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Caffeine as an Ergogenic Aid: A Literature Review of Mechanisms of Action, Performance Effects and Safety Thresholds

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Abstract
Background: Caffeine is the most widely consumed psychoactive substance worldwide, that can be found in coffee, tea, energy drinks, and dietary supplements. Numerous studies have confirmed caffeine's potential to decrease fatigue and increase performance. However, optimal dosing strategies and safety profiles across diverse athletic populations remain under active investigation.
Aim: This study present the current knowledge on the prevalence of caffeine consumption, its physiological mechanisms, its impact on physical performance, and the potential risks associated with its use.

Material and methods. A literature review of studies published in the PubMed and Google Scholar databases was conducted, analyzing the prevalence of caffeine intake, its physiological mechanisms, effects on physical performance, and associated harms.
Results. Caffeine supplementation, ingested approximately 60 minutes before exercise enhance endurance performance. In strength assessments, caffeine has been found to enhance 1RM (bench press, squat, deadlift). However caffeine also has adverse effects, including tremors, tachycardia, gastrointestinal discomfort and in some cases, cardiac arrhythmias, that can occur at doses exceeding 7 mg/kg. Caffeine metabolism can affected by genetic polymorphism, hormonal modulators and age-related factors, influence caffeine's half-life and risk of accumulation.
Conclusions. Caffeine supplementation at 3–6 mg/kg is an effective and generally safe ergogenic enhancer for increasing endurance and muscular strength. However, the narrow margin between optimal and toxic doses can be different at various population. Future research should focus on long-term safety of caffeine supplementation, the factors of inter-individual variability to caffeine safety and potential interactions with other performance-enhancing compounds.

Keywords: caffeine; ergogenic aid; mechanism of action; physical performance; safety; supplementation.

Content

1. Introduction

Caffeine is classified as a mild psychostimulant whose effects, while clearly perceptible to habitual users, are considerably less intense and shorter-lived than those produced by more potent, prescription-grade stimulants; nevertheless, it has achieved global ubiquity and is the most widely consumed psychoactive substance in the world, owing to its presence in an ever-expanding array of foods, beverages, and even some medications enjoyed across diverse cultures and age groups (Ferré 2016; Temple et al. 2017). According to surveys, 87 percent of the U.S. population use caffeine-containing products daily, showing how ingrained it is in their diet, work life, and cultural practices (Frary et al. 2005). The International Olympic Committee (IOC) first designated caffeine as a banned substance in 1984 and the World Anti-Doping Agency (WADA) in 2000 with a starting urinary ceiling of 15 μg/mL, later reduced to 12 μg/mL in 1985 to differentiate between normal dietary consumption and ergogenic doses (Guest et al. 2021). Although its "controlled" status was lifted in 2004—reigniting interest from athletes—WADA continues to monitor urinary caffeine levels at ≤ 12 μg/mL (roughly corresponding to 10 mg of caffeine ingested over a period of hours), while the National Collegiate Athletic Association (NCAA) imposes a restriction above 15 μg/mL (Guest et al. 2021). Large-scale studies of post-competition urine samples from 2004–2008 (over 20 000 samples) and in 2015 with 7 500 samples showed that about three-quarters of athletes have detectable caffeine, with mean concentrations rising significantly over time in athletics, aquatics, rowing, boxing, judo, football, and weightlifting, and by 2015 the highest average levels were observed in cycling, track and field, and rowing, showing these athletes relied heavily on caffeine (Guest et al. 2021). This study aims to outline the existing understanding regarding the prevalence of caffeine intake, its physiological mechanisms, effects on physical performance, and the associated harms.

2. Research materials and methods

A review of the literature available in the PubMed and Google Scholar databases was carried out, focusing on clinical trials, meta-analyses, and systematic reviews related to caffeine consumption, its physiological mechanisms, impact on physical performance, and potential adverse effects. To specifically evaluate the effect of caffeine on exercise performance, the search strategy included keywords such as "caffeine," "ergogenic aid," "mechanism of action," "physical performance," "safety," and "supplementation."

3. Research results

3.1. Mechanism of Action

Caffeine acts through multiple molecular pathways: antagonism of adenosine receptors, mobilization of intracellular calcium stores, inhibition of phosphodiesterase enzymes, and metabolic changes (Fisone et al. 2004; Echeverri et al. 2010; Cappelletti et al. 2015; Mielgo-Ayuso et al. 2019).

3.1.1. Adenosine receptor antagonism

Caffeine is a competitive antagonist of adenosine A_1, A_2A, and A_2B receptors (Echeverri et al. 2010). Tonic adenosinergic signaling is blocked by caffeine, and this blockade underlies its psychostimulant profile-most prominently its capacity for perception-fatigue mitigation and mild analgesic effect (Cappelletti et al. 2015; Mielgo-Ayuso et al. 2019). Crucially, antagonism of A_2A receptors within the corpus striatum and globus pallidus appears to drive its arousal-promoting actions (Cappelletti et al. 2015). Even at relatively low doses, caffeine exhibits high selectivity for these receptors, preventing adenosine from dampening neural circuits involved in motor control and reward processing (Cappelletti et al. 2015). As a downstream consequence, this disinhibition enhances postsynaptic dopamine-D-receptor activity and amplifies dopaminergic signaling within striatal pathways and the nucleus accumbens, collectively contributing to the characteristic increase in motor activity and activation of the brain's reward system observed after caffeine consumption. Additionally, elevated dopamine activity in the central nervous system is believed to be important in the alleviation of exercise-associated pain (Guest et al. 2021). Caffeine's blockade applies to adenosine's effects in the cardiovascular system as well: by antagonizing cardiac adenosine receptors, which exert a negative chronotropic influence, it exaggerates heart rate and can lead to arrhythmias (Cappelletti et al. 2015).

3.1.2. Inhibition of phosphodiesterase

Caffeine functions as a nonselective inhibitor of phosphodiesterase enzymes, and inhibition of these enzymes primarily leads to increased levels of their substrates, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) (Cappelletti et al. 2015). This effect becomes significant only at doses far exceeding those typically achieved by average daily caffeine consumption (Cappelletti et al. 2015). An increase in cAMP results in metabolic, cardiovascular, neurological, and probably fetal development effects (Reddy et al. 2024). cAMP is a second messenger of β_1-adrenergic receptors, which are located in the heart muscle and in the cardiac conduction system (Boularan and Gales 2015). An increase in cAMP concentration exerts effects on the myocardium and on the conduction system, causing inotropic (increase in contractile force), chronotropic (increase in heart rate) and lusitropic (increase in relaxation rate) effects (Rao and Xi 2008). cAMP activates protein kinase A (PKA) by binding to its regulatory subunits (Rao and Xi 2008). Once activated, PKA phosphorylates key proteins that regulate intracellular calcium levels, resulting in enhanced calcium release from the sarcoplasmic reticulum in response to depolarization via L-type voltage-gated calcium channels (VGCC) and ryanodine receptors (RyR2) (Rao and Xi 2008). On the basis of these mechanisms, caffeine produces a positive inotropic effect on cardiac muscle and increased skeletal muscle contractibility, which is primarily attributed to an increase in intracellular calcium concentration (Cappelletti et al. 2015).

3.1.3. Metabolic changes

Consequently, an increase in intracellular cAMP levels sets into motion a series of metabolic changes, the most important of which is the activation of hormone-sensitive lipase (HSL), the primary enzyme in the catecholamine-stimulated lipolysis pathway (Cappelletti et al. 2015). HSL increases lipolysis by converting stored triglycerides in adipocytes to glycerol and free fatty acids, thus modifying lipid and glucose metabolism (Barcelos et al. 2020). On a systemic level, caffeine promotes the release of adrenaline and increases levels of free fatty acids in the blood, both of which spare muscle glycogen during exercise and help sustain workload (Cappelletti et al. 2015; Mielgo-Ayuso et al. 2019). These changes result in enhanced thermogenesis and increased rate of nonoxidative lipid cycling, leading to an increase in resting energy expenditure, where the rate of nonoxidative lipid turnover exceeds the rate of oxidation (Acheson et al. 2004). In addition, elevated cAMP levels further inhibit the activity of glycogen phosphorylase, which lessens the rate of glycogenolysis at rest (Cappelletti et al. 2015).

3.2. The effects of caffeine on enhancing physical activity performance

Caffeine, through the mechanisms described above, exerts a diverse range of effects on the human body, both physiologically and psychologically. Together, the mechanisms described work synergistically to enhance muscle performance while delaying fatigue (Mielgo-Ayuso et al. 2019). By antagonizing adenosine receptors, they reduce the perception of pain and postpone the onset of muscular tiredness (Cappelletti et al. 2015). Concurrently, calcium concentrations within myocytes are increased, thus strengthening contraction and overall contractile force (Ferreira et al. 2022). Furthermore, elevated levels of cAMP within the cell actively inhibit glycogen phosphorylase, an enzyme that catalyzes the hydrolysis of glycogen, therefore conserving metabolic glycogen pools and enhancing metabolic efficiency (Cappelletti et al. 2015). As muscle cells receive more available energy substrates, they are able to last longer, which translates to increased endurance, strength and decreased discomfort (Guest et al. 2021).

3.2.1. Endurance exercise performance

A substantial body of research has consistently demonstrated that caffeine exerts a clear ergogenic effect on endurance exercise performance, manifesting in improvements in key markers such as time to exhaustion and time-trial completion times (Barcelos et al. 2020). Most investigations into caffeine's influence on prolonged, oxygen-dependent exercise have been conducted in trained cyclists, offering a well-controlled and reproducible model for studying how acute caffeine ingestion modulates performance during sustained efforts (Wang et al. 2022). Researchers commonly employ both time-to-exhaustion protocols and time-trial tests to assess the effects of various interventions on endurance performance (Southward et al. 2018). Moreover, mean power output (MPO) is frequently used in time-trial tests as an objective, physics-based metric for comparing endurance efforts (Southward et al. 2018).

MPO is calculated by dividing total mechanical work (in joules) by the duration of the effort (in seconds), according to the fundamental relation:

$$\boldsymbol{P} = \frac{\boldsymbol{W}}{\boldsymbol{T}}$$

P - power (W)
W - work (J)
T - time (s)

Standardization based on mean power output enables direct comparison of sustained mechanical output across protocols of varying duration (Southward et al. 2018). Studies focused on caffeine's use to enhance endurance commonly use two methodologies: time-to-exhaustion (TTE) or time-trial (TT) tests (Southward et al. 2018). TTE protocols exhibit greater variability and lack real-world relevance-small changes in power output can dramatically alter how long an athlete can continue, in contrast to TT, whereas power increases, completion time decreases proportionately (Southward et al. 2018). Regardless of exercise mode-be it cycling, running, cross-country skiing, or swimming-caffeine doses between 3 and 6 mg/kg body mass boost performance by 2–4 % reliably (Guest et al. 2021). However, the magnitude of these ergogenic effects can differ depending on factors such as the athlete's training status, the specific exercise modality employed, and whether a TTE or TT protocol is used (Wang et al. 2022; Southward et al. 2018). In support of these observations, a meta-analysis of 46 randomized, placebo-controlled trials focusing on TT performance reported that caffeine ingestion increased mean power output by an average of 2.9 ± 2.2 % (effect size [ES] = 0.237; P = 0.002) and reduced completion time by 2.22 ± 2.59 % (ES = 0.41; P < 0.001) compared with placebo, reinforcing the roughly linear relationship between power enhancements and faster trial times (Southward et al. 2018). Importantly, caffeine doses between 3 and 6 mg/kg have equivalently positive effects, meaning more sensitive individuals wishing to minimize side effects while maintaining benefits may use lower doses (Southward et al. 2018). In another meta-analysis, endurance TT events lasting at least five minutes were examined under laboratory conditions (Shen et al. 2019). Performance was evaluated either by the time required to complete a fixed workload or by the total work completed within a predetermined time. A decrease in completion time or an increase in work output was considered indicative of a positive caffeine effect. Across 56 comparisons, the performance difference between caffeine and placebo ranged from –3.0 % to 15.9 %, with an average improvement of 2.9 % (SD 2.7) (Shen et al. 2019). In a separate meta-analysis of a combined sample of 75 recreational and trained runners performing TTE tests at a constant submaximal treadmill speed, caffeine doses of 3–9 mg/kg (administered mostly in capsules, with two studies using 300 mg caffeinated gum) increased time to exhaustion by an average of 16.97 % ± 14.65 % (Wang et al. 2022). This ergogenic effect was observed in both recreational (Hedges' g = 0.469) and trained runners (Hedges' g = 0.344), with low between-study heterogeneity (I^2 = 3.8 %), indicating consistent benefits across conditioning levels (Wang et al. 2022).

3.2.2. Muscular strength

Researchers investigating the impact of caffeine on muscular strength most often utilize the one-repetition maximum (1RM) test alongside handgrip dynamometry (Bilondi et al. 2024). The 1RM protocol determines the heaviest load an individual can lift once while maintaining proper form; it encompasses both the lowering (eccentric) and lifting (concentric) phases of muscle action (Grgic et al. 2020). Because it closely replicates the multi-joint movements characteristic of many resistance exercises and common functional tasks, and because it requires only basic equipment-a barbell and weight plates-it is widely regarded as the "gold standard" for assessing dynamic strength. Extensive research has confirmed its safety and reliability across diverse populations, including children, older adults, and various clinical groups (Grgic et al. 2020). Complementing dynamic strength assessments like the 1RM, handgrip strength testing offers a straightforward yet highly informative evaluation of overall muscular function, particularly within clinical contexts (Szaflik et al. 2025). During this assessment, the participant is seated with the shoulder adducted, elbow flexed to 90°, and both forearm and wrist aligned neutrally; the participant then exerts maximal voluntary force on a calibrated handgrip dynamometer (Szaflik et al. 2025). In addition to its ease of administration, handgrip strength is a well-established biomarker: it provides diagnostic insight into an individual's nutritional status and serves as a valuable prognostic tool for predicting a range of health outcomes, including postoperative complications, injury susceptibility, type 2 diabetes onset, changes in bone mineral density, cognitive decline, sarcopenia, and even all-cause mortality (Szaflik et al. 2025). Meta-analytic evidence further supports the modest ergogenic benefits of caffeine on strength performance (Bilondi et al. 2024): across multiple studies, caffeine supplementation produced a small but statistically significant increase in dynamic strength, with a pooled effect size (ES) of 0.17 (95 % CI: 0.11–0.23; $p < 0.001$) in 1RM tests, and a slightly larger ES of 0.23 (95 % CI: 0.11–0.36; $p < 0.001$) for handgrip strength, indicating that acute caffeine ingestion can lead to measurable improvements in both overall and localized force production (Bilondi et al. 2024). In a more focused investigation, a randomized, double-blind, placebo-controlled, crossover study enrolled 21 resistance-trained participants to compare the effects of two caffeine doses-6 mg/kg (CAF6) and 8 mg/kg (CAF8)-against placebo on maximal strength performance (Ferreira et al. 2022). When compared to placebo, the higher 8 mg/kg dose produced substantial and statistically significant gains in all three tested lifts: bench press 1RM increased from 94.2 ± 2.5 kg to 100.1 ± 1.9 kg; deadlift 1RM rose from 120.7 ± 5.7 kg to 132.8 ± 3.5 kg; and squat 1RM climbed from 119.4 ± 5.4 kg to 130.1 ± 4.9 kg (all $p < 0.001$), each representing a large effect size (> 0.70). In contrast, the lower 6 mg/kg dose did not elicit significant differences (Ferreira et al. 2022). Notably, 45 minutes after ingestion, CAF8 participants experienced a significant elevation in plasma calcium-from 8.5 ± 0.3 mg/dL at baseline to 10.4 ± 0.4 mg/dL ($p = 0.001$; ES ≈ 0.90)-relative to both CAF6 and placebo, and the magnitude of this increase correlated with improvements in 1RM performance, suggesting enhanced calcium availability may mediate caffeine's strength-enhancing effects (Ferreira et al. 2022).

3.3. The toxic effects of high doses of caffeine

In numerous studies, caffeine administered in doses of 3–6 mg/kg body weight has been shown to exert a clear ergogenic effect, enhancing both endurance capacity and mental alertness when consumed approximately one hour before exercise (Guest et al. 2021; Soós et al. 2021). For practical purposes, many practitioners equate a "standard" cup of brewed coffee (about 240 mL) with an average caffeine content of 100–135 mg (Wierzejska and Gielecińska 2024). On the other hand, adverse effects have emerged at significantly higher intake levels. One investigation identified that doses in the range of 7–10 mg/kg begin to approach toxic thresholds, eliciting symptoms such as chills, cutaneous flushing, nausea, headache, palpitations, and tremors (Willson 2018). In a related study, doses around 9–13 mg/kg were reported to impair performance instead of enhancing it, fostering strong side effects such as severe gastrointestinal distress, increased nervousness, mental confusion, impaired attention, and altered sleep patterns (Soós et al. 2021). Taken together, these data suggest a relatively narrow window between the optimal ergogenic dose (3–6 mg/kg) and the onset of unwanted reactions (starting at ~7 mg/kg), underscoring the importance of individualized dosing strategies and careful monitoring of tolerance (Willson 2018). Reports of lethal doses vary: caffeine exhibits toxicity at ~2 g (plasma ~15 mg/L), but lethal doses between 10 and 20 g (plasma ~80 mg/L) have been described (Gahona et al. 2022). In one case, a 39-year-old man ingested 20 g of caffeine tablets, resulting in a serum concentration of 90 mg/L; he presented with ventricular tachycardia (215 beats/min), hypertension, arrhythmias, hypoglycemia, hypokalemia, and metabolic acidosis, and improved after supportive therapy and hemodialysis (Gahona et al. 2022). In another fatal case of an 18-year-old woman, the mechanism was not definitively determined but was attributed to ventricular arrhythmia and respiratory arrest secondary to cerebral edema (Yamamoto et al. 2015).

3.4. Safety of caffeine use

Both caffeine and steroid hormones are metabolized through the cytochrome P450 oxidase system, thus elevated steroid levels delay caffeine clearance (Temple et al. 2017). In women taking oral contraceptives, this effect approximately doubles caffeine's half-life, and during pregnancy, half-life is increased by an average of 8.3 hours (up to 16 hours), increasing exposure for both mother and foetus (Temple et al. 2017). Newborns, particularly preterm, clear caffeine very inefficiently (half-life ~80 hours), though by six months clearance approaches adult rates (Temple et al. 2017). A daily dose of up to 300 mg of caffeine has been defined as safe during pregnancy by the World Health Organization (2016). Nevertheless, caffeine consumption during pregnancy has been associated with higher risks of complications, including miscarriage, impaired foetal growth, and low birth weight (Qian et al. 2020). These harms may also increase the risk of childhood obesity and cognitive development problems (Qian et al. 2020). Additionally, intake of 100 mg per day is linked to a statistically significant decrease in birth weight-foetuses weighed on average 28 g less compared to controls ($p = 0.002$) (Bracken 2003).

4. Discussion

This current literature review suggests that caffeine supplementation, typically between 3 and 6 mg per kilogram of body weight, induces clear ergogenic effects for endurance and strength performance. Caffeine can reach those effects through various mechanism, such as: adenosine receptor antagonism, phosphodiesterase inhibition, and lipolysis promotion, reducing perceived exertion, augmenting muscle energy metabolism, and increasing calcium availability for muscle contractions. However the margin between therapeutic and potentially toxic doses is very narrow: side effects begin to appear at doses of 7 mg/kg and become worse above 9 mg/kg to also include nervous-system and gastrointestinal disturbances. There is wide inter-individual variability in caffeine metabolism due to genetic, hormonal status, and age determinants, so individual dosing is required.

5. Conclusion

Caffeine supplementation at 3–6 mg/kg is an effective and generally safe ergogenic enhancer for increasing endurance and muscular strength. However, the narrow margin between optimal and toxic doses can be different at various population. Special caution in caffeine supplementation should be exercised in susceptible populations, including pregnant women, persons with cardiovascular conditions, and children. However, the narrow margin between optimal and toxic doses can be different at various population. Future research should focus on long-term safety of caffeine supplementation, the factors of inter-individual variability to caffeine safety and potential interactions with other performance-enhancing compounds. In conclusion, when utilized appropriately, caffeine has been effective in endurance and strength improvement; however, its use should be based on the principles of individualization.

Disclosure

Author's contribution

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