Caffeine and other sympathomimetic stimulants: modes of action and effects on sports performance

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Abstract

Stimulants, illegal and legal, continue to be used in competitive sport. The evidence for the ergogenic properties of the most potent stimulants, amphetamines, cocaine and ephedrine, is mostly insubstantial. Low doses of amphetamines may aid performance where effects of fatigue adversely affect higher psychomotor activity. Pseudoephedrine, at high doses, has been suggested to improve high intensity and endurance exercise but phenylpropanolamine has not been proven to be ergogenic. Only caffeine has substantial experimental backing for being ergogenic in exercise. The mode of action of these stimulants centres on their ability to cause persistence of catecholamine neurotransmitters, with the exception of caffeine which is an adenosine receptor antagonist. By these actions, the stimulants are able to influence the activity of neuronal control pathways in the central (and peripheral) nervous system. Rodent models suggest that amphetamines and cocaine interact with different pathways to that affected by caffeine. Caffeine has a variety of pharmacological effects but its affinity for adenosine receptors is comparable with the levels expected to exist in the body after

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moderate caffeine intake, thus making adenosine receptor blockade the favoured mode of ergogenic action. However, alternative modes of action to account for the ergogenic properties of caffeine have been supported in the literature. Biochemical mechanisms that are consistent with more recent research findings, involving proteins such as DARPP-32 (dopamine and cAMP-regulated phosphoprotein), are helping to rationalize the molecular details of stimulant action in the central nervous system.

Introduction

In 2005 the WADA (World Anti-Doping Agency) detected 509 cases of stimulant abuse in sport in samples analysed at its accredited laboratories worldwide. This represented 11.8% of the total number of banned substance detections. Almost half of the cases of stimulant abuse involved amphetamines and ephedrine. In 2007 the use of amphetamines, amphetamine derivatives, propanolamine and ephedrine will continue to be illegal in competition. However, caffeine (1,3,7-trimethylxanthine) and pseudoephedrine will be accepted at any level (as has been the case since 2004). When stimulated by sympathomimetic drugs, the sympathetic nervous system sets up changes to a variety of physiological processes commonly associated with the so-called ‘fight-or-flight’ reaction. These changes are mediated via neurotransmitters such as adrenaline (epinephrine) and noradrenaline (norepinephrine) which activate specific subtypes of cell surface α and β adrenoreceptors which are coupled to G-proteins. However, these sympathomimetic stimulants can gain direct access to the brain by crossing the blood–brain barrier and are then able to exert a direct influence on brain function. Their key action on binding is to prolong the lifetimes of the catecholamine neurotransmitters with the exception of caffeine which is an adenosine receptor antagonist (Figures 1, 2 and 3 (also see Table 1 of Bouchard et al. [1] for a survey of receptor subtypes and responses in various tissues other than the brain)).

The present chapter will examine caffeine and the other major stimulants that are being used in sport for evidence of ergogenic properties. Caffeine will be considered in greater depth than the other major stimulants as it is the only stimulant that has been widely accepted as being ergogenic by a large body of recent studies. Also, a wealth of information exists in the literature describing putative mechanisms for the action of caffeine on cellular and molecular processes.

Amphetamines (cocaine)

Amphetamines elicit a variety of effects which include euphoria, analgesia, heightened aggression and improved attentiveness. However, the appearance of these effects is highly dose-dependent and users become tolerant so that they must progressively increase the dose to maintain the desired effects. The
Figure 1. Sites of action of amphetamines at dopaminergic neuronal synaptic junctions

Upper panel: the ‘life cycle’ of dopamine. In the presynaptic terminal, DA is synthesized from the amino acid, tyrosine which is hydroxylated to form DOPA under the influence of tyrosine hydroxylase (TH). DA is taken up into synaptic vesicles via the vesicular monoamine transporter, VMAT. DA is released into the synaptic cleft upon fusion of the vesicles with the nerve terminal membrane. DA binds to dopamine receptors (D) on the postsynaptic membrane which elicits responses mediated by G-proteins. The signal transmission is ended by the uptake of DA from the synaptic cleft into the presynaptic nerve terminal via the energy-dependent action of a dopamine transporter (DAT) in the membrane. Cytosolic DA is degraded by the action of monoamine oxidase (MAO) which is thought to be located in the outer membrane of the mitochondria. Lower panel: sites of action of amphetamines. Amphetamines boost the level and lifetime of DA in the synaptic cleft of the dopaminergic neuron as follows. Cytosolic levels of DA in the presynaptic nerve terminal are boosted by three major actions: (i) amphetamines increase the enzyme activity of TH; (ii) amphetamines induce the reversal of the action of VMAT so that DA is actively transported out of the synaptic vesicles; and (iii) amphetamines decrease the enzymic activity of MAO. The presynaptic nerve terminal DAT is induced to reverse its ‘normal’ action and transport cytosolic DA out into the synaptic cleft.

proposal that amphetamines improve performance in sports requiring strength, power and endurance is debatable. A few older studies report positive effects on the performance of particular muscle groups but many studies also indicate that there may be no significant effect (see Table 2 of Bouchard et al. [1]). Despite this lack of consensus, a significant number of studies report that low doses of amphetamines do enhance the ability to perform psychomotor tasks [1]. The improvement in attention span and ability to concentrate helps combat the deleterious effects of fatigue. Thus the participants of a wide
Presynaptic nerve

Synaptic cleft

Postsynaptic nerve

Figure 2. Sites of action of stimulants at noradrenergic neuronal synaptic junctions

Upper panel: aspects of the ‘life cycle’ of noradrenaline. Noradrenaline (NA) in synaptic vesicles is released into the synaptic cleft. This process is regulated by the action of α2 autoreceptors on the presynaptic nerve membrane. Increasing levels of NA in the synaptic cleft activate the α2 autoreceptors which leads to the inhibition of exocytosis of NA from the synaptic vesicles. NA stimulates responses by binding to α1, β1, and β2 type adrenoreceptors on the postsynaptic nerve membrane. The effects of NA are curtailed by re-uptake into the presynaptic nerve terminal via a monoamine transporter in the membrane. Lower panel: sites of action of stimulants. Ephedrine, pseudoephedrine and phenylpropanolamine stimulate adrenergic neurons by: (i) preventing the action of NA on α2 autoreceptors on presynaptic nerves. This modulation of the ‘normal’ negative feedback mechanism results in increased rates of exocytosis of NA into the synaptic cleft; (ii) directly binding to the α1, β1, and β2 type adrenoreceptors and stimulating G-protein-coupled responses (indicated as *); and (iii) resisting their own degradation by inhibiting the action of monoamine oxidase (MAO). Amphetamines (and cocaine) bind directly to the monoamine transporter and block re-uptake of NA into the presynaptic nerve.

Mechanism of action

A key neurotransmitter type that is influenced by amphetamines (and cocaine) involves dopaminergic neuronal pathways. The action of these stimulants boosts the extracellular levels of DA (dopamine) and the ways in which this is accomplished have two major features not employed by the other types of stimulant. One feature is the ability of amphetamines to direct the efflux of DA from the storage vesicles in the presynaptic nerve terminal into the surrounding cytosol. The other feature is their ability to cause the DA transporter in the plasma membrane to operate in reverse and thus enhance the efflux of the cytosolic pool of DA into the synapse [2] (see Figure 1).
A major dopaminergic neuronal pathway associated with the basal ganglia is active in controlling motor functions. This so-called direct pathway possesses neurons that express type D1 DA receptors and it is these that are stimulated by increased DA levels brought about by amphetamine (and cocaine). Activation of a G-protein associated with the D1 receptor leads to increased levels of active PKA (cAMP-dependent protein kinase; protein kinase A). The action of PKA is to boost levels of phosphorylation of a small protein named DARPP-32 (dopamine and cAMP-regulated phosphoprotein), at a specific amino acid residue, Thr34 [3]. This form of phosphorylated DARPP-32, together with direct involvement of PKA, results in enhanced levels of phosphorylation of a variety of downstream target proteins. Through the ensuing modulation of the activity of a number of receptor and ion channel types, changes to the excitability of the neurons of the direct pathway lead to stimulation of motor activity. The ventral striatum of rodent brains has been shown to be the focus of action of amphetamines (and cocaine) as described above. It is worth noting that caffeine (discussed below) exerts its psychomotor effects in a different region to this one and also influences a different neuronal pathway (see below).

Amphetamines (and cocaine) also stimulate noradrenergic neurons by blocking re-uptake of noradrenaline into the presynaptic nerve terminal (Figure 2).
**Ephedrine, pseudoephedrine and phenylpropanolamine**

The sympathomimetic drugs ephedrine, pseudoephedrine and phenylpropanolamine are several times less potent than amphetamines, but at relatively high doses (up to 150 mg/70 kg) they can improve alertness and induce euphoric states. Phenylpropanolamine has not been reported to exhibit ergogenic properties [1]. The use of ephedra, herbal preparations originating in the Far East, whose major active components are ephedrine and pseudoephedrine, has caused concern in recent years. A report by Haller and Benowitz [4] commissioned by the American FDA (Food and Drug Administration) concluded that adverse events associated with 62% of 140 reports of their occurrence (including 10 deaths) were possibly or probably related to ephedra alkaloids. Andraws et al. [5] reviewed the cardiovascular effects of ephedra alkaloids and concluded that they pose a significant health risk. Bouchard et al. [1] carried out a meta-analysis of studies that examined the effects of ephedrine on exercise performance and suggested that half of the six studies showed that ephedrine can be ergogenic. However, careful examination of the results showed that only one study by Bell et al. [6] provides clear evidence that ephedrine at a high dose may improve endurance exercise. In this case, ephedrine improved the time taken by subjects to run 10 km. The three studies showing beneficial effects of ephedrine set out to explore the influence of ephedrine in combination with caffeine. Two of the studies found no evidence for interaction or potentiation between these stimulants, but an earlier study by Bell et al. [7] involving subjects cycling at high intensities for around 15 min until exhaustion seemed to show that neither caffeine nor ephedrine on their own produced an ergogenic effect but only when in combination. Since these studies, Jacobs et al. [8] have reported that a high dose of ephedrine can significantly improve short-term high-power muscle endurance involving carrying out bench and leg presses until exhaustion.

A meta-analysis of studies to assess support for pseudoephedrine exhibiting ergogenic properties, again by Bouchard et al. [1], showed that only one out of the five studies concluded that pseudoephedrine may be ergogenic. The study by Gill et al. [9] reports that high doses of pseudoephedrine (180 mg) improve maximum torque in an isometric knee extension exercise as well as peak power in a 30 s Wingate trial. These effects are attributed to the induction by pseudoephedrine of catecholamine release from the presynaptic terminals of neurons (Figure 2). Also, recently, Hodges et al. [10] reported that pseudoephedrine enhances middle-distance running performance. A high dose (2.5 mg/kg of body weight) was shown to reduce the time of a 1500 m run by 2.1%, a modest but significant ergogenic effect. No obvious side effects were reported by the subjects.

Clearly, as it is the more recent studies of the effects of ephedrine and pseudoephedrine on exercise performance that seem to suggest that they may be ergogenic, more research needs to be carried out involving these stimulants.
Caffeine

There are few of us today that have not indulged in the stimulatory effects of caffeine and the use of caffeine as a sports-related enhancement drug is well documented. Ingested caffeine is absorbed via the gastrointestinal tract by all organs, muscles and adipose tissue. Caffeine is consumed from well-known natural (coffee, tea, chocolate) and ‘unnatural’ dietary sources (cola drinks, caffeine tablets) as well as from several types of medication. Caffeine is often used in combination with analgesic and diuretic drugs to amplify their pharmacological potency. Caffeine abuse is very difficult to define and detect, mainly due to the social acceptance of this stimulant. The WADA removed any limitations on the use of caffeine in sport in 2004. Studies carried out by Graham and Spriet [11] and Spriet et al. [12] highlight the link between high caffeine dose consumption and enhanced performance during extended periods of exercise. Indeed, the performance-enhancing effects of caffeine are described for both prolonged aerobic exercises and for prolonged activities which involve resistance [13]. Its effects are significant for increasing the time taken to reach exhaustion levels, with reports of up to 20–50% extension on the time taken to encounter fatigue. The effects of caffeine on short periods of intense aerobic activity (5–30 min) have been reported to be significantly beneficial [14], but its effects on very short-term (anaerobic) exercise, e.g. sprinting, are inconclusive [14].

Cellular and molecular processes influenced by caffeine and its first-stage metabolites

It is a widely held view that the physiological and therefore the performance-enhancing effects of caffeine are due to caffeine itself (which has a half-life of 2.5–10 h for doses less than 10 mg/kg) and not due to its first-stage metabolites of which the majority are the dimethylxanthines (paraxanthine, theobromine and theophylline) which do not accumulate in the tissues to any significant extent. However, these metabolites have been suggested to exert physiological effects in some reports. For instance, Hetzler et al. [15] suggested that non-esterified fatty acids are mobilized by paraxanthine after an intravenous administration of caffeine to human subjects and Greer et al. [16] reported that theophylline elevates blood glycerol levels and muscle cAMP levels. The subsections that follow examine information gained from in vitro studies (for the most part) that focus on cellular and molecular processes that can be influenced by caffeine and its first-stage metabolites. The concentration of methylxanthine required to elicit many of the effects is much higher than that experienced at ‘physiological’ doses (see Figure 4 for estimates of the methylxanthine concentrations required to evoke 50% of maximum effect on the cellular and molecular processes examined below).

Muscle contraction

Studies using amphibian muscle demonstrated that caffeine is able to induce twitching of the muscle fibres without contraction and complete muscle
contraction in a dose-dependent manner by lowering the membrane potential at which the minimum mechanical response appears [16a]. The resting membrane action potential is unaffected. Threshold responses for potentiation were recorded at 1–2 mM with maximal activation at 5–10 mM. Membrane depolarization occurred at 3 mM and above. These studies have been reviewed by Magkos and Kavouras [14]. It appears that caffeine is able to induce Ca\(^{2+}\) release from the SR (sarcoplasmic reticulum) into the cytosol of the muscle cell. Increases in intracellular Ca\(^{2+}\) were also observed in the presence of paraxanthine, theophylline and theobromine at similar concentrations to caffeine [17]. These methylxanthines, including caffeine, appear to interfere with the excitation–contraction coupling mechanism which is hypothesized to occur as follows. The Ca\(^{2+}\)-release channel in the SR, composed of four ryanodine receptors, is activated by \(\geq 100 \mu M\) caffeine in a Ca\(^{2+}\)-dependent manner, which renders two of the ryanodine receptors more sensitive to endogenous activators e.g. Ca\(^{2+}\), ATP. At millimolar concentrations of caffeine, a Ca\(^{2+}\)-independent activation occurs. When the Ca\(^{2+}\)-release channel opens, Ca\(^{2+}\) is released from the SR lumen. This Ca\(^{2+}\) then binds to troponin and activates the myofilaments causing muscle contraction. The SR Ca\(^{2+}\)-ATPase pumps the intracellular Ca\(^{2+}\) back into the SR and then the muscle relaxes [18].

In frog muscle, caffeine at 0.25–2 mM concentration can also release a contraction-regulating peptide called oscillogen which may play a role in the long-lasting activation of the skeletal muscle [19,20].

**PDEs (phosphodiesterase isoenzymes)**

Caffeine (and other methylxanthines) inhibit cyclic nucleotide PDEs which catalyse the hydrolysis of the 3’-phosphoester bond of cAMP and cGMP to produce AMP and GMP respectively, i.e. caffeine may affect neurotransmission signalling and decrease and/or eliminate hormone activity. Thus caffeine leads to an increase in intracellular concentrations of cAMP and cGMP [21].
cAMP is a major second messenger involved in the regulation of lipolysis in adipose tissue and the relative inhibitory potency of methylxanthines towards adipose PDE correlates well with their ability to stimulate adipose cell lipolysis [22]. The synthetic, highly substituted methylxanthines are the most powerful PDE inhibitors, with theophylline the next most effective and caffeine itself the least effective of them all.

**Glycogen metabolism**
Glycogen metabolism is subject to several levels of tight regulation and a key component that is subject to interference by caffeine is the allosteric enzyme GP (glycogen phosphorylase). GP exists in two forms, an active phosphorylated form and a relatively inactive unphosphorylated form. Caffeine inhibits both forms of GP by binding at the nucleoside-inhibitor site and thus its effects are reversed by increasing the level of AMP. Caffeine has been shown to work in a potent synergy with glucose which binds at the catalytic site to effectively inhibit GP [23,24]. Kavinsky et al. [25] have also suggested that glucose and caffeine may play indirect roles in converting glycogen synthase from an inactive into an active form, thereby promoting glycogen preservation.

**Na⁺/K⁺ pump**
The Na⁺/K⁺ pump is an enzymic membrane protein complex also known as the Na⁺/K⁺-ATPase. This pump is responsible for maintaining an electrochemical gradient by transporting intracellular Na⁺ out of the cell into the extracellular fluid and transporting K⁺ back into the cell. Membrane potentials, cell volume and secondary active transport of solutes are supported by the electrochemical gradient. At rest, 20–30% of the ATP production of the cell is used to drive the pump. Caffeine and the dimethylxanthines have been shown to increase Na⁺/K⁺-ATPase activity with paraxanthine being more potent than caffeine. These compounds are thought to act indirectly on the pump, perhaps by mechanisms involving Ca²⁺-release or cAMP [26].

**Inhibition of PI (phosphoinositide) metabolism**
The PIs are lipid-like molecules with an inositol ring which are subject to phosphorylation and dephosphorylation by PI kinases and phosphatases. The PIs act as second messengers in a number of cellular reactions. PI metabolism appears to be inhibited by caffeine and theophylline by acting on the kinases (for a review see [27]).

**Adenosine receptors**
PDE inhibition and cAMP accumulation were once thought to be the mechanisms which explained the physiological effects of caffeine and the methylxanthines. However, the last two decades have exposed a relationship between methylxanthines and the adenosine receptors whereby these compounds neutralize and counteract the effect of adenosine. The
methylxanthines were shown to be more potent as adenosine receptor antagonists than as PDE inhibitors. This antagonism was demonstrated to occur in a variety of tissues including adipocytes, smooth and striated muscle cells, cardiac cells and platelets. Caffeine and theophylline have been identified as adenosine antagonists but other xanthine derivatives have proved to be more potent and more receptor specific [28,29]. Adenosine A₁, A₂A, A₂B and A₃ are the transmembrane protein receptors that have so far been identified on the cell surface. A variety of reactions are mediated by adenosine binding to these receptors. The binding of the xanthine derivatives to the adenosine-binding site on the receptor does not generate any reactions. The A₃ adenosine receptor is the only one of the four that remains unaffected by the presence of methylxanthines. Caffeine and theophylline are effective antagonists for A₁, A₂A and A₂B with theophylline being the more potent [30]. However, the binding affinity of A₂B and A₃ receptors is very low for adenosine compared with A₁ and A₂A. Thus it seems that the action of caffeine is manifested by de-inhibition of the A₁ and A₂A receptors.

The adenosine A₁ receptors (in rodent brains) are found principally in presynaptic nerve terminals where they exercise an inhibitory effect on neurotransmitter release on binding adenosine. The action of caffeine, by blocking adenosine binding to this receptor type, has been linked to stimulation of arousal, vigilance and ability to concentrate [31]. Although A₁ receptors are widely distributed throughout the brain, A₂A receptors are restricted to regions linked to dopaminergic neurons such as the striatum and the olfactory tubercle. The postsynaptic areas of a class of neuron in the striatum (of the basal ganglia), called medium-sized spiny neurons, are enriched in this adenosine receptor subtype. It is believed that these neurons influence high level control of motor functions linking emotional states and physical activity. Thus they are a natural focus in studies that seek to understand the mechanism of the psychostimulant action of caffeine. Two major neural routes have been proposed associated with the basal ganglia that exert complementary control over motor activity. The neurons of the so-called ‘direct pathway’ stimulate activity whereas those of the so-called ‘indirect pathway’ inhibit it. Type D₁ DA receptors occur in the direct pathway whereas DA D₂ receptors are found alongside the A₂A receptors of the indirect pathway. An antagonistic interaction exists between these two receptor types. Thus DA-binding to the D₁ receptors directly stimulates motor activity and at the same time binding of DA to the D₂ receptors opposes the adenosine-mediated inhibitory effects (disinhibits) of the indirect pathway and thus boosts the motor stimulation elicited by activation of the direct pathway. A variety of studies support the view that caffeine boosts motor activity, for the most part, by targeting the activity of the indirect pathway and inhibiting it through blockade of the A₂A receptors and thus complementing the effect of DA binding to the D₂ receptors. Davis et al. [32] have suggested that the efficacy of caffeine in delaying the onset of fatigue operates via a similar mechanism to that described above.
DARPP-32
A small 32 kDa protein named DARPP-32 has been identified as a key element in the transmission of intracellular signals which modulate motor activity. Stimulation of A2A receptors results in increased levels of the form of DARPP-32 phosphorylated at Thr$^{34}$ (via cAMP activation of PKA). This leads to amplification of levels of phosphorylation of various downstream target proteins with the effect that neuronal activity has an inhibitory influence on locomotor activity. The evidence linking DARPP-32 and the mode of action of caffeine as a rapid psychomotor stimulant is now compelling [33]. Caffeine, by blocking A$_{2A}$ receptors on neurons in the indirect pathway, causes increased levels of the alternative phosphorylated form of DARPP-32 which is phosphorylated at Thr$^{75}$ (via deactivation of the cAMP/PKA cascade). This alternative phosphorylated form of DARPP-32 is itself a potent inhibitor of PKA and takes part in a positive-feedback mechanism that boosts its own levels. The consequence of this is an increase in levels of dephosphorylation of key ‘downstream’ target proteins with the effect that the neurons of the indirect pathway are inhibited and thus their ‘dampening effect’ on the stimulation of motor activity by the direct neuronal pathway is significantly diminished.

The action of caffeine in vivo: relevance to exercise
One of the earlier attempts to explain the ergogenic effects of caffeine on endurance exercise proposes that caffeine enhances lipid oxidation so that glycogen stores may be spared and used to extend the limits of endurance [34]. Most studies report that caffeine elevates the level of adrenaline in the circulation (at rest as well as during exercise) and many also note increased levels of non-esterified fatty acids [34a]. A variety of studies have supported [34] and detracted from this ‘glycogen-sparing’ hypothesis [35]. The majority of the most recent studies report a lack of consistent and/or significant results to lend support [16,36]. If caffeine is operating by ‘glycogen-sparing’ it should be observed that it switches fuel use from carbohydrate to lipid oxidation. The measurement of the RER (respiratory exchange ratio) is interpreted to reflect the predominant fuel substrate that is being utilized. The fact that the studies conducted by Graham et al. [36] failed to show any change in RER values after caffeine ingestion contributed to their conclusion that the glycogen-sparing mechanism could not be responsible for the ergogenic effects of caffeine that have been reported.

The effects of caffeine on short periods of activity, e.g. sprinting, as discussed earlier, are inconclusive but there is some support for caffeine being ergogenic in certain types of high-intensity short term (up to several minutes in duration) exercise (where >100% $\dot{V}O_{2\text{max}}$ is achieved) [37]. Clearly, mechanisms of action other than ‘glycogen-sparing’ must be operating in these cases and Doherty et al. [37] propose that caffeine may exert its effect by lowering the subject’s perception of effort and thus ameliorating their feeling of fatigue. This explanation is consistent with the highly researched effects that caffeine
has been shown to have on higher functions of the central nervous system [31,38] via its ability to bind to adenosine receptors. However, Mohr et al. [39] reported studies using tetraplegic subjects, who have no central control of limb muscles, that suggest that fatigue in the electrically stimulated ‘paralysed’ muscles could be significantly delayed by the action of caffeine. The tetraplegic subjects did not show raised levels of adrenaline in their blood which is contrary to the situation usually reported for fully functional subjects. Mohr et al. [39] argue that as effects on muscle endurance caused by caffeine cannot be attributed to central nervous system adenosine receptor blockade or changes in energy substrate utilization (the RER is unaffected) then a direct action of caffeine (=55 μM) on the muscle motor units must account for the ergogenic effect. The authors speculate that effects of caffeine on the Ca\(^{2+}\) metabolism of the muscle cells may account for this.

Since the plasma caffeine concentration after normal doses are ingested is unlikely to exceed a few tens of micromolar, the current consensus of opinion is that the physiological effects of caffeine and the other methylxanthines are mainly due to their action as adenosine antagonists [31]. All the other caffeine-induced activations and inhibitions required higher concentrations of caffeine than those found in physiological conditions after caffeine administration (Figure 4). However, some of the effects of caffeine mentioned other than adenosine receptor blockade cannot be entirely dismissed and, indeed, one (or more) of them probably underlies the ergogenic effect of caffeine discussed by Mohr et al. [39] above. Physiological agents such as, for example, cADP ribose can increase the sensitivity of the Ca\(^{2+}\)-release mechanism from the SR to caffeine [40]. In addition, although caffeine of less than 100 μM may not be able to induce significant Ca\(^{2+}\) release, there may be enough of a release to induce some potentiation. Note that twitch potentiation in the rat soleus muscle was observed after exposure to 10–100 μM caffeine [41]. Subcontracture of muscles may also be induced by caffeine and paraxanthine at these micromolar concentrations, but this remains unproven. An increase in Na\(^{+}/K^{+}\)-ATPase activity may be involved but whereas micromolar concentrations of paraxanthine may increase Na\(^{+}/K^{+}\)-ATPase activity in vivo, caffeine at physiological levels is unlikely to have any effect.

There is other evidence to suggest that the caffeine effects observed at in vitro concentrations may still occur in vivo with the lower physiological levels of this stimulant. For instance, Winder [42] suggested that this may be the case for the caffeine-induced stimulation of adipocyte lipolysis. Also, in the case of GP, the presence of glucose allows micromolar levels of caffeine to become effective at inhibiting the active form of this enzyme (but probably in the liver rather than in the muscle) [14].

**Conclusions**

The evidence that stimulants that are currently banned from sport are beneficial in improving performance in competition is not substantial. Although plausible
mechanisms that are consistent with the anticipated ergogenic effects of these stimulants have been put forward, the great variety of factors that influence sporting performance and its measurement conspire to confound our ability to reach clear conclusions. However, more rigorous studies in recent times are helping us to reach this goal. The doses of amphetamines, cocaine or ephedrine being used in sport are as likely to be performance degrading as enhancing and carry considerable risk of serious health problems. Pseudoephedrine and phenylpropanolamine on the other hand appear to be rather ineffective, although there is some evidence suggesting that pseudoephedrine in high doses may improve endurance exercise. Only caffeine has been convincingly shown to improve performance in endurance activities and its use is currently not prohibited at any dose. Future studies of caffeine in particular will help to clarify its mode of action. Increasing knowledge of the functional anatomy of the brain, the biochemical processes and the complex interactions of the various neurotransmitter and receptor types will aid this endeavour.

Summary

• There is limited evidence to show that the illegal stimulants amphetamine and cocaine and the controlled drug ephedrine give ergogenic benefits in sport, while pseudoephedrine may benefit endurance exercise and phenylpropanolamine seems ineffective overall.
• Caffeine is ergogenic in endurance exercise and has a number of pharmacological effects.
• More recent evidence supports the view that caffeine has the ability to improve short-term high-intensity exercise.
• Blockade of adenosine receptors associated with the central nervous system is the most favoured mode of action to explain the ergogenic properties of caffeine.
• In general, stimulants operate by causing persistence of catecholamine neurotransmitters with the exception of caffeine which is an adenosine receptor antagonist. By these actions the stimulants are able to influence the activity of neuronal control pathways in the central (and peripheral) nervous system which go on to stimulate locomotor regions.

I would like to thank my wife Pamela for preparing the figures.

References
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