mechanism by inhibiting both adenosine and phosphodiesterase activity and preventing degradation of cAMP. Aspirin has a similar effect via its inhibition of prostaglandin synthesis. Thus, it is conceivable that either of these mechanisms could potentiate the thermogenic effects of ephedrine. Because of this, some of the more popular weight-loss supplements on the market today combine ma huang (ephedrine), guarana (caffeine), and white willow bark extract (aspirin) [257].

**Caffeine and ephedrine ingestion on anaerobic exercise performance**

Ingestion of a combination of caffeine (C) and ephedrine (E) prolongs time to exhaustion during high-intensity aerobic exercise. CNS stimulation by C and E was proposed as part of the mechanism for the improvement. It was thought that this arousal might also be of benefit during anaerobic exercise. The purpose of this study was to investigate the effect of C, E, and C+E ingestion on performance of anaerobic exercise. Two groups were used to evaluate the effect of C and E on anaerobic performance. Group 1 (WIN) consisted of 16 healthy untrained male subjects who performed a 30-s Wingate test. Group 2 (MAOD) consisted of 8 healthy untrained male subjects who performed a supramaximal (125 % VO$_{2\text{peak}}$) cycle exercise trial to exhaustion to determine maximum accumulated oxygen deficit. The trials commenced 1.5 h after ingesting either C (5 mg/kg), E (1 mg/kg), a combination of C+E, or a placebo (P). All trials were randomized and double blind. Blood samples were assayed for lactate and glucose post drug ingestion just before exercise, and again 3, 5, and 10 min post exercise. Catecholamines were measured in the preexercise and 10-min postexercise blood samples. Ephedrine increased power output during the early phase of the Wingate test, whereas C increased time to exhaustion and O$_2$ deficit during the MAOD test. C, E, and C+E increased blood lactate, glucose, and catecholamine levels. It was concluded that the improvement in anaerobic exercise performance is likely a result of both stimulation of the CNS by E and skeletal muscle by C [258].
Combination with pseudoephedrine

Caffeine (CAF) improves performance in both short- and long-duration running and cycling where performance relies on power output and endurance capacity of leg muscles. No studies have so far tested the effects of CAF while using the double-poling (DP) technique in cross-country skiing. When using the DP technique, arm muscles provide the speed-generating force and therefore play an important role in performance outcome. The metabolism of arm muscles differs from that of leg muscles. Thus, results from studies on leg muscles and CAF may not be directly applicable to exercises while using the DP technique in cross-country skiing. The purpose of one study was therefore to investigate the effects of CAF on exercise performance in DP. Ten highly trained male cross-country skiers performed a placebo (PLA) and CAF trial using a randomized, double-blind, crossover design. Performance was assessed by measuring the time to complete an 8-km cross-country DP performance test (C-PT). CAF (6 mg/kg) or PLA was ingested 75 min before the C-PT. CAF ingestion reduced the time to complete the 8-km C-PT. The subjects maintained higher speed and HR throughout the C-PT, and lactate was higher immediately after the C-PT with CAF exposure compared with PLA. Subjects reported lower RPE at submaximal intensities during CAF compared with PLA, although HR was similar. It was concluded that CAF intake enhances endurance performance in an 8-km C-PT, where arm muscles limit performance. CAF ingestion allowed the participants to exercise with a higher HR and work intensity possibly by reducing perception of effort or facilitating motor unit recruitment [259].

Both caffeine (CAF) and pseudoephedrine (PSE) are proposed to be central nervous system stimulants. However, during competition, CAF is a permitted substance, whereas PSE is a banned substance at urinary levels >150 microg/mL. As a result, one study aimed to compare the effect of CAF versus PSE use on cycling time trial (TT) performance to explore whether the legal stimulant was any less ergogenic than the banned substance. Here, 10 well-trained male cyclists or triathletes were recruited for participation. All athletes were required to attend the laboratory on four separate occasions—including a familiarization trial and three experimental trials, which required participants to complete a simulated 40 km (1,200 kJ) cycling TT after the ingestion of either 200 mg CAF, 180 mg PSE or a nonnutritive placebo (PLA). The results showed that the total time taken and the mean power produced during each TT was not significantly different between trials, despite a 1.3 percent faster overall time (57 s) after CAF consumption. Interestingly, the time taken to complete the second half of the TT was significantly faster in CAF as compared with PSE (by 99 s), with magnitude based inferences suggesting a 91 percent beneficial effect of CAF during the second half of the TT. This investigation further confirms the ergogenic benefits of CAF use during TT performances and further suggests this legal CNS stimulant has a better influence than a supra-therapeutic dose of PSE [260].

Combination with synephrine

Little is known concerning the potential ergogenic effects of p-synephrine supplementation. Therefore, the purpose of the present study was to examine the effects of supplementation with p-synephrine alone and in combination with caffeine on free-weight resistance exercise performance. Twelve healthy, college-aged men performed a control (CT) resistance exercise protocol consisting of 6 sets of squats for up to 10 repetitions per set using 80% of their one repetition-maximum (1RM) with 2 min of rest in between sets. Each subject was randomly assigned (in double-blind, balanced manner) to a treatment sequence consisting of use of 3 supplements: p-synephrine (S; 100 mg), p-synephrine + caffeine (SCF; 100 mg of p-synephrine plus 100 mg of caffeine), or a placebo (P). For each supplement treatment (separated by 1 week), subjects consumed the supplement for 3 days prior to each protocol and the morning of each protocol, and subsequently did not consume any supplements for 3
days following (i.e. wash-out period). On each protocol day, subjects reported to the lab at a
standard time, consumed a supplement, sat quietly for 45 min, performed the resistance
exercise protocol, and sat quietly for 30 min post exercise. Performance (repetition number,
force, velocity and power), blood lactate, and ratings of perceived exertion (RPE) data were
collected during each protocol. Supplements SCF and S produced a significantly greater
number of repetitions performed than CT (by 11.0 ± 8.0 %) and P (by 6.0 ± 7.0 %) and a 10.6
± 12.0 percent greater increase in volume load per protocol than CT and P. Most of the
differences were seen during the last 3 sets. Mean power and velocity for all 6 sets were
significantly higher in SCF compared to CT and P by about 6.2 ± 8.0 percent. No supplement
effects were observed in RPE or blood lactate, and no adverse side effects were observed or
reported. It was concluded that S and SCF augmented resistance exercise performance
(total repetitions, volume load) without increasing blood lactate or RPE. The addition of
caffeine in SCF increased mean power and velocity of squat performance. These results
indicate supplementation with S and SCF can enhance local muscle endurance during
resistance exercise [261].

Combination with theobromine

The combination of theobromine and caffeine, methylxanthines found in chocolate, has
previously been shown to improve mood and cognition. However, it is unknown whether
these molecules act synergistically. This study tested the hypothesis that a combination of
caffeine and theobromine has synergistic effects on cognition, mood and blood pressure in
24 healthy female subjects. The effects of theobromine (700 mg), caffeine (120 mg) or the
combination of both, or placebo were tested on mood (the Bond-Lader visual analog scale),
psychomotor performance (the Digit Symbol Substitution Test) and blood pressure before
and at 1, 2 and 3 h after administration. Theobromine alone decreased self-reported calmness
3h after ingestion and lowered blood pressure relative to placebo 1 h after
ingestion. Caffeine increased self-reported alertness 1, 2 and 3h after ingestion and
centeredness 1 and 2 h after ingestion, and increased blood pressure relative to placebo (at
1 h). The combination of caffeine+theobromine had similar effects as caffeine alone on
mood, but with no effect on blood pressure. There was no treatment effect on performance.
Together these results suggest that theobromine and caffeine could have differential effects
on mood and blood pressure. It was tentatively concluded that caffeine may have more CNS-
mediated effects on alertness, while theobromine may be acting primarily via peripheral
physiological changes [262].

Combination with creatine

Caffeine and creatine are 2 of the most widely available and used compounds in sport.
Although the use of either is not considered a doping infraction, the evidence does suggest
ergogenic potential in certain sports. The purpose of one paper was to review the
pharmacology and potential mechanism(s) of action of caffeine and creatine as they pertain
to possible use as an ergogenic aid in sport. Previous review articles on caffeine and
creatine use in sport were screened for relevant information and references, and studies for
review and recent articles (2007 onwards) were obtained and reviewed using a PUBMED
search with the terms “caffeine AND exercise”, “creatine and creatine monohydrate AND
exercise”, and appropriate linked articles were evaluated. Caffeine taken before (3-6 mg/kg)
or during (1-2 mg/kg) endurance exercise enhances performance, through central nervous
system and direct muscle effects. Creatine monohydrate supplementation at higher (approx.
20 g/day × 3-5 days) or lower (approx. 5 g/day × 30 days) doses increases skeletal muscle
total and phosphocreatine by 10-20 percent. Creatine supplementation appears to minimally
but significantly enhance high-intensity sport performance and the mass and possibly
strength gains made during resistance exercise training over the first few months. Although caffeine and creatine appear to be ergogenic aids, they do so in a sport-specific context and there is no rationale for their simultaneous use in sport. Higher doses of caffeine can be toxic and appear to be ergolytic. There is no rationale for creatine doses in excess of the recommendations, and some athletes can get stomach upset, especially at higher creatine doses [263].

The influences of creatine and caffeine supplementation associated with power exercise on lean body mass (LBM) composition are not clear. The purpose of one study was to determine whether supplementation with high doses of creatine and caffeine, either solely or combined, affects the LBM composition of rats submitted to vertical jumping training. Male Wistar rats were randomly divided into 8 groups: sedentary (S) or exercised (E), placebo (Pl), creatine (Cr), caffeine (Caf) or creatine plus caffeine (CrCaf). The supplemented groups received creatine (load: 0.430 g/kg of body weight for 7 days; and maintenance: 0.143 g/kg of body weight for 35 days, caffeine (15 mg/kg of body weight for 42 days) or creatine plus caffeine. The exercised groups underwent a vertical jump training regime (load: 20 to 50 % of body weight, 4 sets of 10 jumps interspersed with 1 min resting intervals), 5 days/wk, for 6 weeks. LBM composition was evaluated by portions of water, protein and fat in the rat carcass. Exercised animals presented a lower carcass weight (11 %), as compared to sedentary animals. However, no effect of supplementation was observed on carcass weight. There were no significant differences among the groups for percentage of water in the carcass. The percentage of fat in the group SCr was higher than in the groups SCaf and ECr. A higher percentage of protein was observed in the groups EPl and ECaf when compared to the groups SPl and SCaf. The percentage of fat in the carcass decreased, while those of water and protein increased in exercised animals, compared to sedentary animals. Caffeine groups presented reduced percentage of fat when compared to creatine supplemented groups. It was concluded that high combined doses of creatine and caffeine does not affect the LBM composition of either sedentary or exercised rats, however, caffeine supplementation alone reduces the percentage of fat. Vertical jumping training increases the percentages of water and protein and reduces the fat percentage in rats [264].

Nutritional supplementation is a common practice among athletes, with creatine and caffeine among the most commonly used ergogenic aids. Hundreds of studies have investigated the ergogenic potential of creatine supplementation, with consistent improvements in strength and power reported for exercise bouts of short duration (≤30 seconds) and high intensity. Caffeine has been shown to improve endurance exercise performance, but results are mixed in the context of strength and sprint performance. Further, there is conflicting evidence from studies comparing the ergogenic effects of coffee and caffeine anhydrous supplementation. Previous research has identified independent mechanisms by which creatine and caffeine may improve strength and sprint performance, leading to the formulation of multi-ingredient supplements containing both ingredients. Although scarce, research has suggested that caffeine ingestion may blunt the ergogenic effect of creatine. While a pharmacokinetic interaction is unlikely, authors have suggested that this effect may be explained by opposing effects on muscle relaxation time or gastrointestinal side effects from simultaneous consumption. One review aimed to evaluate the ergogenic potential of creatine and caffeine in the context of high-intensity exercise. Research directly comparing coffee and caffeine anhydrous is discussed, along with previous studies evaluating the concurrent supplementation of creatine and caffeine [265].

**Effect on strength and sprint**

The purpose of one study was to determine the effect of 5 d of creatine (CRE) loading alone or in combination with caffeine anhydrous (CAF) or coffee (COF) on upper and lower body strength and sprint performance. Physically active males (n=54; Mean ± SD; Age = 20.1 ±
2.1 yrs; Weight = 78.8 ± 8.8 kg) completed baseline testing, consisting of one-repetition maximum (1RM) and repetitions to fatigue (RTF) with 80 percent 1RM for bench press (BP) and leg press (LP), followed by a repeated sprint test of five, 10 s sprints separated by 60 s rest on a cycle ergometer to determine peak power (PP) and total power (TP). At least 72 hr later, subjects were randomly assigned to supplement with CRE (5 g creatine monohydrate, 4 times/d; n=14), CRE+CAF (CRE + 300 mg/d of CAF; n=13), CRE+COF (CRE + 8.9 g COF, yielding 303 mg caffeine; n=13), or placebo (PLA; n=14) for 5 d. Serum creatinine (CRN) was measured prior to and following supplementation and on day six, participants repeated pre-testing procedures. Strength measures were improved in all groups, with no significant time × treatment interactions. No significant interaction or main effects were observed for PP. For TP, a time × sprint interaction was observed, with no significant interactions between treatment groups. A time × treatment interaction was observed for serum CRN values that showed increases in all groups except PLA. Four subjects reported mild gastrointestinal discomfort with CRE+CAF, with no side effects reported in other groups. These findings suggest that neither CRE alone, nor in combination with CAF or COF, significantly affected performance compared to PLA [266].

Combination with salbutamol

The main aim of one study was to evaluate the comparative and additive effects of caffeine and albuterol (short-acting beta2-agonist) on the severity of exercise induced bronchoconstriction (EIB). Ten asthmatic subjects with exercise-induced bronchoconstriction participated in a randomized, double-blind, double-dummy crossover study. One hour before an exercise challenge, each subject was given 0, 3, 6, or 9 mg/kg of caffeine or placebo mixed in a flavored sugar drink. Fifteen minutes before the exercise bout, an inhaler containing either albuterol (180 microg) or placebo was administered to each subject. Pulmonary function tests were conducted pre- and post-exercise. Caffeine at a dose of 6 and 9 mg/kg significantly reduced the mean maximum percentage fall in post-exercise FEV1 compared to the double-placebo and baseline. There was no significant difference in the post-exercise % fall in FEV1 between albuterol and the 9 mg/kg dose of caffeine. Interestingly, there was no significant difference in the post-exercise percentage fall in FEV1 between albuterol and albuterol with 3, 6 or 9 mg/kg of caffeine. Similar changes were observed for the post-exercise percentage fall in FVC, FEF (25-75 %) and PEF. These data indicate that moderate (6 mg/kg) to high doses (9 mg/kg) of caffeine provide a significant protective effect against EIB. It is feasible that the negative effects of daily use of short-acting beta2-agonists by asthmatic athletes could be reduced simply by increasing caffeine consumption prior to exercise [267].

Combination with sodium bicarbonate

The combined supplementation of caffeine and sodium bicarbonate may have a potential ergogenic effect during intermittent exercise tasks such as judo; however, its effect in this sport has not been tested. To investigate the isolated and combined effects of caffeine (CAF) and sodium bicarbonate (NaHCO3) on judo performance. Ten judokas performed four supplementation protocols (i) NaHCO3, (ii) CAF, (iii) NaHCO3 plus CAF and (iv) placebo (cellulose) followed by three Special Judo Fitness Tests (SJFT) interspaced with 5-min rest. In the first SJFT, the combined supplement (NaHCO3 + CAF) resulted in a higher number of throws compared to placebo (24.4 ± 0.9 and 23.2 ± 1.5 throws respectively). There was no significant difference between conditions for the second SJFT. In the third SJFT, NaHCO3 and NaHCO3 + CAF resulted in increased throws when compared to placebo (23.7 ± 1.6, 24.4 ± 1.0, and 22.0 ± 1.6 throws). When the total throws performed in the three SJFT were summed, they were higher than placebo only for NaHCO3 + CAF (68.8 ± 4.4 and 72.7 ± 3.1
Post-exercise plasma lactate after each SJFT was higher in all experimental conditions compared to placebo. There was no significant difference in RPE across the conditions. The results of the current study show that the combined supplementation of caffeine and sodium bicarbonate increases judo performance [268].

To determine the effects of ingesting caffeine (CAFF) and sodium bicarbonate (SB), taken individually and simultaneously, on 3-km cycling time-trial (TT) performance 10 well-trained cyclists, age 24 years, participated in this acute-treatment, double-blind, crossover study that involved four 3-km cycling TTs performed on separate days. Before each TT, participants ingested either 3 mg/kg body mass (BM) of CAFF, 0.3 g/kg BM of SB, a combination of the two (CAFF+SB), or a placebo (PLAC). They completed each 3-km TT on a laboratory-based cycle ergometer, during which physiological, perceptual, and performance measurements were determined. For statistical analysis, the minimal worthwhile difference was considered about 1 percent based on previous research. Pretrial pH and HCO3 were higher in SB and CAFF+SB than in the CAFF and PLAC trials. Differences across treatments for perceived exertion and gastric discomfort were mostly unclear. Compared with PLAC, mean power output during the 3-km TT was higher in CAFF, SB, and CAFF+SB trials (2.4 %, 2.6 %, 2.7 % respectively), resulting in faster performance times (-0.9, -1.2, -1.2 % respectively). Effect sizes for all trials were small (0.21-0.24). Thus, when ingested individually, both CAFF and SB enhance high-intensity cycling TT performance in trained cyclists. However, the ergogenic effect of these 2 popular supplements was not additive, bringing into question the efficacy of coingesting the 2 supplements before short-duration high-intensity exercise. In this study there were no negative effects of combining CAFF and SB, 2 relatively inexpensive and safe supplements [269].

The purpose of one study was to investigate the effects of sodium bicarbonate (NaHCO₃), caffeine, and their combination on repeated 200-m freestyle performance. Six elite male freestyle swimmers ingested sodium bicarbonate (0.3 g/kg), caffeine (6.2 + 0.3 mg/kg), a combination of both, and placebo on 4 separate occasions before completing 2 maximal 200-m freestyle time trials separated by 30 min. No significant differences were observed for performance but drop-off in performance time from first to second trial, however, was significantly greater when caffeine was ingested than with bicarbonate or the combination. This is likely because of the lower blood pH and slower recovery of blood HCO₃ after caffeine ingestion. These findings suggest that the ergogenic benefit of taking caffeine alone for repeated 200-meter swimming performance appears limited. When combined with sodium bicarbonate, however, its negative impact on repeated maximal exercise performance is reversed [270].

The purpose of this investigation was to determine the effect of ingested caffeine, sodium bicarbonate, and their combination on 2,000-m rowing performance, as well as on induced alkalosis (blood and urine pH and blood bicarbonate concentration, HCO₃⁻, blood lactate concentration, gastrointestinal symptoms, and rating of perceived exertion (RPE). In a double-blind, crossover study, 8 well-trained rowers performed 2 baseline tests and 4 × 2,000-m rowing-ergometer tests after ingesting 6 mg/kg caffeine, 0.3 g/kg body mass (BM) sodium bicarbonate, both supplements combined, or a placebo. Capillary blood samples were collected at preingestion, pretest, and posttest time points. Pairwise comparisons were made between protocols, and differences were interpreted in relation to the likelihood of exceeding the smallest worthwhile-change thresholds for each variable. A likelihood of >75 percent was considered a substantial change. Caffeine supplementation elicited a substantial improvement in 2,000-m mean power, with mean (± SD) values of 354 ± 67 W versus placebo with 346 ± 61 W. Pretest bicarbonate reached 29.2 ± 2.9 mmol/L with caffeine + bicarbonate and 29.1 ± 1.9 mmol/L with bicarbonate. There were substantial increases in pretest bicarbonate and pH and posttest urine pH after bicarbonate and caffeine + bicarbonate supplementation compared with placebo, but unclear performance effects. It was concluded that rowers' performance in 2,000-m efforts can improve by about 2 percent with 6
mg/kg BM caffeine supplementation. When caffeine is combined with sodium bicarbonate, gastrointestinal symptoms may prevent performance enhancement, so further investigation of ingestion protocols that minimize side effects is required [271].

**Combination with sodium citrate**

The aim of one study was to investigate whether caffeine and/or sodium citrate have an ergogenic effect on the 1500 m exercise performance in elite wheelchair athletes. A placebo-controlled, randomized, cross-over and double-blind study design was conducted with the four treatments placebo, caffeine, sodium citrate and the combination of caffeine and sodium citrate. Nine healthy, elite wheelchair racing athletes (category T53/54) completed the study. All athletes were national team members, including several Paralympic Games, World and European Championship medalists. The athletes performed a 1500 m time trial four times on a wheelchair training roller. Time to complete 1500 m, pH, bicarbonate and sodium concentration as well as lactate concentration were measured. The time to complete 1500 m was not significantly different between the four treatments (placebo; caffeine; sodium citrate; combination. However, pH and bicarbonate concentrations were significantly increased with sodium citrate ingestion compared to placebo. Moreover, maximal lactate concentrations were significantly higher in the caffeine and the combination treatment compared to placebo. The supplementation with sodium citrate and/or caffeine did not provide an ergogenic effect on the 1500 m exercise performance in wheelchair elite athletes [272].

**Combination with carbohydrates**

The oral presence of carbohydrate (CHO) and caffeine (CAF) may independently enhance exercise performance, but their influence on performance during prolonged exercise is less known. To determine the independent and combined effects of CHO and CAF administered in chewing gum during a cycling time-trial (TT) following prolonged exercise 11 male cyclists (32.2 ± 7.5 years, 74.3 ± 6.8 kg, 60.2 ± 4.0 ml/kg/min \( \text{O}_2\text{peak} \)) performed 4 experimental trials consisting of 90-min constant-load cycling at 80 performance of their second ventilatory threshold (207 ± 30 W), followed immediately by a 20-km TT. Under double-blinded conditions, cyclists received placebo (PLA), CHO, CAF, or a combined (CHO+CAF) chewing gum at 0, 5, 10, and 15-km points of the TT. Overall TT performance was similar across experimental and PLA trials. Compared with PLA, mean power output tended to be higher in the first two quarters of the TT with CHO and was substantially improved in the last two quarters during CAF and CHO+CAF trials. There were no differences in average heart rate and only small changes in blood glucose, which were unrelated to performance. Blood lactate was substantially higher post TT for CAF and CHO+CAF. It was concluded that following prolonged constant-load cycling, the oral presence of CHO and CAF in chewing gum, independently or in combination, did not improve overall performance, but did influence pacing [273].

**Feeling smart: effects of caffeine and glucose on cognition, mood and self-judgment**

During education and early career, young adults often face examinations and assessment centers. Coffee and energy drinks are convenient and commonly used to enhance or maintain performance in these situations. Whether these macronutrients improve performance in a demanding and drawn-out multi-task situation is not clear. Using double-blind, placebo-controlled studies, it was set out to examine the effects of caffeine and glucose in an assessment center-like situation, under natural consumption conditions, in a group of young adults who were heterogeneous with respect to consumption patterns. It was measured multi-task performance including logical thinking, processing speed, numeric and
verbal memory, attention and the ability to concentrate, and mood over a two-hour period. Caffeine and glucose were administered in common beverages with appropriate placebo controls allowing the assessment of psychological effects of expectancy. Importantly, and in contrast to most previous studies, participants retained their habitual caffeine and sugar intake (studies 1 and 2) as this represents common behavior. Based on the bulk of literature, we hypothesized that (i) caffeine enhances attentional performance and mood, while performance in more complex tasks will remain unchanged, and that (ii) glucose enhances performance on memory tasks accompanied with negative mood. The results provide evidence that neither caffeine nor glucose significantly influence cognitive performance when compared with placebo, water, or no treatment controls in a multi-task setting. Yet, caffeine and, by trend, placebo improve dispositions such that participants perceive preserved mental energy throughout the test procedure. These subjective effects were stronger after 24 h caffeine abstinence (study 3). Future studies will have to address whether these mood changes actually result in increased motivation during a challenging task [274].

**Caffeinated carbohydrate-gel ingestion**

To investigate the effect of ingesting a caffeinated carbohydrate gel (CC) 10 minutes prior on 2000-m rowing performance compared with a carbohydrate-only placebo gel (CP) a counterbalanced, single-blind, crossover study design was employed (n=13). All participants completed 1 familiarization trial followed by 2 experimental rowing time trials. The experimental trials were performed 10 min after ingesting CP (21.6 g of carbohydrate, 0 mg caffeine) or CC (21.6 g carbohydrate, 100 mg caffeine), and heart rate (HR), oxygen consumption (VO₂), carbon dioxide production, minute ventilation (VE), respiratory-exchange ratio (RER), rating of perceived exertion (RPE), gastrointestinal discomfort (GI), and thirst perception (Thirst) were recorded every 200 m. Blood lactate [La⁻] was recorded immediately before and after exercise. A paired samples t test identified a significant improvement in 2000-m performance of 5.2 ± 3.9 s. Two-way repeated-measures ANOVA revealed no significant treatment effect for HR, VO₂, VE, RPE, GI, or thirst for CP and CC, respectively. Paired-samples t tests revealed no treatment effect for postexercise [La⁻] between CP and CC. It was concluded that a relatively low dose of caffeine (1.3 ± 0.1 mg/kg body mass) in an isotonic carbohydrate gel ingested only 10 min before performance improved 2000-m rowing time [275].

**In football**

One study aimed to investigate whether isolated or combined carbohydrate (CHO) and caffeine (CAF) supplementation have beneficial effects on performance during soccer-related tests performed after a previous training session. Eleven male, amateur soccer players completed 4 trials in a randomized, double-blind, and crossover design. In the morning, participants performed the Loughborough Intermittent Shuttle Test (LIST). Then, participants ingested (i) 1.2 g/kg body mass/h CHO in a 20 percent CHO solution immediately after and 1, 2, and 3 h after the LIST; (ii) CAF (6 mg/kg body mass) 3 h after the LIST; (iii) CHO combined with CAF (CHO+CAF); and (iv) placebo. All drinks were taste-matched and flavourless. After this 4-h recovery, participants performed a countermovement jump (CMJ) test, a Loughborough Soccer Passing Test (LSPT), and a repeated-sprint test. There were no main effects of supplementation for CMJ, LSPT total time, or best sprint and total sprint time from the repeated-sprint test. There were also no main effects of supplementation for heart rate, plasma lactate concentration, rating of perceived exertion (RPE), pleasure-displeasure, and perceived activation. However, there were significant time effects, with heart rate, plasma lactate concentration, RPE, and perceived activation increasing with time, and pleasure-displeasure decreasing with time. In conclusion, isolated and/or combined CHO and CAF supplementation is not able to improve soccer-related performance tests when performed after a previous training session [276].
In badminton

The aim of one investigation was to investigate the effect of ingesting carbohydrate and caffeine solutions on measures that are central to success in badminton. Twelve male badminton players performed a badminton serve accuracy test, coincidence anticipation timing (CAT) and a choice reaction time sprint test 60 min before exercise. Participants then consumed 7 mL/kg body mass of either water (PLA), 6.4 percent carbohydrate solution (CHO), a solution containing a caffeine dose of 4 mg/kg (CAF) or 6.4 percent carbohydrate and 4 mg/kg caffeine (C+C). All solutions were flavoured with orange-flavoured concentrate. During the 33 min fatigue protocol, participants were provided with an additional 3 mL/kg body mass of solution, which was ingested before the end of the protocol. As soon as the 33 min fatigue protocol was completed, all measures were recorded again. Short serve accuracy was improved following the ingestion of CHO and C+C compared with PLA. Long serve accuracy was improved following the ingestion of C+C compared with PLA. Absolute error in CAT demonstrated smaller deteriorations following the ingestion of C+C compared with PLA. Choice reaction time improved in all trials with the exception of PLA, which demonstrated a reduction, although C+C was faster than all trials. These findings suggest that the ingestion of a caffeinated carbohydrate solution before and during a badminton match can maintain serve accuracy, anticipation timing and sprinting actions around the court [277].

There has been interest in whether the combining of carbohydrates and caffeine would have a synergistic effect. The supplied carbohydrate serves as a potential substrate while caffeine serves as a neurological stimulant. It has been reported that the co-ingestion of caffeine and carbohydrate led to a 4.6 percent improvement over carbohydrate-only solution in endurance performance. Those authors reported that caffeine increases the oxidation of exogenous carbohydrate during exercise. It has also been reported a synergistic effect when carbohydrates and caffeine were combined compared to either of the components separately and a placebo during a short term, high intensity cycling exercise [278].

Caffeine plus carbohydrates or fat

It was examined the effect of caffeine co-ingested with either carbohydrate or fat on metabolism and performance in eight endurance-trained subjects who performed a random order of four experimental trials consisting of 120 min of steady-state ergometer cycling at 70 \% of maximal \( O_2 \) uptake (SS) followed by a time trial in which subjects completed a set amount of work as quickly as possible. One hour before SS subjects ingested either 2.6 g/kg carbohydrate (CHO); 2.6 g/kg CHO + 6 mg/kg caffeine (CHO + CAF); 1.2 g/kg fat with 2000 U I.V. heparin (FAT); or 1.2 g/kg fat with 2000 U I.V. heparin + 6 mg/kg caffeine (FAT + CAF). The rate of carbohydrate oxidation was higher and the rate of fat oxidation lower with carbohydrate than fat ingestion. Yet despite lower carbohydrate use with fat feeding, the time taken to complete the time trial was less after carbohydrate than after fat ingestion. It was concluded that caffeine co-ingested with either carbohydrate or fat meals has no additive effect on substrate utilization or exercise performance and that carbohydrate ingestion before exercise improves subsequent time trial performance compared with fat ingestion [279].

Combination with epigallocatechin

Different outcomes of the effect of catechin-caffeine mixtures and caffeine-only supplementation on energy expenditure and fat oxidation have been reported in short-term studies. Therefore, a meta-analysis was conducted to elucidate whether catechin-caffeine mixtures and caffeine-only supplementation indeed increase thermogenesis and fat oxidation. First, English-language studies measuring daily energy expenditure and fat
oxidation by means of respiration chambers after catechin-caffeine mixtures and caffeine-only supplementation were identified through PubMed. Six articles encompassing a total of 18 different conditions fitted the inclusion criteria. Second, results were aggregated using random/mixed-effects models and expressed in terms of the mean difference in 24 h energy expenditure and fat oxidation between the treatment and placebo conditions. Finally, the influence of moderators such as BMI and dosage on the results was examined as well. The catechin-caffeine mixtures and caffeine-only supplementation increased energy expenditure significantly over 24 h (4.7 % and 4.8 %, respectively). However, 24 h fat oxidation was only increased by catechin-caffeine mixtures. A dose-response effect on 24 h energy expenditure and fat oxidation occurred with a mean increase of 0.53 kJ/mg and 0.02 g/mg for catechin-caffeine mixtures and 0.44 kJ/mg and 0.01 g/mg(-1) for caffeine-only. In conclusion, catechin-caffeine mixtures or a caffeine-only supplementation stimulates daily energy expenditure dose-dependently by 0.4-0.5 kJ/mg administered. Compared with placebo, daily fat-oxidation was only significantly increased after catechin-caffeine mixtures ingestion [280].

The aim of one study was to evaluate the combined effects of a 10-week exercise program with ingestion of caffeine and epigallocatechin-3-gallate (EGCG) on body composition, cardiovascular fitness, and strength in overweight and obese women. In a double-blind, placebo-controlled approach, overweight and obese women (n=27) were randomly assigned to treatment groups with exercise (an active-supplementing group with exercise (EX-Act) and a placebo group with exercise (EX-PL)) or without exercise (an active-supplementing group without exercise (NEX-Act) and a placebo group without exercise (NEX-PL)). All participants consumed 1 drink per day for 10 weeks; EX-Act and EX-PL participated in a concurrent endurance and resistance training program. Changes in body composition were assessed using a 4-compartment model. Changes in muscle mass (MM) were evaluated using a DXA-derived appendicular lean-soft tissue equation. There was a significant time × treatment interaction for MM and total cholesterol (TC), and a significant time × training interaction for peak oxygen consumption and upper-body and lower-body strength. Significant differences between the EX groups and NEX groups for percentage change in MM and peak oxygen consumption, and upper-body and lower-body strength, were revealed. Clinical markers for hepatic and renal function revealed no adverse effects. TC significantly decreased for the active-supplementing groups (EX-Act, NEX-Act). The current study suggests that implementing a caffeine-EGCG-containing drink prior to exercise may improve MM, fitness, and lipid profiles in overweight women [281].

Caffeine with phosphatidylserine

Phosphatidylserine (PS) may attenuate the adverse effects of physical fatigue. Therefore, it was investigated the effects of a multi-ingredient supplement containing 400 mg/d PS and 100 mg/d caffeine (supplement, SUP) for 2 weeks on measures of cognitive function (CF), reaction time (RT), and mood (MD) following an acute exercise stress. It is hypothesized that PS will maintain preexercise CF and RT scores, while attenuating postexercise fatigue. Participants completed 2 acute bouts of resistance exercise (T1 and T2) separated by 2-week ingestion of SUP or control (CON). Outcome measures were assessed pre- and postexercise. When collapsed across groups, a significant decrease in RT performance was seen in the 60-second reaction drill from pre- to postexercise at T1. All other RT tests were similar from pre- to postexercise at T1. Reaction time was not significantly changed by PS. When collapsed across groups, a significant increase in performance of the serial subtraction test was seen. A significant increase (8.9 % and 7.1 %) in the number of correct answers and a significant decrease (8.0 % and 7.5 %) in time to answer were seen from pre- to postworkout at T1 and T2, respectively. A significant increase in total MD score from pre- to postworkout was observed for CON but not for PS at T2. Phosphatidylserine significantly attenuated pre- to postexercise perception of fatigue compared to CON. Ingestion of SUP for
14 days appears to attenuate postexercise MD scores and perception of fatigue, but does not affect CF or RT, in recreationally trained individuals [282].

**Combination with amitryptilin**

The interaction of caffeine (1 mg/kg) and amitriptyline (15 mg/kg) on the immobility time during Porsolt’s forced swimming test was investigated in female Wistar rats. Vehicle-treated animals had a significant increase of immobility time during the second day of the test. Amitriptyline only prevented the increase of immobility time during the second session. While caffeine alone prevented the increase of immobility time in both groups, the methylxanthine abolished the effect of amitriptyline, leaving the antidepressant action. These results suggest that the anti-immobility effect of amitriptyline is mediated in part by endogenous adenosine [283].

**Combination with amino acids**

Heat and hypoxia exacerbate central nervous system (CNS) fatigue. It was therefore investigated whether essential-amino-acid (EAA) and caffeine ingestion attenuates CNS fatigue in a simulated team-sport specific running protocol in a hot and hypoxic environment. Sub-elite male team-sport athletes (n=8) performed a repeat-sprint running protocol on a non-motorized treadmill in an extreme environment on four separate occasions. Participants ingested one of four supplements: a double placebo, 3 mg/kg body mass of caffeine+placebo, 2x7 g EAA (Musashi Create™)+placebo, or caffeine+EAA prior to each exercise session using a randomized, double-blind crossover design. Electromyography (EMG) activity and quadriceps evoked responses to magnetic stimulation were assessed from the dominant leg at pre-, half-time, and post-exercise. Central activation ratio (CAR) was used to quantify completeness of quadriceps activation. Oxygenation of the pre-frontal cortex was measured via near-infrared spectroscopy. Mean sprint work was higher (+174J) in the caffeine+EAA condition versus EAA alone. The decline in EMG activity was less (13 %) in caffeine+EAA versus EAA alone. Similarly, the pre-to-post exercise decrement in CAR was significantly less (-2.7 %) when caffeine+EAA were ingested compared to placebo. Cerebral oxygenation was lower (-5.6 %) in the caffeine+EAA condition compared to LNAA alone. Co-ingestion of caffeine and EAA appears to maintain muscle activation and central drive, with a small improvement in running performance [284].

**Combination with taurine**

Consumption of energy drinks is common among athletes; however, there is a lack of research on the efficacy of these beverages for short-duration, intense exercise. The purpose of one research was to investigate the acute effects of a low-calorie caffeine-taurine energy drink (AdvoCare Spark) on repeated sprint performance and anaerobic power in National Collegiate Athletic Association Division I football players. Twenty football players (age 20) participated in a double-blind, randomized crossover study in which they received the energy drink or an isoenergetic, isovolumetric, non-caffeinated placebo in 2 trials separated by 7 days. The Running Based Anaerobic Sprint Test, consisting of six 35-m sprints with 10 s of rest between sprints, was used to assess anaerobic power. Sprint times were recorded with an automatic electronic timer. The beverage treatment did not significantly affect power or sprint time. However, there was a significant interaction effect between caffeine use and the beverage for sprint times as well as for anaerobic power, indicating a confounding effect. In conclusion, a caffeine-taurine energy drink did not improve the sprint performance or anaerobic power of college football players, but the level of
caffeine use by the athletes likely influenced the effect of the drink [285].

**Experimental**

Caffeine enhances endurance performance; however, its effect on accumulated lactate remains unclear. Conversely, taurine, which also enhances endurance performance, decreases accumulated lactate. In one study, the effect of combination of caffeine and taurine on endurance performance was assessed. Mice ran on a treadmill, and the accumulated lactate was measured. In addition, muscle fibers from the gastrocnemius muscle of the mice were stained with ATPase and analyzed. The use of caffeine and taurine over a 2 week period enhanced endurance performance. Moreover, taurine significantly decreased the accumulated concentration of lactate over long running distances. However, the diameter of the cross-sections and ratios of Types I, IIA, and IIB muscle fibers were not affected [286].

**Combination with carnitine**

The purpose of one study was to examine whether caffeine (CAF), carnitine (CAR), or CAF+CAR mixture administration affects exercise endurance time via carnitine metabolism. Water (CON), CAF, CAR, or CAF+CAR mixture was administered to five male rugby athletes participating in this study by a randomized double-blind fashion who were made to ride a cycle ergometer for exercise. The CAF effect on exercise endurance time was small, but the CAR trial significantly increased the exercise endurance time compared with CON trial; a further CAF+CAR mixture trial had greater effects on the exercise endurance time than those of a CON, CAF, or CAR trial. A CAR or CAF+CAR mixed trial increased urinary nonesterified carnitine (NEC) and total carnitine (TCAR), but no changes were observed in acid-soluble acylcarnitine (ASAC) and acid-insoluble acylcarnitine (AIAC) excretion. A CAR or CAF+CAR mixed trial resulted in higher levels of plasma NEC, ASAC, and TCAR fractions than the CON and CAF trials did on exhaustion time. Total cholesterol, triglyceride, and free fatty acid in blood were significantly increased at exhaustion time, but they were not affected in the CAF or the CAR trial. These results suggest that carnitine ingestion could promote fat oxidation, resulting in higher endurance performance in athletes, and especially these ergogenic effects of carnitine coingested with caffeine may be greater than those of carnitine alone [287].

**Caffeine combined with carnitine and choline decreases body fat and serum leptin**

The effect of a combination of caffeine, carnitine and choline with or without exercise on changes in body weight, fat pad mass, serum leptin concentration and metabolic indices was determined in 20 male, 7-wk-old Sprague-Dawley rats. They were given free access to a nonpurified diet without or with caffeine, carnitine and choline at concentrations of 0.1, 5 and 11.5 g/kg diet, respectively. In a 2x2 factorial design, one-half of each dietary group was exercised, and the other half was sedentary. Body weight and food intake of all rats were measured every day for 28 d. Rats were killed and blood and tissue samples were collected and analyzed for biochemical markers. Food intake of the groups was not different, but the body weight was significantly reduced by exercise in both dietary groups. Fat pad weights and total lipids of epididymal, inguinal and perirenal regions were significantly reduced by the supplements as well as by exercise. Regardless of exercise, supplements significantly lowered triglycerides in serum but increased levels in skeletal muscle. Serum leptin concentrations were equally lowered by supplements and exercise. Serum leptin was correlated with body weight fat pad weight and serum glucose. It was concluded that the indices of body fat loss due to dietary supplements were similar to those due to mild exercise, and there were no interactive effects of the two variables [288].
Combination with ecstasy (methyleneoxymethamphetamine, MDMA)

Concomitant consumption of caffeine with recreational psychostimulant drugs of abuse can provoke severe acute adverse reactions in addition to longer term consequences. The mechanisms by which caffeine increases the toxicity of psychostimulants include changes in body temperature regulation, cardiotoxicity and lowering of the seizure threshold. Caffeine also influences the stimulatory, discriminative and reinforcing effects of psychostimulant drugs. In this review, we consider our current understanding of such caffeine-related drug interactions, placing a particular emphasis on an adverse interaction between caffeine and the substituted amphetamine, 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”), which has been most recently described and characterized. Co-administration of caffeine profoundly enhances the acute toxicity of MDMA in rats, as manifested by high core body temperature, tachycardia and increased mortality. In addition, co-administration of caffeine enhances the long-term serotonergic neurotoxicity induced by MDMA. Observations to date support an interactive model of drug-induced toxicity comprising MDMA-related enhancement of dopamine release coupled to a caffeine-mediated antagonism of adenosine receptors in addition to inhibition of PDE. These experiments are reviewed together with reports of caffeine-related drug interactions with cocaine, d-amphetamine and ephedrine where similar mechanisms are implicated. Understanding the underlying mechanisms will guide appropriate intervention strategies for the management of severe reactions and potential for increased drug-related toxicity, resulting from concomitant caffeine consumption [289].

Combination with green tea and cayenne powder

Thermogenic (TRM) supplements are often used by people seeking to decrease body weight. Many TRM supplements are formulated with multiple ingredients purported to increase energy expenditure and maximize fat loss. However, in the past some TRM ingredients have been deemed unsafe and removed from the market. Therefore, it is important to verify the safety of multi-ingredient TRM supplements with chronic consumption. To assess the safety of daily consumption of a multi-ingredient TRM supplement over a 28-day period in healthy adults. Twenty-three recreationally active adults (11M, 12F; 27 ± 5) were randomly assigned either to consume a multi-ingredient TRM supplement (SUP; n=9) or remain unsupplemented (CRL; n=14) for 28 days. Participants maintained their habitual dietary and exercise routines for the duration of the study. Fasting blood samples, resting blood pressure, and heart rate were taken before and after the supplementation period. Samples were analyzed for complete blood counts, comprehensive metabolic, and lipid panels. Significant group by time interactions were present for diastolic BP, creatinine, estimated glomerular filtration rate (eGFR), chloride, CO2, globulin, albumin:globulin (A/G), and high-density lipoprotein (HDL). Dependent t-tests conducted on significant variables revealed significant within-group differences in SUP for diastolic BP, creatinine, eGFR, globulin, A/G, and HDL, and in CRL for CO2 between time points. Each variable remained within the accepted physiological range. Results of the present study support the clinical safety of a multi-ingredient TRM containing caffeine, green tea extract, and cayenne powder. Although there were statistically significant intragroup differences in SUP from pre- to postsupplementation for diastolic BP, creatinine, eGFR, globulin, A/G, and HDL, all remained within accepted physiological ranges and were not clinically significant. In sum, it appears as though daily supplementation with a multi-ingredient TRM is safe for consumption by healthy adults for a 28-day period [290].
Combination with sodium phosphate

To assess the effects of sodium phosphate (SP) and caffeine supplementation on repeated-sprint performance a randomized, double-blind, Latin-square design was performed. Eleven team-sport males participated in four trials: (1) SP (50 mg/kg of free fat-mass daily for six days) and caffeine (6 mg/kg ingested 1h before exercise); SP+C, (2) SP and placebo (for caffeine), (3) caffeine and placebo (for SP) and (4) placebo (for SP and caffeine). After loading, participants performed a simulated team-game circuit (STGC) consisting of 2×30min halves, with 6×20-m repeated-sprint sets performed at the start, half-time and end of the STGC. There were no interaction effects between trials for first-sprint (FS), best-sprint (BS) or total-sprint (TS) times. However, SP resulted in the fastest times for all sprints, as supported by moderate to large effect sizes and “likely” to “very likely” chances of benefit, compared with placebo. Compared with caffeine, SP resulted in “possible” to “likely” chances of benefit for FS, BS and TS for numerous sets and a “possible” chance of benefit compared with SP+C for BS (set 2). Compared with placebo, SP+C resulted in moderate ES and “possible” to “likely” benefit for numerous sprints, while caffeine resulted in a moderate ES and “likely” chances of benefit for a number of sets. It was concluded that while not significant, ES and qualitative analysis results suggest that SP supplementation may improve repeated-sprint performance when compared with placebo [291].

Acceleration of caffeine metabolism of tobacco and cannabis

Tobacco and marijuana accelerate caffeine metabolism, which reduces the time caffeine circulates in the body. Oral contraceptives slow it down, so they have the opposite effect. Researchers have identified genes that influence a person's natural risk of caffeine metabolism, which might explain why some people are exquisitely sensitive to caffeine while others are not [292].
INFLUENCE OF CAFFEINE ON BIOMONITORING DATA

Effect of smoking and caffeine

Smoking appears to enhance the body’s clearance of dioxins and dioxin-like polychlorinated biphenyls (PCB) by inducing CYP1A2 activity based on studies with a limited number of participants. This hypothesis was evaluated by using data from National Health and Nutrition Examination Survey. Specifically, adult participants were identified and the sums of their serum lipid-adjusted concentrations of 12 polychlorinated dibenzo-p-dioxins/polychlorinated dibenzofurans (PCDD/PCDF) congeners, 33 PCB (total), 26 non-dioxin-like PCB, and 6 mono-ortho (dioxin-like) PCB were determined. In addition to evaluating the association of smoking, the association of caffeine consumption and the interaction between them was evaluated. Data analysis included regression models that were fitted with age, gender, race/ethnicity, and body mass index (BMI). Smokers had significantly lower concentrations of total PCDD/PCDF than nonsmokers. New to this study, a significant interaction between caffeine consumption and smoking for total PCB was found. When caffeine was consumed less than once a day, smokers had higher concentrations of total PCB than nonsmokers. However, when caffeine was consumed at least once a day, smokers had lower concentrations than nonsmokers. A significant interaction between age and caffeine consumption frequency for each of the PCB groups was also observed. The differences in concentration between younger and older age groups were greater when caffeine was consumed at least once a day than when caffeine was consumed less frequently. Smoking and caffeine consumption need to be considered in the interpretation of human biomonitoring data because they appear to affect the serum concentrations of these chemicals [292].

Impact on testosterone levels

Interest in the use of caffeine as an ergogenic aid has increased since the International Olympic Committee lifted the partial ban on its use. Caffeine has beneficial effects on various aspects of athletic performance, but its effects on training have been neglected. To investigate the acute effect of caffeine on the exercise-associated increases in testosterone and cortisol in a double-blind crossover study 24 professional rugby-league players ingested caffeine doses of 0, 200, 400, and 800 mg in random order 1 hr before a resistance-exercise session. Saliva was sampled at the time of caffeine ingestion, at 15-min intervals throughout each session, and 15 and 30 min after the session. Data were log-transformed to estimate percent effects with mixed modeling, and effects were standardized to assess magnitudes. Testosterone concentration showed a small increase of 15 percent (90 % confidence limits + 19 %) during exercise. Caffeine raised this concentration in a dose-dependent manner by a further small 21 percent (+ 24 %) at the highest dose. The 800-mg dose also produced a moderate 52 percent (+ 44 %) increase in cortisol. The effect of caffeine on the testosterone:cortisol ratio was a small decline (14 %; + 21 %). It was concluded that caffeine has some potential to benefit training outcomes via the anabolic effects of the increase in testosterone concentration, but this benefit might be counteracted by the opposing catabolic effects of the increase in cortisol and resultant decline in the testosterone:cortisol ratio [293].

Impact on potassium levels

There was one report of severe hypokalemia in two young bicycle riders due to massive caffeine intake [294].
Impact on glutamine acid levels

It was investigated the effects of caffeine on the ammonia and amino acid metabolism of elite soccer players. In the double-blind, randomized study, the athletes (n=19) received 5 mg·kg caffeine or lactose (LEX, control) and performed 45 min of intermittent exercise followed by an intermittent recovery test (Yo-Yo IR2) until exhaustion. The caffeine-supplemented athletes were divided into two groups (CEX and SCEX) depending on their serum caffeine levels (< 900 % and > 10,000 %, respectively). The data were analyzed by ANOVA and Tukey's post hoc test. Caffeine supplementation did not significantly affect the performance. Exercise changed the blood concentrations of several amino acids and increased the serum concentrations of ammonia, glucose, lactate, and insulin. The LEx group showed an exercise-induced increase in valine (29 %), which was inhibited by caffeine. Higher serum caffeine levels abolished the exercise-induced increase in alanine (110-160 %) and glutamate (42-61 %). In response to exercise, the SCEX subjects did not exhibit an increase in uremia and showed a significantly lower increase in their serum arginine (15 %), citrulline (16 %), and ornithine (ND) concentrations. The data suggest that caffeine might decrease systemic urea by decreasing the glutamine serum concentration, which decreases the transportation of ammonia to the liver and thus urea synthesis [224].

Impact on creatinine levels

The purpose of this investigation was to assess the acute effects of caffeine ingestion on short-term, high-intensity exercise (ST) after a period of oral creatine supplementation and caffeine abstinence. Fourteen trained male subjects performed treadmill running to volitional exhaustion (Tlim) at an exercise intensity equivalent to 125 percent VO2max. Three trials were performed, one before 6 d of creatine loading (0.3 g/kg/day baseline), and two further trials after the loading period. One hour before the postloading trials, caffeine (5 mg/kg) or placebo was orally ingested in a cross-over, double-blind fashion. Four measurements of rating of perceived exertion were taken, one every 30 s, during the first 120 s of the exercise. Blood samples were assayed for lactate, glucose, potassium, and catecholamines, immediately before and after exercise. Body mass increased over the creatine supplementation period, and this increase was maintained for both caffeine and placebo trials. There was no increase in the maximal accumulated oxygen deficit between trials; however, total VO2 was significantly increased in the caffeine trial in comparison with the placebo trial. In addition, caffeine Tlim was significantly greater than both baseline and placebo Tlim. RPE was also lower at 90 s in the caffeine treatment in comparison with baseline. As indicated by a greater Tlim, acute caffeine ingestion was found to be ergogenic after 6-d of creatine supplementation and caffeine abstinence [295].

Impact on sex-hormone binding globulin levels

Findings from observational studies suggest that sex hormone-binding globulin (SHBG) and endogenous sex hormones may be mediators of the putative relation between coffee consumption and lower risk of type 2 diabetes. The objective of one study was to evaluate the effects of caffeinated and decaffeinated coffee on SHBG and sex hormone levels. After a two-week run-in phase with caffeine abstention, we conducted an 8-week parallel-arm randomized controlled trial. Healthy adults (n=42) were recruited from the Boston community who were regular coffee consumers, nonsmokers, and overweight. Participants were randomized to five 6-ounce cups of caffeinated or decaffeinated instant coffee or water (control group) per day consumed with each meal, mid-morning, and mid-afternoon. The main outcome measures were SHBG and sex hormones [i.e., testosterone, estradiol,
dehydroepiandrosterone sulfate]. No significant differences were found between treatment groups for any of the studied outcomes at week 8. At 4 weeks, decaffeinated coffee was associated with a borderline significant increase in SHBG in women, but not in men. At week 4, we also observed several differences in hormone concentrations between the treatment groups. Among men, consumption of caffeinated coffee increased total testosterone and decreased total and free estradiol. Among women, decaffeinated coffee decreased total and free testosterone and caffeinated coffee decreased total testosterone. The data do not indicate a consistent effect of caffeinated coffee consumption on SHBG in men or women, however results should be interpreted with caution given the small sample size. This is the first randomized trial investigating the effects of caffeinated and decaffeinated coffee on SHBG and sex hormones and our findings necessitate further examination in a larger intervention trial [296].

Impact on hematological variables

To evaluate the effect of caffeine on white cell distribution and muscle injury markers in professional soccer players during exercise 22 male athletes completed a placebo controlled double blind test protocol to simulate a soccer match, followed by a Yo-Yo intermittent recovery test. Exercise caused an increase in packed cell volume that was enhanced by caffeine. Caffeine and exercise had a synergistic effect on the blood lymphocyte count, which increased by about 38 percent after exercise, and by an additional 35 percent when combined with caffeine. Caffeine promoted an exercise independent rise in circulating monocytes, and a synergistic action of exercise and caffeine was observed on segmented neutrophils. Caffeine promoted thrombocytosis. Plasma adenosine deaminase, aspartate aminotransferase, and lactate dehydrogenase concentrations were enhanced by exercise, and alanine transaminase concentration was enhanced in both groups, with a synergistic effect of caffeine. It was concluded that the pronounced increase in the white cell count in the group receiving caffeine appeared to be caused by greater muscle stress and consequently more intense endothelial and muscle cell injury. The use of caffeine may augment the risk of muscle damage in athletes [297].

Effect on lymphocyte counts and subset activation

Caffeine ingestion is associated with increases in the concentration of plasma epinephrine and epinephrine is associated with alterations in immune cell trafficking and function following intensive exercise. Therefore, the purpose of this study was to investigate the effect of caffeine ingestion on plasma epinephrine concentration, lymphocyte counts and subset activation in vivo, as measured by the expression the CD69 surface antigen, before and after intensive cycling. On two occasions, following an overnight fast and 60 h abstention from caffeine containing foods and drinks, eight endurance trained males cycled for 90 min at 70 percent VO\textsubscript{2max} 60 min after ingesting caffeine (6 mg/kg body mass; CAF) or placebo (PLA). Venous blood samples were collected at pre-treatment, pre-exercise, post-exercise and 1 h post-exercise. Plasma epinephrine concentrations were significantly higher in CAF compared with PLA at pre-exercise. Compared with pre-treatment, numbers of CD4(+) and CD8(+) cells decreased by 54 and 55 percent, respectively, in CAF at 1 h post-exercise but did not significantly differ in PLA. Compared with PLA, in CAF the percentage of CD4(+)CD69(+) cells was 5-fold higher at post-exercise and 5.5-fold higher at 1 h post-exercise. Compared with PLA, in CAF the percentage of CD8(+)CD69(+) cells was 2-fold higher at pre-exercise and 1.7-fold higher at post-exercise. These findings suggest that caffeine ingestion is associated with alterations in lymphocyte subset trafficking and expression of CD69 in vivo following prolonged, intensive exercise [298].
Stability studies of caffeine in urine

The stability of caffeine in urine samples has been studied. A high-performance liquid chromatography (HPLC) method for the quantification of caffeine in urine samples was validated for that purpose. The method consists of a liquid-liquid extraction at alkaline pH with chloroform-2-propanol (9:1, v/v) with a salting out effect. 7-Ethyltheophylline was used as internal standard (ISTD). Analyses were performed with an Ultrasphere ODS C18 column using water/acetonitrile (90:10, v/v) as a mobile phase at a flow rate of 1 ml/min. Ultraviolet absorption at 280 nm was monitored. Extraction recoveries for caffeine and 7-ethyltheophylline were 81.4 ± 6.0 and 87.3 ± 5.7 percent, respectively. The calibration curves were demonstrated to be linear in the working range of 6-30 microg/mL. The limit of detection and the limit of quantitation were estimated as 0.7 and 2.0 microg/mL, respectively. Precisions in the range of 1.5-9.2 and 4.1-5.8 percent were obtained in intra- and inter-assay studies, respectively, using control samples containing 10, 14 and 26 microg/mL of caffeine. Accuracies ranging from 2.9 to 7.4 percent for intra-assay experiments, and from 3.9 to 5.4 percent in inter-assay studies were obtained. Stability of caffeine in urine samples was evaluated after long- and short-term storage at different temperature conditions. The batches of spiked urine were submitted to sterilization by filtration. No adsorption of the analyte on filters was observed. Before starting stability studies, batches of reference materials were tested for homogeneity. For long-term stability testing, caffeine concentration in freeze-dried urine stored at 4 degrees C and in liquid urine samples stored at 4, -20, -40 and -80 degrees C was determined at several time intervals for 18 months. For short-term stability testing, caffeine concentration was evaluated in liquid urine stored at 37 degrees C for 7 days. The effect of repeated freezing (at -20 degrees C) and thawing was also studied for up to three cycles. The stability of caffeine was also evaluated in non-sterile samples stored at -20 degrees C for 18 months. No significant changes were found [299].
LABORATORY TECHNIQUES

Quantitative determination of caffeine on reversed-phase C8 thin-layer chromatography plates using a surface sampling electrospray ionization system with tandem mass spectrometry detection is reported. The thin-layer chromatography/electrospray tandem mass spectrometry method employed a deuterium-labeled caffeine internal standard and selected reaction monitoring detection. Up to nine parallel caffeine bands on a single plate were sampled in a single surface scanning experiment requiring 35 min at a surface scan rate of 44 microm/s. A reversed-phase HPLC/UV caffeine assay was developed in parallel to assess the mass spectrometry method performance. Limits of detection for the HPLC/UV and thin-layer chromatography/electrospray tandem mass spectrometry methods determined from the calibration curve statistics were 0.20 ng injected (0.50 microL) and 1.0 ng spotted on the plate, respectively. Spike recoveries with standards and real samples ranged between 97 and 106 percent for both methods. The caffeine content of three diet soft drinks (Diet Coke, Diet Cherry Coke, Diet Pepsi) and three diet sport drinks (Diet Turbo Tea, Speed Stack Grape, Speed Stack Fruit Punch) was measured. The HPLC/UV and mass spectrometry determinations were in general agreement, and these values were consistent with the quoted values for two of the three diet colas. In the case of Diet Cherry Coke and the diet sports drinks, the determined caffeine amounts using both methods were consistently higher (by approximately 8 % or more) than the literature values [300].

Isotope-dilution mass spectrometry has been employed successfully in numerous fields of analytical chemistry enabling the establishment of fast and reliable procedures. In equine sports, xanthine derivatives such as caffeine and theobromine are prohibited, and doping control laboratories analyze horse urine specimens regarding these illicit performance-enhancing drugs. Theobromine has to exceed a threshold level of 2 microg/mL, hence a robust and reliable quantitation is required. Stably deuterated theobromine and caffeine were synthesized by the reaction of xanthine or theobromine with iodomethane-d3 in the presence of N-methyl-N-trimethylsilyltrifluoroacetamide or potassium carbonate in acetonitrile, respectively. Both compounds were characterized by nuclear magnetic resonance spectroscopy and electrospray ionization tandem mass spectrometry, and a robust and fast assay for the qualitative and quantitative analysis of theobromine in equine urine samples was validated. Urine specimens were extracted by means of solid-phase extraction cartridges, and concentrated extracts were analyzed by liquid chromatography interfaced to a triple-quadrupole mass spectrometer. In addition, the dissociation behavior of deuterated analogues to caffeine and theobromine allowed proposals for fragmentation routes of xanthine derivatives after atmospheric pressure ionization and collisionally activated dissociation [301].

The stability of caffeine in urine samples has been studied. A high-performance liquid chromatography (HPLC) method for the quantification of caffeine in urine samples was validated for that purpose. The method consists of a liquid-liquid extraction at alkaline pH with chloroform-2-propanol (9:1, v/v) with a salting out effect. 7-Ethyltheophylline was used as internal standard (ISTD). Analyses were performed with an Ultrasphere ODS C18 column using water/acetonitrile (90:10, v/v) as a mobile phase at a flow rate of 1 ml/min. Ultraviolet absorption at 280 nm was monitored. Extraction recoveries for caffeine and 7-ethyltheophylline were 81 ± 6.0 and 87 ± 6 percent, respectively. The calibration curves were demonstrated to be linear in the working range of 6-30 microg/ml. The limit of detection and the limit of quantitation were estimated as 0.7 and 2.0 microg/mL, respectively. Precisions in the range of 1.5-9.2 and 4.1-5.8 percent were obtained in intra- and inter-assay studies, respectively, using control samples containing 10, 14 and 26 microg/mL of caffeine. Accuracies ranging from 2.9 to 7.4 percent for intra-assay experiments, and from 3.9 to 5.4 percent in inter-assay studies were obtained. Stability of caffeine in urine samples was evaluated after long- and short-term storage at different temperature conditions. The batches of spiked urine were submitted to sterilization by filtration. No adsorption of the analyte on
filters was observed. Before starting stability studies, batches of reference materials were tested for homogeneity. For long-term stability testing, caffeine concentration in freeze-dried urine stored at 4 degrees C and in liquid urine samples stored at 4, -20, -40 and -80 degrees C was determined at several time intervals for 18 months. For short-term stability testing, caffeine concentration was evaluated in liquid urine stored at 37 degrees C for 7 days. The effect of repeated freezing (at -20 degrees C) and thawing was also studied for up to three cycles. The stability of caffeine was also evaluated in non-sterile samples stored at -20 degrees C for 18 months. No significant loss of the compound was observed at any of the investigated conditions [302].
The ergogenic effects of caffeine on athletic performance have been shown in many studies, and its broad range of metabolic, hormonal, and physiologic effects has been recorded, as one review of the literature shows. However, few caffeine studies have been published to include cognitive and physiologic considerations for the athlete. The following practical recommendations consider the global effects of caffeine on the body: lower doses can be as effective as higher doses during exercise performance without any negative coincidence; after a period of cessation, restarting caffeine intake at a low amount before performance can provide the same ergogenic effects as acute intake; caffeine can be taken gradually at low doses to avoid tolerance during the course of 3 or 4 days, just before intense training to sustain exercise intensity; and caffeine can improve cognitive aspects of performance, such as concentration, when an athlete has not slept well. Athletes and coaches also must consider how a person's body size, age, gender, previous use, level of tolerance, and the dose itself all influence the ergogenic effects of caffeine on sports performance [304].

The position of the International Society of Sports Nutrition regarding caffeine supplementation and sport performance was in 2010 summarized by the following seven points [305]:

- Caffeine is effective for enhancing sport performance in trained athletes when consumed in low-to-moderate dosages (about 3-6 mg/kg) and overall does not result in further enhancement in performance when consumed in higher dosages (>9 mg/kg)

- Caffeine exerts a greater ergogenic effect when consumed in an anhydrous state as compared to coffee

- It has been shown that caffeine can enhance vigilance during bouts of extended exhaustive exercise, as well as periods of sustained sleep deprivation

- Caffeine is ergogenic for sustained maximal endurance exercise, and has been shown to be highly effective for time-trial performance

- Caffeine supplementation is beneficial for high-intensity exercise, including team sports such as soccer and rugby, both of which are categorized by intermittent activity within a period of prolonged duration

- The literature is equivocal when considering the effects of caffeine supplementation on strength-power performance, and additional research in this area is warranted

- The scientific literature does not support caffeine-induced diuresis during exercise, or any harmful change in fluid balance that would negatively affect performance
THE CHANGING LANDSCAPE OF CAFFEINE RESEARCH

Caffeine research in exercise and sport settings has changed in the past few years. In addition to a greater interest in examining the potential ergogenic effects of low caffeine doses in a variety of situations, research has also examined [021]

- using time-trial performance tests to simulate real world situations versus exercise to exhaustion measures
- administering divided low doses of caffeine before and during exercise and sport
- administering caffeine in alternate forms such as carbohydrate electrolyte solutions (CESs), gels, bars, gums and chocolate
- caffeine administration in team-sport settings with sport-specific simulations of performance
- the ergogenic effects of caffeine in near-elite and elite athlete populations
- the variable effects of caffeine and the realization that while some generalizations can be made, attention to individual responses and trialing with caffeine ingestion is needed with all athletes
REFERENCES


053. Fiala KA, Casa DJ, Roti MW. Rehydration with a caffeinated beverage during the nonexercise periods of 3 consecutive days of 2-a-day practices. Int J Sport Nutr Exerc Metab 2004; 14: 419-29.


188. Barry RJ, Clarke AR, Johnstone SJ. Caffeine and opening the eyes have additive effects on resting arousal measures. Clin Neurophysiol 2011; 122: 2010-5.


