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Theacrine as a Potential Caffeine Alternative for Enhanced Ergogenic and Cognitive Performance in Athletes: A Call to Action and Brief Review

Short Review

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Abstract

Theacrine supplementation has begun recent investigation aimed to increase athletic performance. Although existing literature has examined theacrine's potential to increase physical and cognitive performance via adenosine receptor inhibition alongside its promotion of overall health and slight cognitive enhancement. Therefore, theacrine ostensibly exists as a caffeine substitute for attenuating both physical and mental fatigue. This article aims to (a) demonstrate the structural/mechanistic similarities of caffeine & theacrine, (b) showcase their existing performance roles, and (c) establish the need for future investigations on theacrine as a potential ergogenic aid in physically active populations to both prophylactically prevent fatigue and augment performance.

Key Words: adenosine; nootropic; resistance training

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Introduction

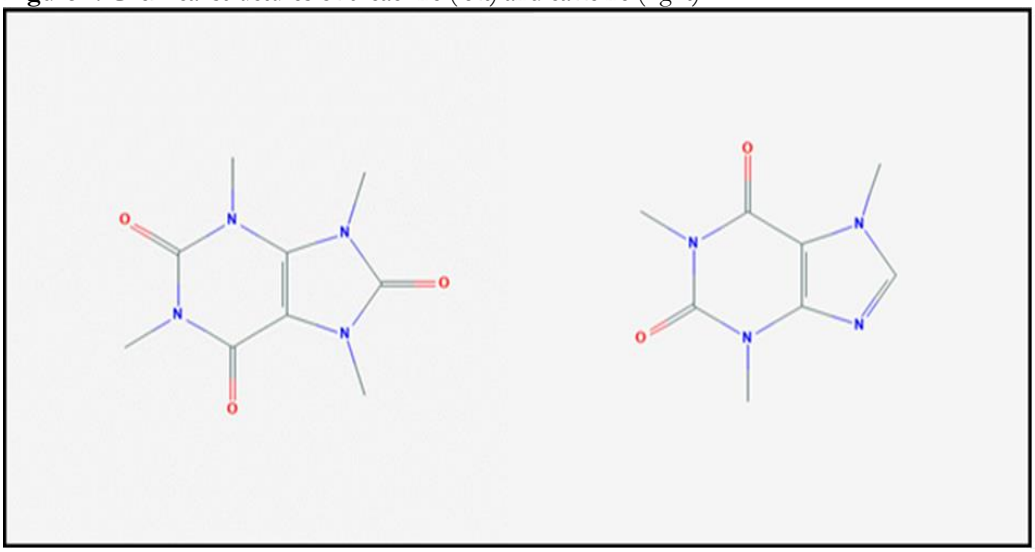
Drug and supplement use in sports has taken root in mainstream active demographics to enhance athletic performance. Commonly, they are referred to as ergogenic aids and are varied and widely used by athletes [1]. These agents are typically defined by their ability to enhance bioenergetics, including energy production, control, and efficiency. The list of these ergogenic aids is continually expanding and widespread in the varying types [1]. Drugs and supplements like anabolic steroids, human growth hormone (HGH), erythropoietin/blood doping, creatine, and caffeine are broad-ranging examples utilized by athletes to find a competitive edge in their sport; this is historically true in endurance-based sports and is growing amidst the resistance training literature. Although they are still relatively new to the sports world, several athletic demographics, team physicians, and recreational gym-goers are unfamiliar with the benefits and risks associated to such products [1,2]. Caffeine being a commonly used supplement is a well-established ergogenic aid with multiple studies demonstrating enhanced performance through a wide range of capacities through various mechanisms via increased reaction time, attention, and information processing [1-3]. Nootropic (known for higher integrative brain mechanisms) effects have been related to A1 adenosine receptor antagonism in the hippocampus and cortex [3-5]. However, these benefits have enabled abusive caffeine supplementation patterns in athletes and non-athletes alike via pre-workout, energy drinks, and coffee consumption [2]. Despite its widespread use there has been an association between caffeine consumption and adverse symptoms related to its usage [3]. Researchers found consistent and significant positive associations between measures of maximal lifetime caffeine consumption, caffeine-induced toxicity, addiction, and infrequent cognitive decline [3,6]. The compound, theacrine (1,3,7,9-tetramethyluric acid), may therefore represent a means to produce the benefits of the former without significant adverse effect. Theacrine is a compound structurally resembling caffeine but with the addition of both another methyl group on carbon-9 and an extra ketone group; the latter changes the caffeine-associated xanthine into a uric acid moiety [7,8]. It is a naturally occurring, purine alkaloid compound sharing the same genus as

green tea, which has further been clinically proven for medicinal uses among several health-promoting properties [9,10]. Considering the prevalence of caffeine as an abused ergogenic aid and the potential for theacrine to either largely replace or supplement the former, the evidence surrounding the latter is surprisingly sparse. Therefore, the purpose of this review is to (a) showcase the structural similarities and mechanisms of both caffeine & theacrine, (b) demonstrate caffeine and theacrine's existing roles in performance, and (c) establish the need for future research to investigate theacrine's role as a potential ergogenic aid in physically active populations, ultimately supporting its succeeding role as both a prophylactic tool against fatigue and towards augmenting performance.

Structural Similarities and Mechanisms of Caffeine & Theacrine

Whilst structurally similar to caffeine (see Figure 1), theacrine is thought to have several comparable neurological benefits. One such effect is a theacrine-mediated, dose-dependent analgesic property displayed in mice and when compared to 10mg/kg indomethacin (reference drug) the potency of theacrine as an analgesic agent was not significantly less [11,12]. Other benefits of theacrine supplementation have potential as neuroprotective agents against neuropathy (i.e. Parkinson's disease) by preventing apoptosis of dopaminergic neurons via directly facilitating sirtuin-3-mediated (SIRT3) superoxide dismutase 2 (SOD2) deacetylation [13]. Theacrine supplementation may also help with reducing stress and anxiety in low doses. A rodent model looking at acute restraint stress following seven days of 10-30mg/kg theacrine supplementation resulted in reduced liver enzymes and greater antioxidant capacity, indicating attenuated immobilization stress [10]. In terms of performance, the enhancing properties of theacrine have been thought to involve adenosine antagonism via locomotion reduction, similar to other adenosine antagonists such as caffeine [7,9]. Adenosine alters cell function by activating four G-protein-coupled receptors (A1, A2A, A2B, and A3) found in cell membranes across the body, including the central nervous system. The regulation of cAMP formation is the key intracellular signaling pathway, with A1 and A3 receptor activation inhibiting adenylate cyclase, as well as A2A and A2B receptor stimulation-mediated enzyme activation [11,14]. While theacrine is not known to commonly cause A1 or A2A receptor inhibition, some data has shown that with low doses (48mg/kg) via intraperitoneal injections had some adenosine inhibition [7,9,14]. This antagonism is the major reasoning behind caffeine utilization in sporting events, training, and general consumer use, hence theacrine's ostensible benefits via similar mechanisms [7,9,10,15,16]. Furthermore, regular usage of caffeine may result in habituation and overuse due to an adenosine receptor upregulation, ultimately leading to an eventual reduction in its ergogenic effects [17,18]. Strategies aimed to reduce the incidence of this habituation are also unfortunately sparse. Theacrine may nevertheless amend this issue being inherently less addictive than caffeine, whereby individuals are able to consume relatively higher doses without adverse effect [7,19,20]. Previous mouse data illustrates that a lethal dose of theacrine was shown to be around 810.6mg/kg, which is an inordinately large dose relative to typical dosing regimens (200-400mg/day) [21,22]. In humans, this compound was found to have no tachyphylatic (reduced response of a drug, rendering it less effective) response in doses upwards of 300mg a day [21,23]. Notwithstanding positive pharmacokinetics, theacrine in relatively high doses (>375mg) demonstrates deleterious reductions in body weight gain in overall lean muscle mass, bone density, decreased weight of the testes and epididymis, attenuated spermatogenesis, and several other physiological detriments in healthy male populations [12,20,21,24]. Both caffeine and theacrine are quickly absorbed through the gastrointestinal tract, metabolized via the liver, and have the ability to easily cross the blood brain barrier [6]. In comparison, caffeine is rapidly absorbed to almost near completion (up to 90%) by the stomach lining with peak plasma concentrations occurring within 20 to 40 minutes. As a result, this leads to quicker uptake and thus, toxicity is reached more expeditiously; theacrine, however, is absorbed and eliminated less readily, thus lasting for longer timeframes secondary to caffeine's (3-to-10) hour half-life. Furthermore, fatal poisoning is extremely rare in theacrine, similar to its structural counterpart [19,25]. Andrade et al. [26] further exacerbates that at high doses (>5g/kg), caffeine intoxication can become lethal. Commonly, inhibition of adenosine receptors interacting with the sympathetic nervous system via beta-receptor activation can insinuate arrhythmias. In toxic doses, caffeine directly correlates to deleterious adverse effects (hypertension, cardiac dysrhythmias, supraventricular and ventricular tachyarrhythmias, hypokalemia, hyperglycaemia, rhabdomyolysis, renal failure and hyperlacticaemia), ultimately leading to death if left unchecked [26,27]. Therein, while caffeine has demonstrated deleterious outcomes amidst impractical dosing regimens, its overall safety remains unfavorable relative to theacrine's safer pharmacokinetics [20]. Although theacrine's (20-to-24) hour half-life is notably longer when compared to its counterpart, this nootropic's aforementioned safety along with its potential to attenuate the onset of general fatigue has a budding potential role in enhancing athletic performance [19,25,28].

Figure 1. Chemical structures of theacrine (left) and caffeine (right) [7,11]



Caffeine and Theacrine for Athletic Performance

Athletes and resistance trained individuals are constantly exposed to mentally fatiguing stimuli which ultimately causes subjectively-associated and sport-specific performance decrements (i.e. decreased force output and muscular endurance) [29]. Specifically, previous investigations have demonstrated post-game increases in subjective anger, confusion, depression, fatigue, and mood disturbances in rugby and soccer players [29-32]. To combat these potential performance issues, caffeine supplementation was employed as a nootropic to help athletic performance. Caffeine supplementation has been extensively studied in various demographics, demonstrating improvements in both physical and cognitive parameters in athletic populations (see Table 1). Furthermore, comprehensive review articles and position statements across many established peer-reviewed journals have continued to display the crucial benefits of caffeine on physical performance; this nearly ubiquitous compound does so by increasing reaction time, power output, and endurance. Caffeine is one of the most widely used behavioral stimulants in the world, empirically supported in relative doses of 3-9 mg/kg bodyweight [7,15,16]. However, theacrine as an ergogenic aid is currently still under investigation amidst various age and training demographics. To date, the results surrounding this compound are disappointingly scarce, whereby strikingly few trials have displayed theacrine-associated performance improvements [30,33-36]. Among athletic populations, theacrine has fallen short of its predecessor in terms of physical performance enhancement, even given similar mechanisms of action between caffeine and theacrine. Despite typically equivocal findings concerning the latter, it seems logical to predict that both aforementioned compounds should be of relatively similar ergogenic benefit during endurance exercise performance; this would be even more relevant when glycogen depletion would be rate limiting to the performance of endurance training in short-to-mid distance events. This type of exercise is highly dependent on general glycogen and glucose availability [25,37-40]. Unlike caffeine (is most positively supported in aerobic/endurance demographics), theacrine is largely examined as a nootropic [30,33,36,41,42]. Research supporting this compound on aerobic/endurance demographics is meager. Ziegenfuss et al. [22] found that 200mg nor 400mg of theacrine saw any changes in gas exchange, attenuating this supplement's ability to promote a nootropic effect in aerobic/endurance outcomes. Conversely, in strength-and-power activities, findings of caffeine supplementation are inconsistent but can potentially training protocols, subject training ages/ fitness levels, and/or a multiplicity of other extraneous factors. While further research is required to determine the *true* impact of caffeine on strength-power sports, it is undoubtedly abused in this population and therefore warrants the investigation of a comparable substitute [43]. Unfortunately, Cesareo et al. [34] demonstrated in caffeine-habituated participants that 300mg of theacrine (in lieu of caffeine) had no effects on physical or cognitive performance (as measured via a 100-mm anchored visual analogue scales [VAS]), compared to equally dosed caffeine, placebo, or a combination (150mg each) of theacrine and caffeine. This demonstrates that none of the supplemental conditions had any significant effects concerning muscular power or endurance in resistance trained men. Incidentally, only the 300mg caffeine group saw improvements in fatigue and

mood, reinforcing caffeine as the sole reliable supplement for physical endeavors and cognitive enhancement in this investigation. Conversely, Snyder et al [36] and Habowski et al. [42] found that theacrine supplementation modestly increased focus, subjective energy, and core body temperature in a small percentage of participants. Furthermore, this group also saw (scarcely reported) augmented physical and cognitive energy levels without discernable irritability or habituation, alongside enhanced mood, motivation to exercise, and improved perceived focus. Clearly, the evidence supporting use of theacrine in lieu of caffeine is unsubstantiated, but the few studies in strength-power demographics suggest plausible ergogenic benefit with increasing investigations and commensurate data.

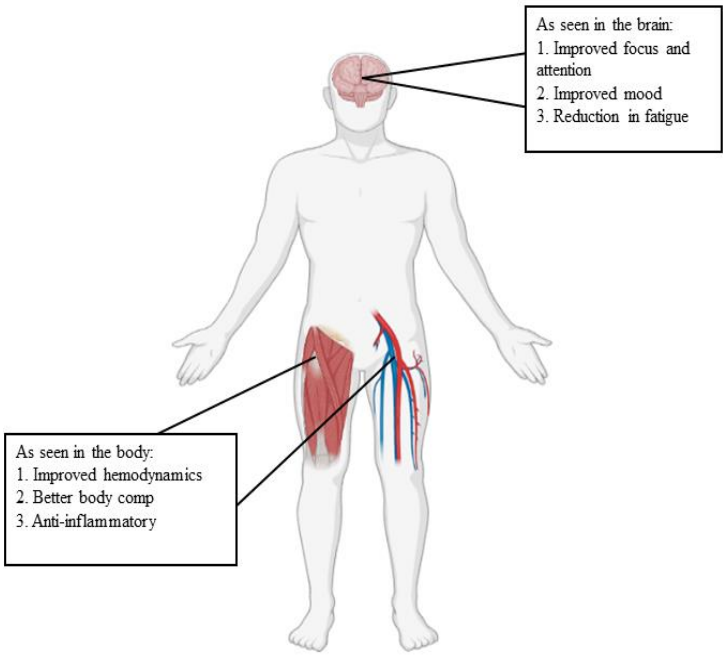
Table 1. Caffeine supplementation in various populations with athletic performance outcomes [17,44-51]

Article	Population	Intervention	Significant Outcomes
Wilk et al. [51]	16 Healthy strength-trained M athletes	1RM bench press test to assess upper-body maximal muscle strength. Ingested a placebo, 9 mg/kg/b.m. of CAF (CAF-9) or 11 mg/kg/b.m. of CAF	no significant differences in 1RM, T-REP, $TUT_{CON,}$ MP, PP, nor MV between PLAC, CAF-9, and CAF-11 groups. Lower PV in the CAF-11 when compared to the PLAC group
Souza et al. [47]	15 healthy non-smoking volunteers (12M, 3F)	90 seconds rest between sets of: lat pulldown, knee flexion, chest press, knee extension, biceps curl, leg press 45°, and triceps curl CAF dose of 4 mg per kg	CAF increased DBP and MAP at rest. Reduction of SBP, MAP and PVR after completion of resistance exercise
Grgic et al. [45]	17 resistance trained M	Muscular power was assessed with seated medicine ball throw and vertical jump exercises consumed placebo or 6 mg kg−1 of anhydrous caffeine 1 h before testing	CAF increased medicine ball throw performance; no effects on muscular endurance
Kovacs et al. [17]	15 healthy and well-trained regular caffeine consuming M	1-h time trial of cycling performance	CAF increased 1-h timed cycling performance
Davenport et al. [44]	14 well-trained cyclists (12 M, 2 F)	30 min cycling, 15 min time trial with RPE measured CAF dose of 200mg	200mg CAF improved performance in fatigue time trial
Wang et al. [50]	10 healthy and well-trained M	Cycling for 2x30 min CAF dose at 3, 6, or 9 mg/kg 1-h before exercise	3 mg/kg of caffeine had positive effects PPO and MPO; 3 mg/kg caffeine decreased RTs
Tarnopolsky et al. [48]	12 healthy M subjects (6 habitual CAF users; 6 non-habitual)	2-min tetanic stimulation of the common peroneal nerve CAF dose at 6mg/kg	Caffeine potentiated the force of contraction during the final minute of the 20-Hz stimulation
Van et al. [49]	14 healthy M subjects	VO_{smax} on a cycle ergometer Either placebo or caffeine doses at 5mg/kg	CAF users had higher EPI concentration after exercise than placebo

Mora-Rodriguez et al. [46]	13 resistance trained M	Squat and bench press at 25%, 50%, 75% and 90% 1RM at maximal velocity Either placebo or CAF doses at 6mg/kg	AMCAF increased propulsive velocity; PMCAF had no significant effects
1RM = 1 repetition maximum, AMCAF = Morning caffeine, CAF = caffeine, CAF-11 = 11mg/kg/b.m., CAF-9 = 9mg/kg/b.m. of caffeine, DBP = Diastolic blood pressure, EPI = Plasma epinephrine, F = female, M = male, MAP = Mean blood pressure, MPO = Mean power-output, MV = Mean concentric velocity, PLAC = Placebo, PMCAF= Evening caffeine, PP = Peak concentric power, PPO = Peak power-output, PV = Peak concentric velocity, PVR = Peripheral vascular resistance, RPE = Rate of perceived exertion, RT = Rest time, SBP = Systolic blood pressure, T-REP = Total number of repetitions, TUTCON = time under tension of concentric contractions			

* The above table is not an exhaustive list of the literature supporting caffeine's efficacy as an ergogenic aid.

Figure 2. Theacrine helps the body at the brain and in the body [9,13,22,41,63,65]



Future Directions of Theacrine Research

Bello et al. [30] explored the possibility that caffeine and theacrine combined may provide modest synergistic cognitive benefits for athletes having to make complex decisions in variable time spans. This is possibility due to theacrine and caffeine peak concentration timing differences, ultimately creating an overlap in supplement concentration curves. For athletic populations, this could suggest that players can maintain a higher level of performance at later stages in a game, training, or any high-level areas of competition [30]. Studies over caffeine in endurance and resistance trained demographics (see Table 1) are numerous and extensive as previously stated [14,15,17,30,35,39,44,45,50-58]. Moderately dosed caffeine is well tolerated with no restrictions towards ingestion; it only becomes arrhythmogenic in higher doses, especially when present with other ingredients can cause various other detrimental side effects (unpredictable toxicity, insomnia, anxiety, irritability, palpitations, shivering, sweating, manic reactions) [59]. Conversely, compared to the growing and relatively more substantial literature on theacrine-mediated effects in endurance/aerobic populations, there is an overwhelming paucity of data on theacrine use in resistance trained demographics where its preferential pharmacokinetics may be best employed [30,36,51,53]. The latter athletes are disproportionately caffeine-dependent as most rely on pre-workout (typically containing high-dose

caffeine amongst other ostensibly beneficial ancillary compounds) becoming the norms in gym culture [60]. Although strength-training-focused demographics have described pre-workout-mediated reaction time, energy, and mental focus improvements, the concomitant relative high caffeine content in these products subsequently incurs adverse effects. Previous findings showcase negative associations with these products, including deleterious gastrointestinal symptoms, cardiac arrhythmia, increased blood pressure, and potential negative effects on lipids and blood glucose [3,6,24,59]. Athletic demographics abuse stimulant drugs, energy drinks, and energy shots containing high amounts of caffeine and other ancillary compounds to gain a potential competitive edge in training or competition but neglect the potentially increased cardiovascular complication risks [1,59,61]. The advantage of this substance is its significant adenosine-mediated effects on dopamine-rich areas of the brain. However, the optimal dosage for theacrine to recreate the same adenosine-mediated dose-response effect is unknown. Therein, future investigations are tasked with discovering reliable alternatives in lieu of caffeine. As previously demonstrated above, theacrine specifically may represent this hitherto nebulous substitution and ultimately provide ergogenic physical and cognitive benefit to active demographics (see Figure 2). Although the current evidence in this regard is equivocal due to both little and inconsistent data, there still remains the optimistic notion that theacrine can supersede or – at least – attenuate excessive caffeine use. Furthermore, the former may ideally ameliorate the unfortunate overconsumption-mediated adverse effects of caffeine, especially in chronically afflicted demographics such as resistance trained individuals.

Conclusion

While preliminary evidence suggests that theacrine activates similar adenosine-mediated signaling pathways to caffeine, it may also incur the benefits of the latter without concomitant habituation; however, the research on this compound is unfortunately too sparse and inconclusive to draw any meaningful conclusions [9,14,16,21]. The importance of theacrine is in its potential to play an even greater beneficial role in health maintenance, which is especially true for abusing demographics such as competitive and recreational resistance trained individuals (see Figure 2). Unfortunately, the data substantiating this compound as an ergogenic aid is inconclusive, muddled by a hitherto undetermined optimal dosing regimen. There is therefore a scientific obligation to further seek out the extent to which this under-researched supplement can improve athletic ability when compared to caffeine (see Table 1). In contrast to the former, theacrine is also undescribed in its effects on substrate utilization and therefore warrants future investigation in this area [15,17,49]. Characterizing the mechanistic differences between these compounds may also serve to improve the contextual use of either in various situations. Furthermore, notwithstanding its meager-to-modest results in isolated use amidst physical and/or cognitive outcomes, theacrine's most promising role may be synergistically alongside caffeine to attenuate the onset of general fatigue [30,33]. In conclusion, theacrine as a supplement should not be perceived as an inferior caffeine substitute via signaling pathway similarities [11,14,16]. Rather, practitioners and potential consumers should ponder its potential to help with athlete caffeine habituation, glean health benefits, as well as consider how a theacrine-caffeine combination may be a potentially stronger and more reliable fatigue-associated prophylactic [9,18,20,30,33]. Although the scientific community has determined theacrine supplementation to be comparably safer to caffeine, much regarding the former remains unknown [17,20,21,62]. Additionally, many of the individual dosing and genetic-mediated differences in theacrine supplementation require elucidation. Regardless, this promising compound has substantial evidence among existing data to back its claims as a nootropic [9,13,22,33,41,63,64]. Therefore, players, sport physicians, coaches, and average gym goers should consider employing theacrine either by itself or coupled with caffeine as an alternative to combating fatigue [30,33,35].

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