

Caffeine and Exercise

Metabolism, Endurance and Performance

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Abstract

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.

Numerous review articles^[1-7] have addressed caffeine and its influence on exercise capacity. To avoid repeating material covered in these articles, this review generally considers recent (i.e. the last 5 years) findings only. In addition, possible underlying mechanisms of caffeine action are examined, how characteristics of individual athletes could alter responses to caffeine are discussed, and areas where further studies are required have been identified. Caffeine use by the general population has not been considered.

Humans have a very long history of consuming caffeine;^[5,8-10] it is the most commonly consumed drug in the world and the health risks are minimal. Perkins and Williams^[11] provided an excellent, brief overview of the research history of caffeine in the exercise sciences. They pointed out that, over a century ago, there were formal, scientific reports regarding the ergogenic properties of caffeine. Dur-

ing the ensuing decades, renowned workers such as Meyerhof and Hill examined the effects of caffeine on muscle *in vitro*, and leading scientists including Boje, Asmussen and Margaria examined its effects in exercising humans.^[11] Perkins and Williams^[11] also documented that the current issues regarding caffeine use in competitive sport are not new: in 1939, Boje recommended that caffeine be banned from use in athletic competition, and caffeine has been forbidden or controlled at various times by various sports' organisations over the last 40 years. In their review in 1962, Weiss and Laties^[12] made insightful comments, which would not be out of place today, regarding concerns about the use of drugs for enhancing performance. They credited Rivers and Webber for publishing the first well-controlled study with suitable controls and placebo administration in 1907. As with so many investigators at that time, Rivers and Webber participated in

their own study. They used a 'Mosso ergometer' to quantify the work done in pulling a weight with a finger and found that caffeine 500mg increased work output.^[12]

Today, with so many high profile drugs available, why should one address caffeine? It can be a very powerful ergogenic aid and it could be useful to athletes in a wide range of activities involving aerobic endurance, strength and/or reaction time. It may be highly beneficial, not only during competition, but also for increasing endurance in training sessions. Caffeine is readily available both in foods and as an inexpensive, over-the-counter drug. It is a legal, socially acceptable drug. In some competitive sports it is not banned, and in others it is controlled or tolerated to a very high level. As with most other drugs, it is impossible to obtain statistics documenting the frequency of caffeine use in sports. However, in 1993, a large survey of Canadian teenagers reported that 27% of respondents had used caffeine in the last year for the specific purpose of enhancing athletic performance.^[13]

1. Mode of Action

Physiological concentrations of caffeine are normally less than 70 $\mu\text{mol/L}$; plasma concentrations of 20 to 50 $\mu\text{mol/L}$ are common. However, the concentrations employed in most *in vitro* investigations ranged from 500 to 5000 $\mu\text{mol/L}$. The physiological significance of such studies is not clear. While several modes of action for caffeine have been identified, the only one that is important, within the physiological concentration range of caffeine, is inhibition of adenosine receptors. Caffeine is very similar in structure to adenosine and can bind to cell membrane receptors for adenosine, thus blocking their action. Adenosine receptors are found in most tissues, including the brain, heart, smooth muscle, adipocytes and skeletal muscle (although the nature of these receptors in skeletal muscle is poorly understood). The ubiquitous nature and varied types of adenosine receptor facilitates caffeine simultaneously affecting a variety of tissues, resulting in a wide range of often interacting responses. This issue is not discussed in detail here, since it has

received much attention in other publications.^[14-18] Nonetheless, such interacting responses complicate the ability to establish which tissues are affected (and which responses occur) first, and which are critical to the ergogenic nature of caffeine.

Caffeine may also have intracellular actions, but it is not clear whether these are direct effects on enzymes or due to post-receptor events. In addition, caffeine is known to stimulate the secretion of adrenaline (epinephrine). This response could produce a number of secondary metabolic changes that could promote an ergogenic action. It also creates a situation in which it is difficult to attribute any one response to an action of caffeine on a specific tissue. For example, an apparently straightforward response, such as increasing adrenaline levels, could be due to stimulation of various brain areas, direct stimulation of the adrenal medulla, or a reaction to cardiovascular changes induced by caffeine. One can study animal models and individual tissues in isolation, but the responses one observes in an integrated organism could be very different. In this review, attempts are made to concentrate, in an integrated fashion, on the responses of humans to physiological doses of caffeine.

2. Forms of Caffeine and Related Compounds

Coffee, tea and other caffeine-containing beverages^[9,10] are consumed by most adults in the world. In some countries, children^[9,10] and even infants^[19] ingest caffeine-containing beverages and foods. In general, society would not approve of a young athlete using a steroid drug or a stimulant, but we do not react negatively to anyone drinking coffee, tea or a cola beverage. Despite caffeinated beverages being a common element in our food, caffeine is not a typical nutrient and is not essential for health. Furthermore, the commercial world is rapidly changing and expanding the availability of caffeine to all ages. There are now energy drinks and gels that are promoted for their caffeine content. Similarly, a wide range of bottled waters and even alcoholic beverages that contain caffeine are now sold.

At what point should caffeine be classified as a drug? To move further into this transition from a common component of our food, to a drug being added or taken for a particular purpose, there are several over-the-counter medications containing from 30 to 100mg of caffeine. These include cold remedies, diuretics, weight loss products, and preparations to help people stay awake. Some of these are referred to as nutraceuticals and/or natural health products. But, how or where do we draw a line? Which are drugs and which are normal components of an individual's diet? Is there a difference between obtaining a potentially ergogenic dose of caffeine from coffee, a cold remedy, a 'wake up' tablet, or a suppository? Are such commercially synthesised forms of caffeine different from the same amount of caffeine ingested in tablets prepared from 'natural' extracts of coffee, tea, mate or guarana?

Many reviews provide lists of the caffeine contents of beverages, foods and medications,^[5,8-10] and it is redundant to reproduce such a list here. The main sources of caffeine are coffee, tea, mate, guarana, and soft drinks. The amount of caffeine in prod-

ucts, foods and beverages varies from country to country depending on factors such as marketing regulations and preparation.^[9,10,20] For example, the caffeine content of coffee varies widely depending on the type of bean, method of coffee preparation, and social traditions of brewing techniques.

2.1 Coffee Versus Caffeine

Does the form in which caffeine is ingested influence the effects? A few studies of endurance exercise^[21-25] have used decaffeinated coffee or regular coffee (or decaffeinated coffee plus caffeine) and then interpreted the results in terms of caffeine administration (see table I). One study^[26] compared these different regimens in high quality runners who ran to voluntary exhaustion at a pace similar to their best time for 10km. As expected, caffeine enhanced their endurance from 32 minutes in the placebo condition to 41 minutes, but ingestion of regular coffee had no impact. Differences in caffeine absorption could not explain the findings, since times to peak plasma caffeine concentrations and the actual caf-

Table I. A summary of studies that generally compared the ergogenic effects of caffeine with those of decaffeinated coffee

Reference	Participants	Solution	Caffeine dose ^a	Protocol ^b	Key results ^c
Costill et al. ^[22]	7 M, 2 F	Decaf ± caf	300mg; (M 4.4, F 5.8)	80% max to exh	Endurance (min): decaf 75.5; caf 90.2*
Butts & Crowell ^[25]	13 M, 15 F	Decaf ± caf	300mg; (M 4.0, F 5.1)	75% max to exh	Endurance (min): decaf M 67.7; caf M 68.5; decaf F 59.9; caf F 68.5
Casal & Leon ^[24]	9 M	Decaf ± caf	400mg; (6.0)	75% for 45 min	FFAs, RER not different
Wiles et al. ^[23]	Protocol (a) 18 M; protocol (b) 10 M	Decaf; reg cof	≈200mg; (2-2.5)	Simulated 1500m run	Total time (sec): decaf 290; reg cof 286 [†] ; last min (km/h): decaf 22.9; reg cof 23.5*
Trice & Haymes ^[21]	8 M	Decaf ± caf	5 mg/kg	Intermittent ex (1 min ex/1 min rest) at 85-90% max	Endurance (min): decaf 61.3; caf 77.5*
Graham et al. ^[26]	9 M	Decaf; decaf + caf; reg cof; caf; pl	4.45 mg/kg	85% max to exh	Endurance (min): decaf 32; decaf + caf 32; reg cof 32; pl 31; caf 41; (caf > all others)

a The caffeine dose was often given as an absolute dose. In these cases, the approximate dose in mg/kg is estimated and presented in parentheses. In 2 studies, men and women received the same absolute dose, resulting in women receiving a substantially larger dose in mg/kg. In 1 study,^[23] the administered solution was 3g of instant coffee; the amount of caffeine administered was therefore estimated.

b The exercise was described as a percentage of maximal oxygen uptake and, in most studies, participants exercised to voluntary exhaustion. In 1 study,^[23] participants in protocol (a) ran a simulated 1500m race as fast as possible; in protocol (b), speed was controlled until approximately the last min (400m), during which participants ran as hard as possible.

c In Costill et al.^[22] data for men and women were not tested separately; in Butts & Crowell,^[25] data for the 2 genders were not combined.

caf = pure caffeine; **decaf** = decaffeinated coffee; **ex** = exercise; **exh** = voluntary exhaustion; **F** = female; **FFA** = free fatty acid; **M** = male; **pl** = placebo; **reg cof** = regular coffee; **RER** = respiratory exchange ratio; * indicates that the difference was significant.

feine concentrations achieved were identical for both the caffeine and regular coffee groups.

Caffeine, a trimethylxanthine, is catabolised by the cytochrome P450 system in the liver to dimethylxanthines. The difference between caffeine and coffee ingestion in the above study^[26] could not be explained by caffeine metabolism, since the pattern of appearance of dimethylxanthines in the circulation was similar in both the coffee and caffeine 'arms' of the trial. However, the expected increase in circulating free fatty acid (FFA) and adrenaline levels was noted only in the caffeine arm. It is unlikely that either FFAs or adrenaline directly enhanced performance (see section 8), but the lack of response of these parameters to regular coffee is objective evidence that coffee does not have the same pharmacodynamic actions as caffeine alone. Does this mean that coffee is of no benefit? Within the limits of this study, yes; but other investigations have shown that coffee can be ergogenic^[21-23] and can increase FFA levels.^[22] Clearly, more comparative studies are needed. Meanwhile, coffee is probably inferior to caffeine alone as an ergogenic aid. Coffee contains hundreds, if not thousands, of compounds. Some of these must be pharmacodynamically active and may therefore counteract some of the effects of caffeine.

2.2 Dimethylxanthines

Is caffeine a unique ergogenic substance? As mentioned above, caffeine is an adenosine-receptor antagonist. The liver demethylates this trimethylxanthine to 3 dimethylxanthines: paraxanthine, theophylline, and theobromine, which are then further catabolised. In humans, the major product is paraxanthine. It and theophylline are also potent adenosine-receptor antagonists (theobromine is much less effective). Normally, as caffeine is metabolised, paraxanthine and theophylline do not increase in the circulation to a concentration considered active. They are therefore unlikely to be of major consequence to the effects of caffeine. However, they can be prepared and used as drugs. Paraxanthine is not biologically available and is not prepared commercially as a pharmacological product. Theophyl-

line is a major component of tea and is a common drug (but it is not regulated by sports' governing bodies). Theophylline has some of the same pharmacodynamic actions as caffeine.^[27] Marsh et al.^[28] reported an ergogenic effect of theophylline in a study involving only 3 participants and, recently, theophylline was found to increase endurance to a similar extent as caffeine.^[29] Because paraxanthine is also likely to be an ergogenic aid, dimethylxanthines in general should be considered performance enhancing drugs and should therefore probably be regulated.

2.3 Caffeine Taken in Combination with Other Compounds

The most obvious example of caffeine interacting with co-ingested compounds is the discussion above of caffeine and coffee. In addition, many new commercial drinks now combine caffeine with carbohydrates and/or electrolytes. A few studies^[30-34] have assessed the effects of caffeine in solution with carbohydrates and/or electrolytes, whereas one study^[35] evaluated caffeine as a calorie-free, decaffeinated cola (see table II).

Unfortunately, 3 of the 6 investigations in table II^[33-35] did not evaluate performance or endurance, and Wemple et al.^[30] simply appraised the effects of a carbohydrate/electrolyte beverage, with and without caffeine, and found no difference between the 2 regimens on a brief, intensive performance cycle after 3 hours of exercise. They therefore demonstrated only that caffeine failed to confer benefit beyond that provided by the carbohydrate/electrolyte beverage. However, the 2 remaining studies in table II provide different information: they suggest that caffeine combined with carbohydrate,^[32] or with carbohydrate plus electrolytes,^[31] may be superior to both carbohydrate, and carbohydrate plus electrolytes, for increasing endurance during prolonged activity. Although both studies lacked all the treatment and control 'arms' needed to make this a definitive statement, these limited findings permit conclusion that caffeine ingestion with carbohydrate and electrolytes is not detrimental to the ergogenic effects of either carbohydrate or electrolytes. To

Table II. A summary of studies that administered caffeine with carbohydrates and/or electrolytes to athletes before exercise

Reference	Participants	Solution ^a	Caffeine dose	Protocol	Key results
Gaesser & Rich ^[35]	8 M	Artificial sweetened decaf cola ± caf	5 mg/kg	Incremental ex	No difference in RER, maximal work rate; caf increased lactate*
Wells et al. ^[33]	10 M	glu/ele ± caf	5 mg/kg	Ran 32.2km	No difference in plasma ele, FFA or RER
Erickson et al. ^[34]	4 M, 1 F	(a) con; (b) fru; (c) caf; (d) glu; (e) b+c	5 mg/kg	90 min at 75-70% max	No differences in RER; con used more glycogen (91 mmol/kg) than caf* or glu*. Solutions b-e all resulted in 62-67 mmol/kg being used
Sasaki et al. ^[32]	5 M	(a) con; (b) suc; (c) caf; (d) b+c	420mg; (=7.2 mg/kg)	Drink 60 and 0 min before, and after, 45 min at 85% of max	Endurance (min): solution (a) 40; (b) 58;* (c) 53;* (d) 57*
Wemple et al. ^[30]	4 M, 2 F	Glu/ele ± caf	Total of 8.7 mg/kg	60% of max for 3h, then 500 rpm at high resistance as fast as possible	No difference in plasma ele, thermoregulation, or in performance (343 and 344 sec)
Kovacs et al. ^[31]	15 M	(a) con; (b) cho/ele; (c) b+ caf; (d) b + caf; (e) b+ caf	(c) 2.1; (d) 3.2; (e) 4.5 mg/kg	Complete a work output estimated to take 1h	Work time (min): (a) 62.5; (b) 61.5; (c) 60.4;* (d) 58.9;** (e) 58.9**

a In Sasaki et al.,^[32] 60 min before exercise in every trial, 200ml of water ± 300mg of caf were consumed. Immediately before exercise and after 45 min, 250ml of water (a), water with 45g of suc, 60mg of caf (c), or both (d), were consumed. In Wemple et al.,^[30] 8 ml/kg of sport drink (glu/ele) ± caf were consumed 1h before exercise and 3 ml/kg at the beginning of, and every 20 min during, exercise. In Kovacs et al.,^[31] a 7% cho/ele drink ± caf was ingested as follows: 8 ml/kg before exercise and 3 ml/kg at 20 and 40 min of exercise. The caf was 150, 225 and 320 mg/L in c, d, and e, respectively.

caf = pure caffeine; cho = carbohydrates; con = control (water); decaf = decaffeinated coffee; ele = electrolytes; ex = exercise; F = female; FFA = free fatty acid; fru = fructose; glu = glucose; M = male; RER = respiratory exchange ratio; suc = sucrose; * indicates that the difference was significant; ** indicates that the results from this treatment were significantly different from those without **.

determine whether the caffeine plus carbohydrate (with or without electrolytes) combination has a truly additive effect requires much detailed work. Furthermore, because the proportion of caffeine/carbohydrate/electrolytes ingested in these studies is probably not found in any currently available commercial beverage, these findings should not be used to endorse any particular product.

Vandenbergh et al.^[36] reported that, when creatine was ingested with caffeine, the ergogenic benefit of creatine loading was lost, even though total muscle creatine increased. While this is an isolated finding, it does point out that when drugs or supplements are combined, the effects of each may be altered. This could have implications for strength athletes who could be attracted to using both creatine and caffeine.

A second example of caffeine acting in combination with other compounds is that as an analgesic adjuvant. Sawynok and Yaksh^[37] point out that, on

its own, caffeine may contribute to amelioration of pain. This may be caused by peripheral actions at the level of a local injury or actions within the CNS by modifying nociceptive processing. These actions could add to the ergogenic potential of caffeine. Furthermore, even low doses of caffeine augment the effects of nonsteroidal anti-inflammatory drugs including aspirin and ibuprofen.^[37]

In the area of bodyweight loss, the combination of caffeine, ephedrine and aspirin ('stacking') has been found^[38,39] to be more effective than caffeine alone and to be a potent metabolic stimulus. There is limited information available about the ergogenic properties of this 'cocktail', but a military based investigation^[40] suggests that the combination is potent. The cocktail is not discussed in detail here, as the information is limited and ephedrine is banned from sports. However, while this mixture is well within what most of us would term true drugs, it is also readily available in North America in 'natural'

products ('herbal' or 'botanical' supplements) in health food stores and is often promoted as a weight loss aid. Thus, use of the mixture should be an area of concern and further research.

3. Optimal 'Prescription' of Use

Does the method of administration influence the effects of caffeine? It is not possible to give a complete answer to this question, as the necessary comparisons have not been done. Caffeine and other methylxanthines can be administered by suppository, intramuscular injection, venous infusion, or oral ingestion. Most investigations have administered caffeine as a pure anhydrous drug orally, either in capsules or dissolved in water. In most studies, oral ingestion has involved a single dose, but, in a few investigations, repeated doses have been given. Which mode or pattern of administration is optimal, and when a given dose of caffeine causes the optimal performance conditions, remains unclear.

3.1 Timing

Most investigators have had the participants ingest a caffeine dose, rest an hour, and then exercise. This protocol has been selected because caffeine is rapidly absorbed and plasma concentrations approximate a maximum level in 1 hour. While this timing for administration and exercise may be optimal, it is remarkable how rarely the investigators have measured the circulating concentration of the drug they are studying. Most studies offer no information about the plasma concentration of caffeine or its variation among study participants. Caffeine is slowly catabolised (half-life is 4 to 6 hours) and individuals maintain a circulating concentration close to this level for 3 to 4 hours. It has been suggested^[3,41] that waiting 3 hours is optimal because this is when caffeine-induced lipolysis produces the highest FFA level. However, this hypothesis has not been tested and the ergogenic role of such lipolysis is very suspect (see section 8). The author is unaware of any systematic examination of lipolysis in relation to the time between caffeine ingestion and exercise onset.

3.2 Dose

Surprisingly, some scientists have given caffeine in an absolute dose, rather than as one indexed for body mass (tables I, II and III present several examples of this). This could create large variability in responses. A few studies have given caffeine per unit lean mass. However, caffeine is both water- and lipid-soluble and it is unlikely that body fat is an important factor in caffeine distribution. As noted above, most investigators have not measured plasma caffeine concentrations of study participants and this severely limits understanding of why some results are inconsistent with the literature. In the author's laboratory, plasma caffeine concentration is routinely measured: giving caffeine indexed to body mass results in a very consistent plasma caffeine concentration in both men and women.^[2] However, it is surprising how often investigators have administered an absolute dose of caffeine to both male and female study participants (see tables I, II and III). The smaller bodyweight of the women generally resulted in their average caffeine dose being approximately 20% higher than that of the men. In addition, most of these investigations did not examine the data for gender differences.

There have been only a few dose-response studies^[11,31,43,51-53] (see table IV). Perkins and Williams^[11] did not find any ergogenic benefit of any caffeine dose, but their protocol led to a very rapid fatigue. Cohen et al.^[43] also failed to show any improvements with 2 different doses of caffeine, while Cadarette et al.^[51] did not find conclusive results. The latter study reported that the middle dose of 4.4 mg/kg was effective, but suggested that this was caused by the results from 1 individual. These findings are difficult to interpret because the investigators also reported that participants in the placebo condition had plasma caffeine concentrations equivalent to a dose of about 3 mg/kg of caffeine.^[31,53] As indicated in section 6, these studies are in the minority in finding no ergogenic effect of caffeine. Examination of doses of 3 to 9 mg/kg at the author's laboratory revealed that even 3 mg/kg was effective for increasing endurance in prolonged exercise. Subsequently, Pasman et al.^[52] confirmed

Table III. A summary of studies that examined the effects of caffeine on performance

Reference	Participants	Caffeine dose (mg/kg)	Protocol	Key results
Ivy et al. ^[42]	7 M; 2 F; trained cyclists	250mg + 250mg (M 6.9, F 8.8)	Cycle for 2h to produce greatest amount of work possible	Caf resulted in 7.4% more work done; 31% more fat oxidised; glu polymer ingestion had no effect on work done
Cohen et al. ^[43]	5 M; 2 F; trained runners	(a) 0; (b) 5; (c) 9	Run 21km in hot, humid environment	No differences in run times
Berglund & Hemmingsson ^[44]	8-10 M; 4-5 F; trained skiers	6	n = 13 raced 23km at altitude; n = 14 raced 20km at sea level. Both were 2 lap courses	Race time ≈55 and 67 min for M and F. All 1 and 2 lap times were faster* with caf except for 2 laps at low altitude (p < 0.10)
Kovacs et al. ^[31]	15 M; trained cyclists	(a) 0; (b) 0; (c) 2.1; (d) 3.2; (e) 4.5	Complete a simulated time trial estimated to last about 1h	Time (min): (a) 62.5; (b) 61.5; (c) 60.4;* (d) 58.9;** (e) 58.9**
MacIntosh & Wright ^[45]	7 M; 4 F; trained swimmers	6	Swim 1500m	Split times caf faster by: 500m =7 sec;* 1000m =8 sec;* 1500m 23 sec;* (20 : 58.8 vs 21 : 21.8 min)
Bruce et al. ^[46]	8 M; trained rowers	(a) 0; (b) 6; (c) 9	Simulated rowing 2000m	Time (sec): (a) 416; (b) 411;* (c) 412*
Wemple et al. ^[30]	4 M; 2 F; active individuals	Glu + ele ± 8.7 caf	60% of max for 3h followed by 500 rpm at high resistance	Time (sec) for 500 rpm: pl 343; caf 344
Wiles et al. ^[23]	18 M; 10 M; trained runners	Decaf or reg cof (=2-2.5)	Simulated 1500m run; (a) run 1500m while controlling speed; (b) run 1100m at 'controlled' speed and then 'kick' to finish	(a) total time (sec); pl 290.2; coffee 286.0;* (b) final 400m (km/h); pl 22.9; coffee 23.5*
Collomp et al. ^[47]	Trained: 3 M; 4 F; untrained: 2 M; 5 F	250mg (=4.3)	Swim 2 × 100m freestyle with 20 min recovery	Trained: caf resulted in =1 sec improvement* in both swims. Untrained: no change in speed
Collomp et al. ^[48]	3 M; 3 F; 'active'	5	One Wingate test, i.e., 30 sec 'all-out' cycling	No difference in peak, average power or in rate of fatigue
Greer et al. ^[49]	9 M; 'active'	6	4 Wingate tests with 4 min rest	No differences in peak, average power or in rate of fatigue
Anselme et al. ^[50]	10 M; 4 F; 'active'	250mg (=3.6)	Repeated 6 sec cycle sprints (5 min rest) with progressively greater resistance	Caf: max power 964 vs 904W*

caf = pure caffeine; **decaf** = decaffeinated coffee; **ele** = electrolytes; **F** = female; **glu** = glucose; **M** = male; **pl** = placebo; **reg cof** = regular coffee; * indicates that the difference was significant; ** indicates that the results from this treatment were significantly different from those without **.

this finding. Bruce et al.^[46] reported that doses of 6 and 9 mg/kg were equally effective in increasing performance/power in a simulation of 2000m rowing. Similarly, Kovacs et al.^[31] found that, when ingesting caffeine with a sport drink, the lowest dose used (≈2.1 mg/kg) was ergogenic, but doses of 3.2 and 4.5 mg/kg had a greater effect. It appears that a dose of 3 to 6 mg/kg is optimal. It is not clear what are the minimal and maximal doses.

Another aspect that has not been examined methodically is comparison of single and repeated doses of caffeine. Most studies have had partici-

pants withdraw from caffeine for 48 hours and have then administered a single, oral dose. A few investigations^[31,32,42,54] have given smaller doses at regular intervals, but have not compared these to a single, pre-exercise dose. Only Kovacs et al.^[31] have reported the plasma caffeine concentrations for such a procedure. Their data suggest that exercise does not impair caffeine absorption and repeated doses should prolong the elevation in plasma caffeine. However, given that even a single dose elevates circulating caffeine concentration for hours, the advantage of repeated doses is not obvious. It might

be a mechanism for achieving a high concentration in an individual who experiences gastric irritation from large doses, and it could have applications for prolonged events and those that extend over days. At this time, there are very limited data for drawing conclusions.

3.3 Urinary Excretion of Caffeine

With regard to urinary caffeine, there are no new developments. Many studies^[31,46,52,55] have demonstrated that the urinary concentration of caffeine is extremely variable and a poor reflection of either dose or plasma concentration. Urinary caffeine concentrations are notoriously inaccurate reflections of caffeine intake. In addition, the International Olympic Committee's acceptable maximum level of 12 µg of caffeine per ml of urine is very generous. A caffeine dose of 3 mg/kg is ergogenic,^[53] and yet, an acute dose of 9 mg/kg results in urinary levels that only approach 12 µg/ml. Furthermore, some sports present opportunities for the competitor to urinate during the activity and/or rest periods. In these situations, the urine collected post-activity would be even less reliable as an indicator of caffeine dose. Thus, it would seem to be very difficult to achieve a urinary caffeine concentra-

tion of 12 µg/ml through a normal dietary intake of caffeine. It is very clear that this 'safety zone' of acceptance could very easily result in many athletes doping with caffeine and not being identified.

4. Caffeine Habits

4.1 Caffeine Habituation

Does an athlete who regularly ingests caffeine still benefit from an acute ingestion of caffeine? Rarely have the caffeine habits of individuals been considered within the context of applied physiology. There is ample evidence from animal models that some tissues adapt to long term exposure to caffeine by up-regulating adenosine receptor number, whereas other tissues adapt by altering post-receptor actions.^[18,56,57] However, these studies also found that some tissues do not appear to adapt to habitual exposure.

When we do not know what tissues are critical in mediating the ergogenic responses to caffeine, it is difficult to speculate about the importance of habituation within specific tissues. In 1991, Dodd et al.^[58] compared habitual caffeine users to caffeine-naïve individuals. At rest, the latter were more responsive in heart rate, ventilation and oxygen con-

Table IV. A summary of studies that compared the effects of ingesting different doses of caffeine in association with exercise

Reference	Participants	Caffeine dose (mg/kg)	Protocol	Plasma caffeine (µmol/L)	Key results
Perkins & Williams ^[11]	14 F	(a) 0; (b) 4; (c) 7; (d) 10	Incremental; 300 kpm + 100 every min	Not measured	Endurance (sec): (a) 299.5; (b) 312.1; (c) 299.8; (d) 303.2
Cadarette et al. ^[51]	4 M; 4 F	(a) 0; (b) 2.2; (c) 4.4; (d) 8.8	Run at 80% to exh	(a) 21.8; (b) 34.4; (c) 48.8; (d) 74.8	Endurance (min): (a) 53.4; (b) 67.8;* (c) 73.4; (d) 57.9
Graham & Spriet ^[53]	8 M	(a) 0; (b) 3; (c) 6; (d) 9	Run at 85% to exh	(a) 0; (b) 18; (c) 41; (d) 69	Endurance (min): (a) 49.4; (b) 60;* (c) 60;* (d) 55.6
Pasman et al. ^[52]	9 M	(a) 0; (b) 5; (c) 9; (d) 13	Cycle at 80% to exh	Not measured	Endurance (min): (a) 47; (b) 58;* (c) 59;* (d) 58*
Cohen et al. ^[43]	5 M; 2 F	(a) 0; (b) 5; (c) 9	Run 21km in heat	Not measured	Endurance (min): (a) ≈88; (b) ≈87; (c) ≈88
Kovacs et al. ^[31]	15 M	(a) 0; (b) 0; (c) 2.1; (d) 3.2; (e) 4.5	Complete a work output estimated to take ≈1h	(a) 0; (b) 0; (c) 10; (d) 15; (e) 24	Time (min): (a) 62.5; (b) 61.5; (c) 60.4;* (d) 58.9;** (e) 58.9**
Bruce et al. ^[46]	8 M	(a) 0; (b) 6; (c) 9	Simulated rowing 2000m	Not measured	Time (sec): (a) 416; (b) 411;* (c) 412*

exh = exhaustion; **F** = female; **M** = male; * indicates that the difference was significant; ** indicates that the results from this treatment were significantly different from those without **.

sumption, but there were no differences during an incremental exercise protocol. One study^[59] compared caffeine-users and non-users and found that they differed only in the degree of increase in plasma adrenaline following caffeine ingestion. Similarly, Bangsbo et al.^[60] found that habitual caffeine users, after 6 weeks of increased caffeine ingestion, had less increase of adrenaline in response to a standard dose of caffeine. Given the lack of evidence for a major role for the caffeine-induced increase in adrenaline (section 8.6), it is impossible to speculate about the importance of this alteration. Wiles et al.^[23] found no relationship between caffeine habits and degree of performance response in 1500m runners, nor did Tarnopolsky and Cupido^[61] find a difference between caffeine users and non-users in degree of caffeine-induced muscle force development. Caffeine habituation needs further study, but thus far the differences caused by caffeine habits do not appear to be major.

4.2 Caffeine Withdrawal

Does an athlete who regularly ingests caffeine need to withdraw from caffeine before using it in competition? If so, what length of time is optimal? Would the days of experiencing lethargy and so on, during the withdrawal, affect the athlete? Generally, scientists have the participants withdraw from caffeine substances for 48 hours before testing. This procedure results in barely detectable levels of caffeine in the circulation. However, the author frequently observes plasma paraxanthine concentrations of 1 to 5 $\mu\text{mol/L}$ after 48 hours of withdrawal. Whether or not this is important remains unclear, and there is no information regarding the impact of caffeine withdrawal on adenosine receptor populations.

Hetzler et al.^[62] reported that withdrawing from caffeine for 0, 2, 12, 24 or 48 hours before ingesting caffeine 5 mg/kg did not alter metabolic responses to steady-state exercise (endurance was not measured). In another study,^[63] the investigators had participants habituate to coffee drinking and then withdraw for 0, 2 or 4 days before ingesting caffeine 6 mg/kg. The days of withdrawal had no effect

on the magnitude of the ergogenic impact. Attempts were made to repeat this protocol (unpublished observations) with a dose of 9 mg/kg. It appeared that, when participants had not withdrawn, they became 'overdosed'. They were mentally confused, could not concentrate (some felt intoxicated – they were very talkative, giddy, could not perform simple functions such as telling time accurately, etc.), and often stopped exercise early because of these feelings. These symptoms are not unlike those of caffeine intoxication.^[64] The author speculates, based on observations of hundreds of participants, that caffeine non-users do not respond qualitatively differently, but that they are more susceptible to reacting negatively to high doses. The hepatic P450 system saturates at a caffeine dose of about 5 mg/kg. Higher doses therefore run the risk of producing disproportionate increases in plasma caffeine concentration. This could suggest that a moderate (3 to 5 mg/kg) dose before exercise and small (1 to 2 mg/kg), repeated doses of caffeine given during prolonged exercise could be superior to a single, large (≥ 9 mg/kg) dose, as the former regimens would not saturate the P450 system.

5. Participant Characteristics

There is very limited information concerning whether all athletes metabolise caffeine in a similar fashion. Any factor that influences the hepatic P450 system should affect caffeine clearance.^[65,66] This would include charbroiled meats, cruciferous vegetables, polycyclic hydrocarbons (smoking), and drugs such as phenobarbital (phenobarbitone) and cimetidine. Theoretically, estrogen should also inhibit caffeine metabolism.^[66,67] However, no differences in caffeine pharmacokinetics were noted in women between the follicular and luteal phases of the menstrual cycle, despite the differences in estrogen level.^[2] It is possible that oral contraceptives and pregnancy^[66,67] could impair the metabolism of caffeine, but this has not been investigated in an exercise situation.

It has been reported that exercise could alter caffeine metabolism and/or excretion.^[68] Close examination of these data illustrates that they are not

internally consistent. The pharmacokinetics of caffeine were compared in men and women (follicular phase of contraceptive non-users), both at rest and when exercising.^[2] There were no differences caused by gender, between rest and exercise, or even between rest and exercise with additional dehydration induced. As noted above, some studies have included both male and female participants, but have not tested for gender differences. The one exception is by Butts and Crowell^[25] who examined large groups of both sexes in a prolonged exercise protocol (see table I). While the effect of caffeine was not significant for either group, the women on average had a much greater increase in endurance time with caffeine (8.6 minutes compared with 0.8 minutes for the men). However, the investigators gave caffeine in an absolute dose and, thus, the women had a larger caffeine ingestion on a bodyweight basis.

It is likely that caffeine has direct actions on muscle (see section 8.8). There is very little known about factors that may influence muscle sensitivity to caffeine or whether this is alterable. Kalow^[69] reported that isolated muscle biopsies of men had a greater sensitivity to caffeine than did those from women. Mitumoto et al.^[70] found that in skinned fibres, slow twitch cells were more than twice as sensitive to caffeine. However, both studies were performed *in vitro* and with pharmacological concentrations of caffeine.

Training status may influence responses to caffeine. Carey and colleagues^[71,72] found that exercise training altered the effects of adenosine on adipose tissue. Similarly, Mauriege et al.^[73] found differences in adenosine sensitivity between adipocytes from lean and obese women. These findings were based on *in vitro* assays of isolated cells and presumably the tissue sensitivity to caffeine would be changed in a similar fashion. LeBlanc et al.^[74] found that trained compared with untrained individuals had a greater response to caffeine while at rest: they had a larger increase in adrenaline, FFAs, and resting metabolism. Unfortunately, the researchers did not investigate exercise responses. Collomp et al.^[47] found that caffeine increased the

swimming speed of trained swimmers, but not that of recreational swimmers. To the author's knowledge, these are the only direct comparisons of trained and untrained individuals. Subjectively, caffeine appears to have a more predictable impact on highly trained individuals. For example, in one study,^[55] an athlete who placed in the top 10 in an Olympic marathon was able to run for ≈ 105 minutes compared with about 75 minutes in the placebo trial. It could be that in highly trained rather than untrained individuals, muscle and other tissues are more responsive, or that athletes have the mental discipline to exercise long or hard enough to benefit more from the caffeine stimulus.

6. Caffeine Ingestion and Exercise Performance

6.1 Endurance for Long Term Exercise

Most investigations have examined exercise endurance in situations where fatigue occurs in 30 to 60 minutes. There can be no doubt that caffeine is ergogenic in these situations,^[21,22,29,32,51-53,55,63,75,76] while only rarely has no effect been found.^[25,77] Since the ergogenic nature of caffeine has been frequently reported in such settings, it is not addressed in detail here. However, even in situations where exhaustion occurs in ≈ 30 minutes, caffeine is effective. Under these circumstances, it is unlikely that muscle glycogen is depleted. In fact, in a recent study,^[29] over 50% of glycogen remained at fatigue, which suggests that sparing of glycogen may not be a limiting factor in this situation.

A number of researchers commonly measure endurance because, in this situation, power is kept constant and exercise time can be quantified. This is easier than protocols in which individuals vary speed or power as they would during a race. The extent to which findings of endurance capacity translate to performance is debatable, but there can be no doubt that caffeine would be a useful training aid. Even in terms of true performance, the debate would only be about how great is the effect, rather than whether or not there is one.

6.2 Speed/Power in Long Term Exercise

Rarely have studies been conducted to evaluate the impact of caffeine on speed or performance in an endurance event (see table III). The author, having failed in attempting this because of factors including small sample sizes and changing environmental conditions, can appreciate the difficulties in conducting a quality study of this sort. Early studies^[11,12,78-80] frequently found improvements in activities such as repeated jumping and bench stepping, as well as cycle and treadmill tests. These studies were frequently conducted with small groups and with protocol designs that are not acceptable today.

Cohen et al.^[43] failed to show a benefit of caffeine ingestion in a small group who ran 21km in a hot, humid environment. In contrast, Berglund and Hemmingsson^[44] found that caffeine did increase the speed of high quality, cross-country skiers in a competitive setting. This study has been criticised because the investigators normalised their data in a complex way. However, any field test is difficult, and skiing is a particularly thankless challenge given how snow conditions can change moment to moment, let alone day to day. To the author's knowledge, this is the only investigation of caffeine ingestion to use elite athletes and to simulate a competition. The researchers studied elite skiers on a 20 to 23km course, both at low and high altitude. They found that, both at the halfway mark and finish, caffeine ingestion resulted in faster performance times. The total time was about 55 to 67 minutes and caffeine resulted in the halfway times being 33 and 101 seconds faster for low and high altitude, respectively. Similarly, finishing times were 59 and 152 seconds faster [all results were significant except for the finish time at low altitude ($p < 0.10$)].

Ivy et al.^[42] had individuals perform 2 hours of cycle exercise and, after caffeine ingestion, the participants generated a 7.3% greater total power output. Similarly, MacIntosh and Wright^[45] found that caffeine ingestion reduced the time for completion of a 1500m swim by 23 seconds. In perhaps the most controlled study, Kovacs et al.^[31] approximated a cycle time trial. Skilled cyclists were told they

had to perform, as quickly as possible, a set amount of work that was estimated to be approximately that of a 1-hour time trial. Ingestion of a carbohydrate/electrolyte solution during this activity tended to be beneficial and, when the solution also contained caffeine, the power output improvement was significantly greater (i.e., performance time was faster).

6.3 Endurance in Short Term, Intense Exercise

This aspect of exercise has received less attention, probably because it is more difficult to quantify. Also, the dominant dogma accounting for the ergogenic properties of caffeine has involved muscle glycogen sparing. Since there is no evidence that glycogen is limiting in such activities, the anticipated negative results may have discouraged investigations. Collomp et al.^[81] reported that when caffeine was consumed short term or for a longer period (250 mg/day for 1 or 5 days), the exercise duration at maximal oxygen uptake ($\dot{V}O_{2max}$) [349 and 341 seconds, respectively] was not significantly greater than for placebo (320 seconds). In contrast, a significant increase in endurance from 4.12 to 4.93 minutes was found in another study.^[82] The author is aware of no other studies of this nature.

There have been several studies in which a progressive exercise protocol was used. In one study,^[11] the exercise resulted in rapid exhaustion within 6 minutes and caffeine had no effect. In 2 other investigations,^[58,83] participants exercised for 15 to 20 minutes and caffeine ingestion caused a small (0.3 to 0.5 minutes) nonsignificant increase in endurance. In contrast, Flinn et al.^[84] reported that caffeine ingestion significantly increased endurance from 14.9 to 17.5 minutes. Marsh et al.^[28] had 3 individuals perform a progressive forearm test while undergoing nuclear magnetic resonance spectroscopy (NMRS) imaging. The researchers found that when the participants had ingested theophylline, the maximal power generated increased 19%. It is estimated from their protocol that endurance increased from 13.5 to 16.8 minutes. While there is considerable variability in investigations that have used progressive work tests, the findings are that

caffeine either has positive effects or causes a non-significant improvement in exercise time.

6.4 Power in Short Term, Intense Exercise

The ability to perform at high intensity has been examined in several studies (see table III). Wiles et al.^[23] had participants simulate a 1500m run, and coffee ingestion produced a significant 4.2-second improvement in running speed. However, it should be noted that these were not elite athletes (times averaged 286 and 290 seconds for caffeine and placebo, respectively). There was no relationship between either habitual caffeine intake or running speed and the degree of improvement with caffeine. Colomp et al.^[47] studied swimmers who swam 100m freestyle. Caffeine ingestion significantly improved the mean time of highly trained swimmers by about 1 second, while untrained athletes showed no improvement.

When activities of shorter duration are examined, the results are more inconsistent, probably because the potential improvement is small and difficult to measure because of the brief, intense nature of the exercise. Anselme and co-workers^[50] reported that caffeine improved maximum power in 6-second sprints, but not in a 30-second Wingate test.^[48] Similarly, no improvement in maximum force or fatigue was noted in a series of 4 Wingate tests.^[49]

These areas are not well studied but it appears that, in exercise lasting at least 60 seconds, caffeine can be ergogenic. Whether caffeine has a positive effect in more intense exercise is controversial, but, once again, there are no studies showing negative effects.

6.5 Strength Activity

It is anecdotally reported that many strength athletes use caffeine to increase their performance. It is not clear whether the perception of improvement is related to maximum strength or power or to the rate of fatigue. This is an area where there is a distinct paucity of quality work. There have been studies^[85-87] with humans that suggested that caffeine enhances myoneural function and contractil-

ity. Supinski et al.^[87] reported that caffeine increased diaphragm contractility by 48%. Lopes et al.,^[88] who studied the adductor pollicis in a small group ($n = 5$), stimulated the ulnar nerve at 10 to 100Hz and found no difference in maximum tension following ingestion of caffeine 500mg. However, during low frequency stimulation there was an increase in submaximal tension – the frequency-force curve was shifted to the left. Kalmar and Cafarelli^[89] performed a detailed study recently and found that caffeine increased maximal voluntary activation: maximal voluntary contraction (MVC) increased 3.5% and the time to fatigue at 50% MVC improved by 26%. They proposed that caffeine altered neural function at supraspinal and/or excitation-contraction sites, but not at the level of the spinal cord or neuromuscular junction. In 1989, Tarnopolsky et al.^[90] measured a number of neuromuscular factors in endurance athletes before and after a 90-minute treadmill run. When the athletes had consumed caffeine, there were no measurable effects on MVC, peak twitch torque, motor unit activation, or half relaxation time. However, the investigators recently^[61] revisited the issue with more sensitive methods. During 2 minutes of tetanic stimulation, caffeine ingestion resulted in increased force development during low, but not during high frequency stimulation. The researchers concluded that the enhanced contractility was caused by local actions on the muscle itself and probably involved excitation-contraction mechanisms (possibly calcium release via the ryanodine receptor).

This aspect of study is in its infancy, but is promising. It suggests that caffeine has direct actions on muscle and that these are independent of metabolic issues. Such studies not only reveal insight regarding possible beneficial effects of caffeine for strength athletes, but also give valuable information regarding possible sites of fatigue and mechanisms of caffeine action.

7. Possible Adverse Effects

Can caffeine ingestion result in an adverse effect on performance? It has been mentioned previously that a negative effect on work performance

was observed when participants received a high dose of caffeine. While a few studies^[11,25,30,48,54,58,77,81,83] did not find caffeine to improve endurance, several of these studies^[11,30,48,81] employed exercise protocols that led to rapid exhaustion. The author knows of no published study that has shown a negative effect of caffeine on performance.

7.1 Fluid and Electrolyte Balance

A frequently suggested adverse effect is a caffeine-induced diuresis leading to fluid and electrolyte loss and a decrease in plasma volume. In a study comparing caffeine to coffee,^[26] urine volume was measured an hour after ingestion of the selected compound and also after exercise. No differences were noted in urine output, and the volume closely matched that of the fluid ingested, regardless of the presence or absence of caffeine. Similarly, studies^[30,31,33,45,77,91] that quantified body-weight loss, sweat rates, plasma volume and electrolytes, and core temperature, did not find any impact of caffeine ingestion. While caffeine is a mild diuretic, it takes several hours for changes in renin to occur.^[92] In the studies involving exercise, activity takes place before this time and presumably overrides the potential for diuresis. There does not appear to be any basis for the common concern that caffeine ingestion will dehydrate athletes. Wemple et al.^[30] clearly demonstrated that caffeine ingestion resulted in a mild diuresis (1843 vs 1411 ml of urine) over 4 hours, but if exercise took place, there was no diuretic effect. Furthermore, in either case, the diuresis did not generate measurable effects on plasma volume, sweat rate, or plasma or urine osmolality.

7.2 Caffeine Dependency

There is no doubt that people can develop a tolerance and dependency for caffeine.^[64,93-95] The tolerance is associated with an up-regulation of adenosine A1 or A2 receptors in at least some tissues, as well as adaptations in post-receptor events (section 4.1). However, most of this information is derived from animal models and/or *in vitro* evaluations of isolated cells. The tissues that are critical

in responses in the intact organism remain unclear, and very little is known about the mechanisms involved.

Physical dependency for caffeine is described extensively by Strain et al.^[64] They pointed out that substance dependency is characterised by tolerance, withdrawal symptoms, taking the substance in larger doses, and persistent desire for the substance, and so on. Caffeine withdrawal is associated with headaches, mood shifts (irritability, anxiety, depression, etc.), drowsiness and fatigue,^[64,93] beginning in 12 to 24 hours, peaking in 24 to 48 hours, and lasting about 7 days. As little as 3 days of caffeine exposure is sufficient to produce withdrawal symptoms.^[64] Not everyone will develop dependency, and the dependency is often mild. Nevertheless, the syndrome is similar to substance dependency syndromes for other psychoactive drugs. Furthermore, a few individuals can present a caffeine-induced anxiety disorder.

8. Mechanisms

If we are to address the various issues surrounding caffeine as an ergogenic aid, it is essential to understand how caffeine results in increased exercise capacity. It has been consistently reported that caffeine enhances endurance in prolonged activity lasting more than 30 minutes. While there are fewer studies of activities lasting 1 to 30 minutes, it appears that both endurance and performance (speed or power) are enhanced in these situations as well. Very often, the explanation for the actions of caffeine is that caffeine stimulates adrenaline secretion and this results in mobilisation of FFAs. This enhanced delivery of fuel to active muscle is thought to result in a 'Randle' effect, increasing fat oxidation and sparing limited and critical muscle glycogen stores. In 1980, Essig et al.^[96] offered this as a possible explanation. It was insightful at the time, but in the last 2 decades, many findings have not been compatible with this theory.

The glycogen-sparing theory is frequently relied on to explain the actions of caffeine. However, there is a serious lack of support and, more recently, there are studies that clearly illustrate that it is not

correct in many circumstances. Unfortunately, most investigations have been very descriptive and lack critical measures. Many studies referred to above did not even measure plasma caffeine concentrations, let alone catecholamines, both of which are fundamental to the glycogen-sparing hypothesis. There are very few reports of data from muscle biopsies, and only 2 investigations^[27,97] have quantified muscle metabolism.

It is becoming apparent that caffeine is a powerful drug that affects most, if not all, tissues. As mentioned in section 1, this is not surprising given the ubiquitous distribution of adenosine receptors. This also means that these investigations with caffeine should be regarded not only as practical studies of athletic performance, but also as important examinations of fundamental aspects of physiological regulatory roles for adenosine.

8.1 Fat Oxidation

Does caffeine enhance fat metabolism? Even if it does, fat oxidation is trivial in some situations when caffeine is ergogenic, such as in short term, intense activity and in resistance activity. In addition, the studies showing that caffeine did not decrease respiratory exchange ratio (RER) and/or increase plasma FFA levels probably outnumber those that found the 'expected' result. In 12 different studies in the author's laboratory, no decrease in RER following caffeine ingestion was observed. In only 6 of these studies were circulating FFA levels increased (mainly at rest before exercise). Yet, in the 9 studies in which endurance was measured, caffeine was ergogenic in 8 (only when Wingate tests were examined was an ergogenic effect not found).

Furthermore, Raguso et al.^[27] reported that theophylline failed to alter either the rate of appearance (Ra) or disappearance (Rd) for FFAs or glycerol. In another study,^[97] while caffeine ingestion increased arterial FFA levels, net uptake of FFAs by the exercising leg was not enhanced (fig. 1) and whole body RER was not altered. Thus, in a wide variety of circumstances, there is little support for the theory that caffeine increases fat oxidation, even though

it may well promote adipose tissue lipogenesis at rest.

There are considerable data demonstrating that caffeine increases adrenaline levels (section 8.6), and a recent study^[97] showed that leg sympathetic stimulation was increased by caffeine. However, FFA mobilisation occurs even in tetraplegics when there is no increase in catecholamine levels.^[76,98] The author speculates that the following scenario occurs with fat metabolism: caffeine antagonises A1 receptors of adipocytes and this enhances lipolysis (this may be supplemented with increased sympathetic activity resulting in adrenergic β -receptor stimulation); the elevation of FFA levels results in increased hepatic uptake of FFAs, some of which are oxidised or esterified to triglycerides; the excess FFAs form ketone bodies, which are released and cleared by several tissues, including skeletal muscle.

8.2 Muscle Glycogen

It is commonly stated that caffeine results in glycogen sparing, and there are many exercise protocols (exercise lasting <30 minutes) in which caffeine has been shown to be beneficial when glycogen does not appear to be limiting. Furthermore,

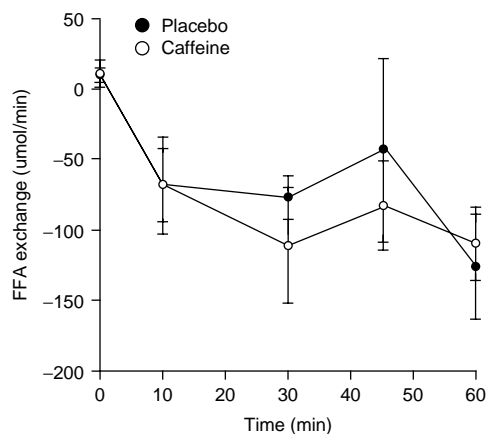


Fig. 1. A summary of net free fatty acid (FFA) exchange across the leg (data from Graham et al.^[97]). Participants ingested either placebo or caffeine 6 mg/kg, rested for 1 hour, and then exercised at 70% maximal oxygen uptake for 1 hour. Negative values are net uptake. Data are means \pm SEM.

the literature is far from consistent regarding the impact of caffeine on muscle glycogen. The initial study by Ivy et al.^[42] demonstrated that caffeine reduced glycogen use during prolonged exercise that was not performed to exhaustion. This was confirmed by Erickson et al.^[34] and by other investigators,^[55] who found that reduced net catabolism occurred only in the first 15 minutes of exercise.

Subsequently, Jackman et al.^[82] found no difference in muscle glycogen use during exercise at $\dot{V}O_{2max}$, although caffeine enhanced endurance time. Similarly, Chesley et al.^[99] found no difference in glycogen after either 3 or 15 minutes of exercise at 85% of $\dot{V}O_{2max}$. Greer et al.^[29] recently found that, while both theophylline and caffeine enhanced endurance time in exercise normally lasting 32 minutes, there was no difference in muscle glycogen, nor was glycogen depleted in the placebo trial. Thus, even if glycogen had been spared, there is no evidence that it was the limiting factor for endurance time. Laurent et al.^[100] reported no glycogen sparing caused by caffeine during 2 hours of exercise at 65% $\dot{V}O_{2max}$. Recently, another study^[97] found that, at 10 and 60 minutes of exercise at 70% of $\dot{V}O_{2max}$, there were no differences in net glycogen catabolism. It is difficult to explain why the first 3 investigations consistently reported glycogen sparing and the more recent studies did not confirm this observation. The obvious possibilities of individual training, exercise intensity, and so on, do not appear to be different between the studies.

It is interesting to note that Chesley et al.^[99] observed that muscle glycogen phosphorylase a (the more active form of the phosphorylase) had a very strong tendency to be increased at 3 minutes of exercise in the caffeine trials. Such a phosphorylase activation should promote rather than spare glycogen catabolism. Vergauwen et al.^[101] actually found that, when the rat hind-limb model was exposed to caffeine during stimulation, glycogen breakdown was enhanced by 40% in the fast-oxidative fibres. However, the researchers also demonstrated that phosphorylase activity was not affected, but that glycogen synthase activity was depressed.

8.3 Blood Glucose

The other component of carbohydrate metabolism, blood glucose, is rarely considered. There are a few reports that blood glucose is increased by caffeine,^[21,27,53,75,91,97] but generally it is not altered. Raguso et al.^[27] found that the Ra for glucose was not influenced by theophylline at rest, or during an hour of exercise at 70% $\dot{V}O_{2max}$, but Rd was decreased. They concluded that this was because of decreased uptake of glucose by active muscle. Direct measurements of leg glucose uptake have been made during very similar exercise. Caffeine resulted in an increase in arterial glucose levels, but in no difference in uptake by the active leg (fig. 2). Subsequently, a decrease in glucose uptake was noted in nonexercising muscle (unpublished results). This could account for the reduced Rd for glucose.

8.4 Lactate

There is one further aspect to carbohydrate metabolism that raises some intriguing issues. It is remarkable how often^[27,48,51,53,55,62,75,81,91,97,99,102] it has been observed that caffeine ingestion increases blood lactate levels. This is paradoxical considering the dogma that carbohydrate sparing is supposed to occur. It is also interesting that this has

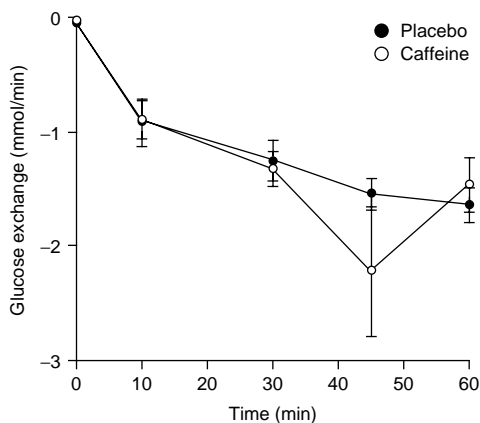


Fig. 2. A summary of net glucose exchange across the leg (data from Graham et al.^[97]). Participants ingested either placebo or caffeine 6 mg/kg, rested for 1 hour, and then exercised at 70% maximal oxygen uptake for 1 hour. Negative values are net uptake. Data are means \pm SEM.

probably been observed more consistently than an increase in FFA levels, and certainly more often than a decrease in RER, in association with caffeine ingestion. However, it is rarely raised in discussions of the metabolic consequences of caffeine. When it has been discussed, the interpretation has been that lactate production is greater than pyruvate oxidation, perhaps because of the latter being suppressed by enhanced fat oxidation. As reviewed above, there is little evidence for increased fat oxidation. Furthermore, measurements of muscle acetyl CoA and citrate^[29,75,97] generally do not support such a mechanism. Muscle lactate measurements in steady-state exercise^[29,97,99] showed no difference when caffeine or theophylline was consumed. Recently, direct evidence was published^[97] that caffeine elevated arterial lactate levels during exercise, but muscle lactate levels and release from the exercising leg were not altered (fig. 3). Similarly, no change in lactate exchange was observed in the nonexercising leg when caffeine was administered (unpublished results), possibly because caffeine was inhibiting lactate clearance, perhaps by the liver.

8.5 Energy Status

Chesley et al.^[99] found that caffeine improved energy status, as evident from less phosphocreatine (PCr) degradation and less accumulation of the predicted free levels of adenosine diphosphate (ADP) and adenosine monophosphate (AMP). However, these changes were found only in the subgroup of participants who had less muscle glycogen use following caffeine ingestion. The significance of this finding is questionable as the participants were divided post hoc into subgroups based on glycogen data, and then examined further for energy status, etc. Marsh et al.^[28] conducted what could be classified as a pilot study using NMRS. They studied 3 individuals who had ingested theophylline and performed progressive forearm exercise. In agreement with Chesley et al.,^[99] Marsh et al.^[28] reported that there was a trend for the inorganic phosphate (Pi)/Pcr ratio to shift in favour of more Pcr with theophylline. Clearly, these findings should be followed up with further investigations.

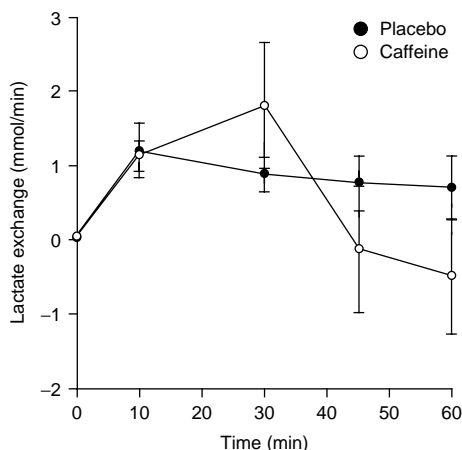


Fig. 3. A summary of net lactate exchange across the leg (data from Graham et al.^[97]). Participants ingested either placebo or caffeine 6 mg/kg, rested for 1 hour, and then exercised at 70% maximal oxygen uptake for 1 hour. Negative values are net uptake. Data are means \pm SEM.

8.6 Catecholamines

The final aspect of the glycogen-sparing model is that of caffeine-induced increases in sympathetic activity. Clearly, caffeine can increase circulating levels of adrenaline.^[29,49,53,55,59,63,75,82,97] Only rarely^[30,90] has this not been observed. However, the increase is quite modest and it is debatable whether this would have metabolic significance. At the very least, the increase is probably not critical to caffeine actions. Tetraplegic humans have a very low level of plasma catecholamines that is not elevated by caffeine.^[76,98] Nevertheless, caffeine caused a 'normal' rise in FFA levels in individuals at rest and, when their muscles were electrically stimulated,^[98] fatigue was delayed.

In addition, Chesley et al.^[103] infused adrenaline to levels very similar to those observed during exercise when caffeine had been administered. The elevated adrenaline level did not result in any difference in muscle glycogen degradation, or in the calculated free levels of lactate, phosphocreatine or adenosine triphosphate (ATP), ADP and AMP. Furthermore, van Baak and Saris^[104] studied the effects of propranolol on exercise (70% $\dot{V}O_{2max}$) responses to caffeine ingestion: endurance increased

from 22.6 to 31.2 minutes ($p = 0.056$), while circulating FFA levels were low and not different between propranolol versus propranolol plus caffeine.

In contrast to data for adrenaline, rarely have studies found an increase in noradrenaline (norepinephrine) levels. However, circulating noradrenaline results from the 'washout' of tissues, and tissue exchange must be measured directly to determine whether or not the sympathetic system is enhanced. Previous data were from mixed venous blood samples, but recently, tissue exchange measurements were made for the exercising leg.^[97] Contrary to previous results, leg noradrenaline release/washout was markedly enhanced during exercise when participants had ingested caffeine.

For the last 2 decades, most studies failed to find a decrease in RER following caffeine ingestion and this was dismissed as being only an indirect measure. More recently, direct determinations of fat oxidation, and of glycogen and glucose metabolism, also failed to support the theory that caffeine shifts metabolism in favour of fat oxidation. Clearly, it is time to consider alternative theories.

8.7 Blood Flow

Rarely have the cardiovascular consequences of caffeine ingestion been considered, perhaps because early studies showed very little change in blood pressure and heart rate for resting or exercising participants. There are several factors associated with caffeine that could be important in cardiovascular regulation, including adenosine-receptor antagonism and enhanced sympathetic activity. Within the cardiovascular system, these factors could result in either central or peripheral actions. Recently, Daniels et al.^[105] found that caffeine ingestion caused an increase in peripheral resistance of the forearm vasculature and a decrease in flow during leg exercise. In another study,^[97] a modest, but significant increase in mean blood pressure (measured by direct arterial catheterisation) was noted during rest and exercise. Since blood flow to the leg was not altered, leg vascular resistance was elevated. The importance of these changes is unknown, but like

the responses described above, they suggest multiple, regulatory roles for endogenous adenosine.

If the ergogenic mechanisms are not those of metabolism, then what are the alternatives? Metabolism does not control muscle function, it is regulated by it. In other words, metabolism occurs as a result of demands for replenishment of ATP consumed by muscle contractions, and so on. How these demands are met may alter the amounts of critical metabolic stores and limit their activity, but to date, there is minimal evidence that aspects of fat or carbohydrate metabolism are changed. The mechanisms that appear to be critical are associated with contractile mechanisms and may involve aspects of excitation-contraction coupling and/or motor unit recruitment.

8.8 Ion Balance

It is likely that many aspects of fatigue involve electrolyte homeostasis. This could involve a suppression in resting membrane potential caused by a loss of potassium or be caused by reduced calcium release from the sarcoplasmic reticulum. Either of these actions would result in less motor unit activation and/or less force production per motor unit. It is clear that potassium ions are lost from the muscle with every depolarisation^[106-108] and that plasma potassium levels subsequently increase. This could result in a reduced resting membrane potential. It has been observed that caffeine ingestion results in less of an increase in plasma potassium during exercise.^[45,109] This could be caused by less washout of potassium from the active muscle or a faster plasma clearance. Lindinger et al.^[109] speculated that either caffeine, or the associated increase in adrenaline, stimulated resting muscle sodium/potassium ATPase to take up more potassium.

There are several lines of evidence to support this hypothesis. Lindinger et al.^[110] have shown that caffeine (in nonphysiological doses) directly stimulates resting muscle potassium uptake. A recent study^[97] demonstrated that, following caffeine ingestion, participants had less increase in arterial potassium, but potassium release from the active leg was not altered. No discrimination could be made

between the possible effects of caffeine and those of adrenaline. The possibility that the signal is caffeine rather than adrenaline is supported by the work of van Soeren et al.,^[98] who found that caffeine ingestion resulted in tetraplegic participants having less of an increase in circulating potassium, while adrenaline was not altered. In contrast, van Baak and Saris^[104] found that, during exercise, plasma potassium levels were elevated with β -blockade, but were no different between caffeine and placebo groups. These studies support the theory that potassium clearance is enhanced. However, critical studies addressing whether or not lower arterial (and hence interstitial) potassium levels moderate fatigue have not been performed.

As reviewed earlier, studies^[61,88,89] suggest that excitation-contraction coupling is enhanced with caffeine. It is well known that pharmacological doses of caffeine can alter calcium exchange by the sarcoplasmic reticulum in isolated muscle preparations, but studying this *in vivo* under physiological conditions will prove to be a great challenge.

8.9 Central Nervous System

As every coffee drinker knows, caffeine can stimulate the CNS. Adenosine receptors are plentiful in many areas of the brain. Often, authors suggest that caffeine 'stimulates the brain'. Clearly, reviews such as those by Fredholm^[17] and Benowitz^[111] and others^[3,112,113] demonstrate that such statements are gross oversimplifications. The CNS consists of many areas with different adenosine-receptor populations. It is not merely that caffeine will bind to one specific set of receptors in one isolated area resulting in a single neural event. The CNS effects are varied and far reaching, probably including altered sympathetic activity, motor recruitment, and perception of fatigue and pain (see section 2.3). The topic of the CNS is vast, and there are many reviews on caffeine and the CNS, but rarely have these been examined with regard to exercise. Furthermore, studies involving humans are normally conducted in carefully controlled environments and therefore have limited application to athletes in competition, who are usually highly aroused and, perhaps, anxious.

Any or all of these factors could be important, but they are not vital. Caffeine increased muscle endurance in tetraplegic patients in one study,^[76] and other investigators^[61,88] found caffeine-induced effects when muscles were electrically stimulated. Thus, the ergogenic effects of caffeine must involve direct actions on peripheral tissues.

9. Ethical Considerations

Is there any reason to be concerned about caffeine as an ergogenic aid? It is difficult to resolve what advice to give athletes. In competition, caffeine is allowed up to a critical limit: it is not 'illegal'. It is a powerful tool to increase exercise capacity in training, and probably also in competition. There are very few adverse effects or health risks. In addition, caffeine is a common part of most people's diets. One could draw parallels to carbohydrate loading, creatine loading, and vitamin, mineral and antioxidant supplementation. However, unlike these examples, caffeine is not a traditional nutrient. Athletes who ingest caffeine are using a drug for the express purpose of gaining an advantage. As such, the author considers it to be doping and unethical. If an athlete has made a conscious decision to take caffeine for the purpose of gaining an advantage and enhancing performance, this could be the first of a series of similar decisions for other drugs. It is not possible at this time to demonstrate what dose of caffeine can be taken without causing an ergogenic effect. However, even if this was known, urinary excretion is too variable to accurately predict the dose ingested (see section 3.3). Given this, the only solutions at this time to create a fair opportunity for all athletes are to recommend either blood analysis or a ban on caffeine in sport.

10. Conclusion

Caffeine is a complex substance that is found in many organic compounds and is consumed by humans in coffee, teas and chocolate. In addition, the food industry is now adding caffeine to a wide assortment of foods and drinks. Caffeine is also found in various 'natural health products' and in many over-the-counter drugs. The effects it has on the

body are wide ranging, probably because of the presence of various adenosine receptors in many tissues.

Caffeine, and probably dimethylxanthines, are ergogenic in most if not all exercise situations. To the author's knowledge, no study has shown that administration of these substances produces negative effects during exercise. The mechanisms involved in actions of these compounds are varied and complex and extend well beyond the traditional explanation of sparing of muscle glycogen to probably involve fundamental aspects of muscle contractility. Many scientists have conducted very descriptive investigations. They should recognise that the effects of caffeine are also demonstrating the consequences of antagonising normal biological function and, as such, may reveal important aspects of physiological regulation. Such results may well have wider implications and apply to both basic and medical sciences.

Acknowledgements

The author gratefully acknowledges the vital support of his co-authors in the various publications cited in his work, and the outstanding technical support of Ms Premila Sathasivam. His work has been supported by Natural Science and Engineering Research Council (NSERC) of Canada, by Sport Canada, and by Gatorade Sport Science Institute.

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