

Caffeine

By Andrew Hamilton BSc Hons MRSC

Everybody's heard of it and over 80% of the world's population are habitual users of the world's most popular psychoactive drug. But caffeine is far more than just a 'pick-me-up'; used correctly it can genuinely enhance sports performance, making it the sports supplement of choice for athletes in the know. Andrew Hamilton explains all...

CONTENTS

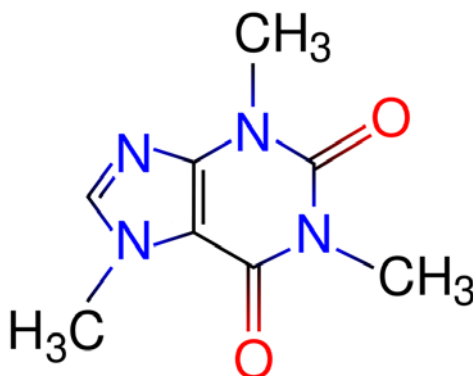
- A. An brief explanation of what caffeine is and its history
- B. Dietary sources of caffeine
- C. How caffeine exerts its effects in the body
- D. What can caffeine do for me?
- E. When should take caffeine?
- F. How much caffeine should I take?
- G. What the best source of caffeine for sport performance?
- H. Frequently asked questions about using caffeine; synergistic nutrients; habitual use vs. non-habitual use; dehydration; recovery; side effects.

A - WHAT IS CAFFEINE?

Caffeine, or to use its full name *1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione* (see figure 1) has been used by humans since paleolithic times. These ancient folk discovered that chewing the seeds, bark, or leaves of certain plants could ease fatigue, lift mood and enhance awareness. It was only discovered much later the effects of consuming caffeine containing plants was increased by steeping them in hot water.

Caffeine is a naturally occurring compound that occurs naturally in over 60 plants and belongs to a family of chemical substances called *xanthine alkaloids*, which also includes naturally occurring compounds such as theobromine and theophylline. In nature, these xanthine alkaloids act as natural pesticides, helping to kill insects trying to feed on the plant containing them. However, when we ingest extracts of plants such as tea, coffee, cocoa, guarana and kola containing them, the effects are very different.

Figure 1 – the chemical structure of caffeine



B- SOURCES OF CAFFEINE IN THE DIET

The best-known sources of caffeine in the diet are caffeine-containing beverages such as, coffee, tea, chocolate and cola. The exact caffeine content these products however depends very much on the variety of tea/coffee/cocoa plant, the time of harvesting, the kind of processing undergone (*eg* roasting etc.) and the methods used to prepare the beverage.

As a rule of thumb, freshly brewed coffee contains high levels of caffeine (over 100mgs per cup), whereas freshly brewed tea contains less than half this amount and roughly the same amount of caffeine per cup as instant coffee (see table 1). Although rich in the mild stimulant theobromine, cocoa products actually contain very little caffeine. Some soft drinks such as cola and a number of drinks marketed as 'energisers' (*eg* Red Bull) also contain significant amounts of caffeine, but this is almost always because the manufacturer has added caffeine rather than an inherent property of the drink itself.

The herb guarana is a very rich source of caffeine and often finds its way into caffeinated beverages. Although promoted as a 'slow release' form of caffeine, the caffeine it contains is identical to that derived from tea, coffee etc; however, when consumed in guarana products, other substances present in the plant appear to slow down the caffeine release.

Table 1 - Typical caffeine contents (mgs) of commonly consumed beverages and foods

Coffee (instant, 8oz cup)	40-108
Coffee (freshly brewed, 8oz cup)	110-150
Coffee (expresso, 2oz cup)	100
Coffee (decaffeinated, instant)	2
Tea (1-minute brew, 8oz cup)	9-33
Tea (5-minute brew, 8oz cup)	20-50
Tea (green, 8oz cup)	15
Cocoa* (8oz cup)	3-11
Chocolate* (70% cocoa solid plain, 1.5oz)	6-
Chocolate* (milk, 1.5oz)	3
Coca Cola (12oz can)	34
Red Bull (8oz)	80

Sources: *Caffeine Content of Food and Drugs. Nutrition Action Health Newsletter. Center For Science in the Public Interest (December 1996); US Dept. of Agriculture; US National Soft Drink Association*

* Also contains theobromine, which exerts a mild stimulatory effect

C - EFFECTS ON CAFFEINE ON THE BODY

Central nervous system effects

Before we go on to discuss how caffeine can enhance sports performance we'll begin by discussing its stimulatory effects on the central nervous system (CNS) and on muscle. Caffeine is a central nervous system stimulant and reduces mental fatigue and tiredness while simultaneously increasing alertness and wakefulness. This in turn can lead to clearer and more focussed thought processes and improved coordination. However, it's important to realise that the CNS plays a central role in physical control and performance, and therefore that the physical and CNS effects of caffeine cannot really be considered separately.

An enhanced CNS function inevitably leads to improved motor coordination (as already mentioned), a reduced perception of fatigue and perceived rate of exertion, all of which are conducive to improved physical performance. Indeed, some scientists now believe that the sensation of muscular fatigue during exercise arises as a result of complex feedback processing by the brain rather than by muscles simply 'running out of fuel' or an accumulation of fatiguing by-products in exercising muscles¹. It is likely therefore that at least some of caffeine's ergogenic effects occur as a result of CNS stimulation.

The effects of caffeine on the CNS occur because caffeine binds to and blocks proteins in the CNS called adenosine receptors. These receptors are where adenosine molecules bind, so the presence of caffeine means their effect is reduced. When adenosine binds to its receptors, it promotes feelings of sedation, lowers heart rate and blood pressure and generally inhibits neural activity. The administration of caffeine therefore tends to produce the opposite effects, principally because it allows a stimulatory neurotransmitter called dopamine to become more influential in determining the balance of neuronal stimulation/inhibition.

Caffeine and calcium ion release

However, caffeine also exerts some direct physical effects on muscle that may also help explain its ergogenic effects. As long ago as 1910, scientists discovered that caffeine administration increased the contractile ability of isolated muscle² and also that this effect was (up to a point) dose dependent³. This almost certainly occurs because caffeine stimulates the release of calcium ions (Ca^{2+}) from a region of the cell known as the sarcoplasmic reticulum. Ca^{2+} ions are involved in the process of initiating a sequence of chemical and electrical events that eventually lead to muscular contraction, and we now know that impaired calcium release can contribute to muscular fatigue⁴. Although the isolated muscle tissue studies on caffeine stimulated Ca^{2+} release used much higher levels of caffeine than would be found after even large amounts of caffeine ingestion, we now know that other naturally occurring molecules in the body such as cyclic ADP-ribose can dramatically increase the sensitivity of the Ca^{2+} release system to caffeine⁵.

Caffeine and enzymes controlling fuel utilisation

Caffeine is known to inhibit an enzyme called glycogen phosphorylase. This enzyme is involved in the breakdown of glycogen (stored muscle carbohydrate) to free glucose units, which are then oxidised in the muscles for energy. Although this might not sound promising for enhanced physical performance, a reduced rate of breakdown of glycogen during exercise could produce a 'glycogen sparing effect' in longer workouts, where more premium grade fuel for high-intensity exercise (carbohydrate) would be towards the end of race could be advantageous.

This effect may be enhanced by another physiological effect of caffeine; ingestion of caffeine is known to enhance the break down of fats for energy (lipolysis) by inhibiting an enzyme called nucleotide phosphodiesterase⁶. When this enzyme is inhibited, the level of a very important signalling molecule called cyclic AMP rises and the resulting high tissue concentrations of cyclic AMP activate another enzyme called hormone-sensitive lipase, which in turn promotes lipolysis. However, while increased fat breakdown and utilisation and glycogen sparing seem to be the perfect combination for endurance athletes, many studies on this effect are inconclusive; the effects are either very short-lived or very variable between individuals.

Other physiological effects

Caffeine exerts a number of other physiological effects on the body, including an enhancement of the sodium-potassium pumping action across cell membranes⁷ (the mechanism that helps to regulate transport of substances in and out of cells) as well as potentiating the effects of ephedrine^{8,9}, a hormone secreted by the adrenal glands, which is capable of increasing energy expenditure and promoting the loss of body fat. However, the precise extent to which these effects contribute to caffeine's ergogenic effect is still poorly understood.

USING CAFFEINE

Okay, now we know what caffeine is and a little bit about how it works in the body, we can get down to the nitty-gritty – *ie* how does caffeine boost performance and how can it be used to produce the maximum sport performance benefits? Among the questions we'll try to answer is how much caffeine to use and when? Exactly what benefits can be expected? Can caffeine be

combined with other sports supplements for a synergistic effect? And what about the drawbacks of caffeine use? What are they and how can they be minimised?

D - What can caffeine do for me?

Endurance events - Over the last 15-20 years, a large number of studies have been published that unequivocally demonstrate the benefits of ingesting caffeine and/or caffeine containing drinks before and during endurance exercise¹⁰⁻²⁴. Typically, caffeine can significantly delay the onset of fatigue during endurance exercise at 70-85% VO₂max lasting more than 30 minutes and enables higher work rates to be maintained during exercise with a reduced perception of effort. Studies have involved cyclists, runners and other endurance athletes in a range of test protocols (time-trials, incremental intensity tests, tests to exhaustion etc.) and over a wide range of distances/durations. The gains in endurance performance that caffeine produces are not vast in absolute terms (typically a few percent), but of course in competitive sport, the difference between winning and being an also-ran is often measured in seconds – even over very long events!

Shorter events – Much of the early research into caffeine and sports performance focussed on endurance running and cycling rather than on shorter, more anaerobic events. This was because many researchers believed that caffeine probably exerted its effects by helping the body spare glycogen and through the increased mobilisation of fatty acids (from fat stores) – both of which would benefit endurance athletes but not necessarily strength or power athletes.

However, in recent years it's become clear that caffeine-mediated CNS stimulation plays a much greater role enhancing performance than was first thought. Consequently there have been more good quality studies into the effects of caffeine in shorter events and the results look promising. For example, a look at the most recent research shows the following:

- Caffeine administered to runners 1 hour before an 8km run produced an average improvement of 23.8 seconds over the distance compared to an inert placebo²⁵;
- Compared to placebo, trained rugby players who underwent simulated rugby play (seven circuits in each of two 40-minute halves separated by a 10-minute break) performed significantly better in sprinting, driving and passing drills when they took caffeine compared to placebo²⁶;
- Intermittent cycle sprinting (2 sets of eighteen 4-second sprints with 2 minutes of active rest in between sprints) resulted in an 8.5% increase in the total amount of sprinting work performed and a 7% increase in mean sprint power when caffeine was consumed²⁷;
- Caffeine produced an improvement of 1.2% in the times for 2000m ergo rowing and a corresponding increase in power of 2.7% compared to placebo²⁸;
- The perception of leg muscle discomfort associated with cycling was significantly reduced in female cyclists when caffeine was administered when compared to placebo²⁹.

However, a few studies on the effects of caffeine during shorter events have produced more inconclusive results; for example studies on sprinting³⁰ and the maximal force developed during strength training³¹ failed to find any benefits of caffeine ingestion. This may be due to a degree of 'inter-individual variability' in response to caffeine that some researchers have observed; shorter duration tests (where performance differences are harder to measure) are more likely to suffer in this respect. *Nevertheless, the overwhelming balance of evidence is that caffeine can and does enhance shorter duration events, where anaerobic power, strength and skill play a larger role.*

E - When should I take caffeine?

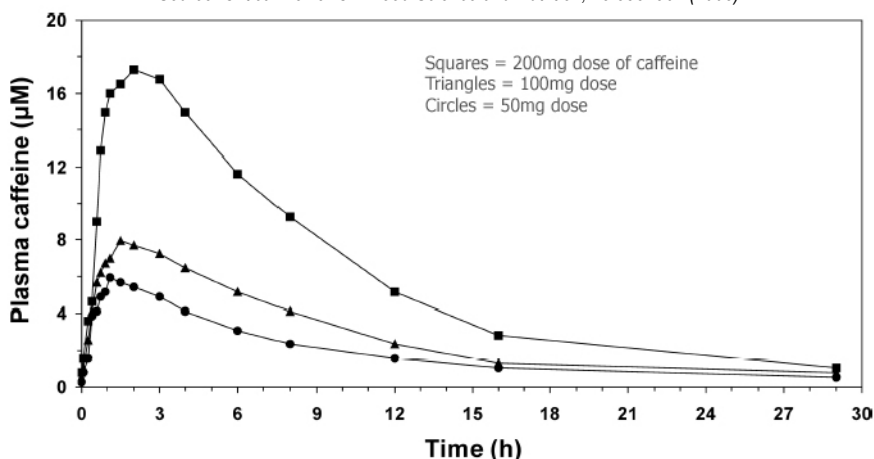
Given that caffeine can offer real performance gains, the obvious questions are how much do I need and when should I take it? Let's start with the second question first. When you ingest caffeine, it's rapidly and completely absorbed from the gastrointestinal tract into the bloodstream. Absorption is complete within approximately 1 hour of ingestion (typically 99% of the ingested

dose is absorbed within 45 minutes)³²⁻³⁵ and is independent of the amount of caffeine ingested - at least at doses up to 10 milligrams per kilo of body weight (700mgs for a 70kg adult!)³⁶.

Once in the body, caffeine concentrations peak anything from 15-120 minutes after ingestion (the smaller the dose, the more rapid the peak), but for the typical doses used in most studies (3-6mgs per kg), peak concentrations occur after around 60 minutes³⁷. Caffeine is only metabolised and broken down slowly (mostly in the liver) with a 'half-life' (the time taken to reduce caffeine concentration in the body by 50%) of around 4-6 hours. This means that peak concentrations can be maintained for a good 2-3 hours after ingestion, even without topping up! (see figure 2)

Figure 2: Blood levels of caffeine following caffeine ingestion

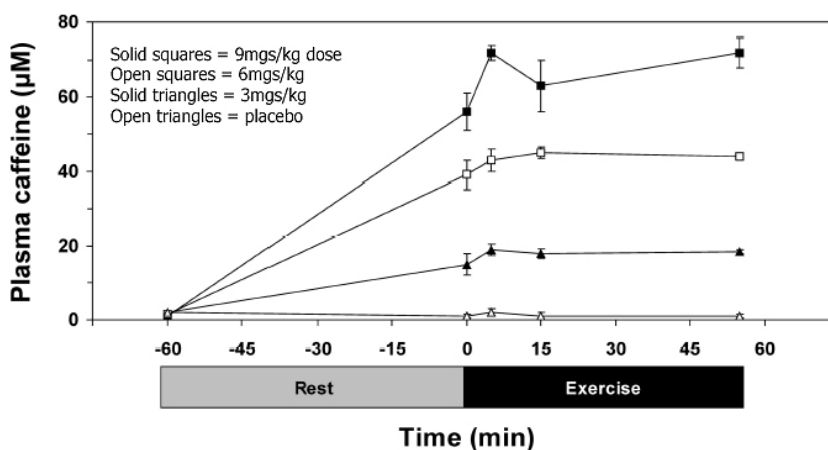
Source: *Critical Reviews in Food Science and Nutrition*, 45:535-562 (2005)



Moreover, caffeine levels in the body appear to be unaffected by subsequent exercise; figure 3 shows blood concentrations of caffeine at rest and during exercise after oral ingestion of different doses:

Figure 3: Blood levels of caffeine following caffeine ingestion and exercise

Source: *Critical Reviews in Food Science and Nutrition*, 45:535-562 (2005)



Studies have shown that the ergogenic effects of caffeine can be sustained for up to 6 hours after ingestion, even after an exhaustive bout of exercise³⁸ and given these findings, it seems reasonable to assume that for most athletes, taking caffeine one hour before training or competition is sufficient to reap the benefits, even when exercise is of very long duration.

However, some studies have reported that taking caffeine in smaller, divided doses may produce performance benefits. For example, a study on cyclists showed that time trial performance improved when caffeine was given in two doses of 3mgs/kg before and at 45 minutes into the time trial than when the same amount was given in a single 6mgs/kg dose before the time trial³⁹.

But the degree of improvement was not large enough to be considered significant and other studies on divided doses of caffeine have failed to show any benefits at all⁴⁰.

More research is needed in this area, but on current evidence, a single dose of caffeine ingested about an hour before exercise seems to work well and should be considered a good starting point for any subsequent experimentation.

F - How much caffeine should I take?

The next question is how much caffeine should you take to gain maximum performance benefits? Although this has been a much-researched subject, there are still no hard and fast rules because the optimum dose may vary a) as a function of the duration and intensity of exercise and b) the particular response to caffeine displayed by an individual.

Before we look at the evidence, it's important to understand how caffeine doses for sport performance are measured and quoted. Because caffeine is distributed throughout the body once ingested and because people vary widely in their body mass, most researchers consider that the best measure of caffeine dose is on a 'per kilogram of body mass' basis.

This is easily obtained by dividing the total amount of caffeine ingested by your body mass in kilos; *eg* if you take 200mgs of caffeine and you weigh 80kgs, your dose rate is $200/80 = 2.5\text{mgs/kg}$. If you're trying to achieve a particular dose rate then the total amount of caffeine you need to ingest is easily calculated by multiplying the dose rate you require by your weight in kilos. For example if you weigh 60kgs and you want to achieve a dose rate of 6mgs/kg, your total dose is $6 \times 60 = 360\text{mgs}$.

In terms of research on optimum caffeine dose rates, a large number of studies have reported a wide range of results. These can be summarised as follows:

- **Events less than 30 minutes' duration** – caffeine doses of 6-9mgs/kg appear to produce significant performance benefits in trained subjects^{41,42}. Lower doses have produced inconclusive results and in untrained subjects, there's little evidence that caffeine produces benefits regardless of dose⁴³⁻⁴⁵.
- **Events from 30-60 minutes' duration** – in runners, doses of 3mgs/kg and 6mgs/kg enhanced performance, but 9mgs/kg had no effect⁴⁶. In cyclists, doses of 5, 9 and 13mgs/kg all produced enhanced performance, and the magnitude of performance gain was the same for all doses⁴⁷, while another cycling study produced performance gains with doses of 2.1, 3.2 and 4.5mgs/kg, the gains being greatest at 3.2 and 4.5mgs/kg⁴⁸.
- **Events over an hour** – intakes of 1-2mgs/kg enhanced cycling performance at the end of 2 hours of cycling to the same degree as 6mgs/kg given at the beginning⁴⁹. Some researchers have suggested that this is because individuals may become more sensitive to caffeine as fatigue accumulates. Also, some studies have shown that large amounts of caffeine (9mgs or more per kilo) may actually be detrimental to performance in prolonged endurance events⁴⁶.

The current consensus of scientific opinion about the likely caffeine dose required to produce an effect can be summarised as follows:

- For events less than 30 minutes, 6mgs/kg;
- For events of 30-60 minutes, 3-6mgs/kg;
- For events over one hour, 3mgs/kg or less.

However, it's important to stress that people don't always respond uniformly to caffeine; these figures should be considered as a good starting point for further experimentation. And if you do

experiment, your goal should be to try and find the *smallest* dose of caffeine that works for you in order to minimise any potentially unwanted side effects (see later).

G - In what form should I take caffeine?

Most of the scientific studies on caffeine and sports performance have been performed with pure caffeine, rather than by drinking tea, coffee etc. There are two very good reasons for this. Firstly, the actual amount of caffeine in your cup of tea or coffee can vary wildly. A recent consumer test of espresso coffees obtained from a number of different retail outlets showed that the actual caffeine content varied from 25mgs to 214mgs in a cup⁵⁰! The fact is that if you use tea and coffee to obtain your caffeine, there's no way of being sure how much caffeine you're ingesting.

The second reason why pure caffeine may be preferable to drinking tea/coffee etc is that some evidence indicates that naturally occurring compounds in these drinks may interfere with the uptake and/or effects of caffeine in the body, thereby reducing its effect⁴⁸. While this phenomenon is poorly understood and more research is needed, *the best way to ensure a reliable and consistent dose of caffeine is to take it in its pure form (eg as a sports nutrition product).*

The only caveat to this advice may be for those who are sensitive to blood sugar swings (*ie* tend to suffer from energy 'dips' or 'troughs'). Very recent research has shown that pure extracted caffeine given at doses of 4.5mgs/kg to healthy men produced more glucose intolerance (*ie* subsequently impaired glucose metabolism) compared to coffee providing the same dose of caffeine⁵¹. This may be because naturally occurring compounds in coffee help to ameliorate some of the unwanted side effects of caffeine, such as disturbed glucose metabolism. *If you are a 'glucose sensitive' individual, you might want to experiment with obtaining caffeine from natural sources.*

H - QUESTIONS ABOUT CAFFEINE USE

By this point, you should have a good understand of what caffeine is, where it's found, how it works in the body, and when and how much to use to enhance performance. However, if you're considering using caffeine, you might have other queries, which we'll try to answer in this next section.

Can caffeine be combined with other sports nutrition products for a synergistic effect?

Most of the work on caffeine has examined the effects of caffeine in isolation, but some intriguing new research carried out last year at the University of Birmingham suggests that caffeine may help increase the rate of carbohydrate absorption and oxidation during exercise, thereby prolonging endurance and increasing carbohydrate oxidation rates⁵². In the study, 8 cyclists cycled at around 64% of their maximum oxygen uptake (VO₂max) (hard!) for 2 hours on three separate occasions ingesting either:

- Placebo (flavoured water);
- Water plus glucose (providing 48g of glucose per hour);
- Water plus 48g of glucose plus 5mgs/kg of caffeine per hour.

The researchers then measured how much of the ingested glucose was being oxidised to produce energy and discovered that giving caffeine increased oxidation rates by an astonishing 26% compared to plain glucose! The most likely explanation is that co-ingestion of caffeine with carbohydrate (glucose) increases intestinal glucose absorption, which is thought to be the main bottleneck in getting carbohydrate to the working muscles during exercise. A study 5 years earlier had shown that co-ingestion of caffeine enhanced the rate of glucose transport across the intestine by 23% while cycling at 70% of VO₂max⁵³.

However, caution is required. Firstly, only one study has been carried out on caffeine and carbohydrate oxidation rates; we really need more studies before we can be sure that this effect

can be replicated in other conditions (*eg* different exercise modes and intensities, different glucose and caffeine feeding rates). Secondly, we don't know whether or by how much caffeine-induced increased carbohydrate oxidation will actually improve endurance performance in real conditions. The theory suggests it will, but until tests have been completed, we can't know for sure. *Taking caffeine in combination with carbohydrate might help increase carbohydrate absorption and prolong endurance (above and beyond the effects of caffeine alone) but we need more studies to be sure.*

Do the potential performance gains of caffeine depend on my current caffeine usage habits?

Probably not. A study looked at the effects of acute caffeine ingestion (6mgs/kg) on exercise performance, hormonal and metabolic parameters during short-term withdrawal from dietary caffeine (for periods of 2 and 4 days) among habitual users who were recreational athletes⁵⁴. The measured increases in performance during a cycle test to exhaustion after ingesting caffeine were found to be consistent whether they continued with their existing caffeine use, or had abstained for 2 or 4 days before the test.

Some studies however have shown that abstaining from caffeine for a few days before use does alter the physiological responses to subsequent caffeine ingestion (*eg* increased levels of circulating fatty acids in the blood and raised levels of stimulatory neurotransmitters)⁵⁵, but there is scant evidence that this affects the potential gains to be had by taking caffeine. However, caffeine abstainers who use caffeine to enhance performance may find the side effects of caffeine more severe and some studies have suggested that the individual response to caffeine may be more variable in subjects who normally abstain⁴³. *If you are already a regular caffeine user (ie you drink tea, coffee, cola etc.), there seems little point in withdrawing caffeine before an event in which you plan to use it.*

Is it true that caffeine use can cause dehydration?

No! Although caffeine can produce a small increase in urinary volume, there's very little evidence that it can cause or contribute to dehydration when used at the doses we've discussed above. A comprehensive meta-study (a study that looks at the results of a whole group of scientific studies on a subject) by American scientists examined 10 studies investigating the consumption of caffeinated drinks and hydration, and found no evidence of fluid or electrolyte imbalances as a result of caffeine use⁵⁶. Some studies have hinted that in hot conditions when dehydration is a problem due to heavy sweating, caffeine ingestion may not be as effective in promoting performance gains⁵⁷. However, this suggests dehydration can affect the ergogenic effects of caffeine – not vice versa. *Provided you're following all the normal recommendations to stay hydrated before, during and after exercise, there's no evidence that caffeine will impair your hydration status.*

Does caffeine impair the ability of muscles to replenish glycogen?

Caffeine is known to impair the efficiency of the hormone insulin, which helps drive glucose into muscles where it can either be oxidised for energy, or synthesised into muscle glycogen (an insoluble form of stored carbohydrate). This has led some to speculate whether caffeine use could interfere with subsequent muscle glycogen replenishment after exercise (remember that the half-life of caffeine is several hours which means there's plenty of caffeine in the system even when you've completed training or competition).

However, a recent study looked at the effects of caffeine on the ability of muscles to resynthesise glycogen after 30, 120 and 300 minutes of glycogen-depleting exercise followed by carbohydrate feeding⁵⁸. Although there was a slighter smaller rise in the activity of an enzyme called glycogen synthase (involved in the synthesis of muscle glycogen from glucose units) when caffeine was ingested, the actual rate of muscle glycogen synthesis was the same as in the non-caffeine trials. *Despite some changes in enzyme and hormonal activity, the theory that caffeine may reduce muscle glycogen synthesis after exercise is not borne out in practice.*

What other side effects can caffeine produce?

Although most people tolerate caffeine well, it is not without side effects. Large amounts of caffeine consumed for long periods of time can lead to a condition known as '*caffeinism*', which is characterised by a wide range of undesirable conditions including nervousness, irritability, anxiety, muscle twitching, sleep disorders and heart palpitations⁵⁹. And because caffeine increases secretion of stomach acid, heavy users may face an increased risk of gastric ulcers.

However, prolonged and continual caffeine use tends to produce *adaptation*, where the body adapts to regular caffeine ingestion by increasing the number of adenosine receptors in the CNS (if you remember, caffeine exerts its effects by blocking adenosine receptors). When adaptation occurs, the stimulatory effects of caffeine become less pronounced when caffeine is used. You can easily tell if you've become adapted to caffeine; eliminating caffeine from your diet will induce a headache combined with mental fatigue and an inability to concentrate, which peaks in intensity about 24-48 hours after caffeine withdrawal! These withdrawal symptoms are caused by a sudden increase in adenosine activity in the CNS.

Acute caffeine use (sudden intakes of large doses of caffeine – *eg* when loading up before an event) can cause some of the symptoms described in *caffeinism* (above), even in those who have become adapted to caffeine. *In individuals who use caffeine habitually, lower doses of caffeine (around 3mgs/kg) are unlikely to provoke undesirable side effects. However, higher doses acute doses (9mgs/kg and above) may produce side effects, especially among light or non-users of caffeine where doses of 9mgs/kg have been reported to produce symptoms of mental confusion and 'inability to focus'⁴⁶.*

Is caffeine legal?

Unlike many ergogenic aids, the use of caffeine to enhance performance in sport is currently legal. Although previously on the World Anti Doping Agency's (WADA) 'banned and restricted substances list', caffeine was removed in 2004 and athletes are now free to use caffeine. However, following concerns raised by some sport physiologists, WADA says it is keeping the situation 'under review', and this is worth bearing in mind. As always, you should check with your own sport's governing body that there are no special regulations concerning caffeine.

SUMMARY

Caffeine may be one of the oldest pharmaceuticals in the book, but when employed correctly, is a proven sport performance enhancer (unlike many other so-called ergogenic aids out there!) with few serious drawbacks. By following the recommendations in this article, you'll have a good base from which to experiment with caffeine for your own use and lift your performances to new levels!

Andrew Hamilton BSc Hons MRSC ASCM

REFERENCES

1. Br J Sports Med 2005; 39: 120-124
2. Proc. R. Soc. Lond. B Biol. Sci 1910; 82:568-574
3. J. Physiol 1968; 194:51-74
4. Exp Physiol 1995; 80:497-527
5. J. Biol. Chem 1990; 268:293-299
6. J Biol Chem 1968; 243: 1705-12
7. J. Biol. Chem 1999; 274:19545-19550
8. Int J Obes 1986; 10: 467-81
9. Metabolism 1991; 40: 323-9
10. Sports Sci. Exch 1990; 3:1-5
11. Conlee, R.K. 1991. *Amphetamine, caffeine, and cocaine*. In: *Perspectives in Exercise Science and Sports Medicine*, Volume 4: Ergogenics—Enhancement of Performance in Exercise and Sport, pp. 285-330. Lamb, D.R., and Williams, M.H. (Eds.). Dubuque, IA:Wm.C. Brown Publishers
12. Int. J. Sport Nutr 1993, 3:103-111
13. Can. J. Appl. Physiol 1994; 19:111-138
14. Sports Sci. Exch 1996; 9:1-5
15. Curr. Comm. ACSM 1999; July:1-3

16. Spriet, L.L., and Hewlett, R.A. 2000. *Caffeine*. In: *Nutrition in Sport*, pp. 379–392. Maughan, R.J., (Ed.). Oxford: Blackwell Science Ltd
17. *Sports Med* 2001; 31:785–807
18. *Can. J. Appl. Physiol* 2001; 26(Suppl):S103–119
19. *Sports Med. Phys. Fitness* 1991; 31:481–489
20. *Sports Med* 1994; 18:109–125
21. *J. Sports Med. Phys. Fitness* 2000; 40:71–79
22. Spriet, L.L. 2000. *Caffeine*. In: *Performance-Enhancing Substances in Sport and Exercise*, pp. 267–278. Bahrke, M.S., and Yesalis, C.E. (Eds.) Champaign, IL: Human Kinetics
23. *Curr. Sports Med. Rep* 2003; 2:213–219
24. Magkos, F., and Kavouras, S.A. 2004. *Caffeine*. In: *Nutritional Ergogenic Aids*, pp. 275–323. Wolinsky, I., and Driskell, J.A. (Eds.). Boca Raton, FL: CRC Press LLC
25. *J Sports Sci.* 2006; 24(4):433-9
26. *Med Sci Sports Exerc.* 2005;37(11):1998-2005
27. *Med Sci Sports Exerc.* 2006;38(3):578-85
28. *Med Sci Sports Exerc.* 2000;32(11):1958-63
29. *Med Sci Sports Exerc.* 2006;38(3):598-604
30. *J Appl Physiol.* 1998;85(4):1502-8
31. *J Sports Med Phys Fitness.* 1991;31(2):147-53
32. *Eur. J. Clin. Pharmacol* 1996; 51:319–325
33. *Pharmacol. Biochem. Behav* 1997; 58:721–726
34. *Lancet* 1973; 1:827
35. *Eur. J. Clin. Pharmacol* 1983; 24:93–98
36. *Clin. Pharmacol. Ther* 1982; 32:98–106
37. *Pharmacol Rev* 1999; 51:83-133
38. *Med Sci Sports Exerc* 2003; 35:1348-1354
39. *J Appl Physiol* 2003; 94:1557-1562
40. *J Appl Physiol* 2002; 93:990-999
41. *Int J Sport Nutr Exerc Metab* 2000; 10:436-437
42. *Med Sci Sports Exerc* 2000; 32 1958 1963
43. *Eur J Appl Physiol* 1991; 62: 424 429
44. *Int J Sport Nutr Exerc Metab* 2004; 14:698-708
45. *Med Sci Sports Exerc* 1975; 7:221-224
46. *J Appl Physiol* 1995; 78:867-874
47. *Int J Sports Med* 1995; 16:225-230
48. *J Appl Physiol* 1998; 85:709-715
49. *J Appl Physiol* 2002a; 93:990-999
50. Desbrow B, et al. *An independent analysis of consumer exposure to caffeine from retail coffees*. *Food Chem Toxic*, 2005
51. *J Nutr.* 2006;136(5):1276-80
52. *J Appl Physiol* 2005; 99: 844–850,
53. *J Appl Physiol* 2000; 89: 1079–1085,
54. *J Appl Physiol.* 1998; 85(4):1493-501
55. *Int J Sports Med.* 1986;7(5):276-80
56. *Int J Sport Nutr Exerc Metab.* 2002;12(2):189-206
57. *Eur J Appl Physiol* 1996; 73:358-363
58. *J Appl Physiol.* 2004; 96(3):943-50
59. *Encyclopaedia of Mental Disorders* <http://www.minddisorders.com/Br-Del/Caffeine-related-disorders.htm>