Review Article on Caffeine Activity

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Abstract

Caffeine (1,3,7-trimethylxanthine) is the most consumed psychoactive substance in the world, acting by means of antagonism to adenosine receptors, mainly A1 and A2A. Coffee is the main natural source of the alkaloid which is quite soluble and well extracted during the brew’s preparation. After consumption, caffeine is almost completely absorbed and extensively metabolized in the liver by phase I (cytochrome P450) enzymes, mainly CYP1A2, which appears to be polymorphically distributed in human populations. Paraxanthine is the major caffeine metabolite in plasma, while methylated xanthine and methyl uric acids are the main metabolites excreted in urine. In addition to stimulating the central nervous system, caffeine exerts positive effects in the body, often in association with other substances, contributing to prevention of several chronic diseases. The potential adverse effects of caffeine have also been extensively studied in animal species and in humans.

Chemical structure of caffeine molecule.
1. Detailed Review

During the past 20 years, a great deal of evidence has accumulated concerning the effects of caffeine consumption on reproduction and pre- and postnatal development. Although the results from studies reviewed for this publication have not been entirely consistent, the bulk of evidence suggests that caffeine intake at dose levels of 5300 mg day\(^{-1}\) may have adverse effects on some reproductive/developmental parameters when exposure takes place during certain periods.

Coffee and caffeine-containing products affect the cardiovascular system, with their positive inotropic and chronotropic effects, and the central nervous system, with their locomotor activity stimulation and anxiogenic-like effects. Thus, it is of interest to examine whether these effects could be detrimental for health. Furthermore, caffeine abuse and dependence are becoming more and more common and can lead to caffeine intoxication, which puts individuals at risk for premature and unnatural death. The present review summarizes the main findings concerning caffeine’s mechanisms of action (focusing on adenosine antagonism, intracellular calcium mobilization, and phosphodiesterase inhibition), use, abuse, dependence, intoxication, and lethal effects. It also suggests that the concepts of toxic and lethal doses are relative, since doses below the toxic and/or lethal range may play a causal role in intoxication or death.

Caffeine is probably the most frequently ingested pharmacologically active substance in the world. It is found in common beverages (coffee, tea, soft drinks), in products containing cocoa or chocolate, and in medications. Because of its wide consumption at different levels by most segments of the population, the public and the scientific community have expressed interest in the potential for caffeine to produce adverse effects on human health. The possibility that caffeine ingestion adversely affects human health was investigated based on reviews of (primarily) published human studies obtained through a comprehensive literature search. Based on the data reviewed, it is concluded that for the healthy adult population, moderate daily caffeine intake at a dose level up to 400 mg day\(^{-1}\) (equivalent to 6 mg kg\(^{-1}\) body weight day\(^{-1}\) in a 65-kg person) is not associated with adverse effects such as general toxicity, cardiovascular effects, effects on bone status and calcium balance (with consumption of adequate calcium), changes in adult behaviour, increased incidence of cancer and effects on male fertility.

The data also show that reproductive-aged women and children are ‘at risk’ subgroups who may require specific advice on moderating their caffeine intake. Based on available evidence, it is suggested that reproductive-aged women should consume 4300 mg caffeine per day (equivalent to 4.6 mg kg\(^{-1}\) by day\(^{-1}\) for a 65-kg person) while children should consume 42.5 mg kg\(^{-1}\) by day\(^{-1}\).

Caffeine toxicity in adults can present a spectrum of clinical symptoms, ranging from nervousness, irritability and insomnia to sensory disturbances, diuresis, arrhythmia, tachycardia, elevated respiration and gastrointestinal disturbances. Caffeine toxicity in children is manifested by severe emesis, tachycardia, central nervous system agitation and diuresis. Chronic exposure to caffeine has been implicated in a range of dysfunctions involving the gastrointestinal system,
liver, renal system and musculature (Stavric 1988, James 1991b).

Although the results of studies on the effects of caffeine on alertness, vigilance and memory are sometimes contradictory in terms of whether caffeine produces beneficial effects or no effects, there is little indication that intake of caffeine (up to approximately 250 mg in a single dose or over a few days) affects these processes in a negative manner (Smith 1998). However, a single caffeine dose of 100 mg was shown to affect short-term memory adversely in one study (Terry and Phifer 1986). Some studies have noted little or no change in mood after the consumption of single doses of caffeine of 32 mg (Lieberman et al. 1987), 100 mg (Svensson et al. 1980) or 200 mg (Swift and Tiplady 1988).

Larger amounts of caffeine (200, 400 or 600 mg as a single dose) have been associated not only with slight increases on an anger/hostility scale, but also with reduced ratings for drowsiness and incoordination (Roache and Griffiths 1987). Caffeine has little effect in producing depression, even at the consumption of more than eight cups of coffee per day (James 1991f). It is unclear why some studies have found effects on mood and others have not.

The self-report survey instrument included detailed questions on types of caffeine-containing beverages, gums and medications consumed, and the amount and frequency of consumption. A diverse variety of 31 specific caffeine-containing products were included as response options in the survey instrument. Respondents were asked to indicate serving size and frequency of use (number of times consumed per day, week, month, or year) for each product they regularly consumed. Participants were asked to write in caffeine-containing beverages they used that were not specifically identified in the questions on the survey. For data analysis, individual caffeine beverage types were grouped into the following categories: coffee, tea, sodas (regular and diet), energy drinks and other. All categories were combined to arrive at aggregate caffeine intake for the total sample including students who were not caffeine consumers and identify regular users of caffeine-containing products.

Aggregate use was calculated as average daily intake for all students surveyed. Regular users were defined as those consuming any caffeine-containing products at least once a week. Identical procedures were employed to analyse data collected from U.S. Army soldiers and Air Force personnel who completed a nearly-identical survey. Caffeine produces its behavioural effects through adenosine receptor antagonism and subsequent changes in many neurotransmitter systems. This results in increased alertness, and caffeine may be especially beneficial in low arousal situations (e.g., working at night, prolonged work, or sleep deprivation).

It improves performance on tasks that are impaired when alertness is low (vigilance and sustained response). Such effects largely reflect increased turnover of central noradrenaline. In addition, it increases the speed of encoding and response to new stimuli, an effect that probably reflects changes in cholinergic functioning. More complex cognitive tasks show less consistent effects of caffeine, which is again consistent with its arousal-increasing effect. Beneficial effects have been observed in simulations of real-life activities such as driving and in interpolated tasks.
2. Conclusion of Review
The current body of research supports the International Society of Sports Nutrition’s position statement on caffeine supplementation and sports performance, summarised as follows:
Caffeine is effective for enhancing sport performance in trained athletes when consumed in low to moderate dosages (~3-6 mg/kg) and, overall, does not result in further enhancement in performance when consumed in higher dosages (≥ 9 mg/kg). Caffeine exerts a greater ergogenic effect when consumed in an anhydrous state* as compared to coffee. It has been shown that caffeine can enhance vigilance during bouts of extended exhaustive exercise, as well as periods of sustained sleep deprivation. Caffeine is ergogenic for sustained maximal endurance exercise, and has been shown to be highly effective for time-trial performance. Caffeine supplementation is beneficial for high-intensity exercise, including team sports such as soccer and rugby, both of which are categorized by intermittent activity within a period of prolonged duration. The literature is equivocal when considering the effects of caffeine supplementation on strength-power performance, and additional research in this area is warranted. The scientific literature does not support caffeine-induced diuresis during exercise or any harmful change in fluid balance that would negatively affect performance.

References


