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Review Article

The Physiologic Benefits of Caffeine and L-Theanine

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Abstract

Dietary supplements have increased in popularity over the past two decades, with nearly 80% of American adults claiming to use at least one dietary supplement. One of the most commonly utilized supplement classes is that related to perceived energy and focus—with an estimated projected revenue exceeding $150 billion by 2031. While not all "energy" supplements contain caffeine or a derivative of this stimulant, most do-and for good reason: caffeine has been extremely well-studied, and it provides a favorable effect for the majority of users. That said, it is not without its concerns, namely the often-noted "crash" in the aftermath of the caffeine high. To offset this, two approaches are common: 1) reduce the dosage of caffeine delivered and 2) pair caffeine with an agent that may complement its effect while not requiring the same dosage of caffeine. One such ingredient is L-theanine. This amino acid has been reported to aid focus and mental clarity. The combination of caffeine and L-theanine has been investigated in controlled trials with success and is a widely used combination within the dietary supplement industry. In this brief review we discuss the noted mechanisms of action of both agents, the peer-reviewed literature supporting their independent and combined use, and the practical applications for individuals considering this dietary supplement duo.

Keywords: Focus; Energy; Performance; Dietary Supplement

Introduction

Dietary supplements are used by most Americans and represent a multi-billion dollar per year industry, which continues to grow [1]. One the most popular and fasting growing segments of the dietary supplement market is the energy products [2]. Within the class, caffeine is ubiquitous and contained within the majority of energy drinks and shots [3], as well as capsules and powders. In addition, the amino acid known as L-theanine is often used in conjunction with caffeine [4], as the combination has been reported to aid mood, focus, reaction time, and cognitive performance [5].

Caffeine described

Caffeine exists as an alkaloid which is naturally found in a variety of plant species, which may have multiple beneficial health properties [6]. It is classified as a methylxanthine and consumed primarily within coffee and tea, which have been shown to be health-enhancing beverages [7]. It is contained to a lesser amount within cola and certain foods (e.g., chocolate), in addition to several medications. Finally, it is used in synthetic form within a variety of dietary supplements [8]-most notably energy drinks, powders, and capsules.

Due to the lack of nutritional value present in caffeine, coupled with its ability to stimulate the central nervous system (CNS), promote an increase in fat mobilization, and an improvement in perceived energy and mood, it may be considered a drug—possibly due to its withdrawal_related symptoms [9]. That said, caffeine continues to be one of the most commonly consumed psychoactive substances [10] and is generally viewed as safe [11] at dosages up to 400 mg daily [12]. In the United States, caffeine consumption averages approximately 180 mg daily [11], which equates approximately to the amount found within two 8-ounce cups of coffee. While the most common vehicle for caffeine administration appears to be brewed coffee, many individuals ingest energy drinks and other dietary supplements containing caffeine, typically with a per serving dosage of 200 mg or more.

Caffeine metabolism and dosage

Once ingested, caffeine is metabolized in the liver via the cytochrome p450 enzyme system and can enter all body tissues. Peak plasma concentrations occur approximately 40-60 minutes following administration and caffeine has been shown to have a half-life of 2-8.5 hours, which is likely influenced by dosing and the individual consumer [13]. With this in mind, many individuals consume caffeine one hour before exercise or other events in which caffeine's effects may be desired.

The optimal dosage of caffeine has yet to be determined, likely due the great deal of variation that exists in caffeine tolerance, as

some individuals are considered habitual users (>300 mg/day) while others are nonusers (<50 mg/day) [14]. Therefore, some individuals observe an effect at a relatively low dosage of 150-200 mg, while many others experience little to no effect even at relatively high dosages of 250+ mg. This is supported by research [15], as dosages from 3-6 mg/kg (210 mg – 420 mg for 70 kg person) have been noted to have some ergogenic benefit, the effects may not be as pronounced as higher dosages (> 9 mg/kg; 630 mg for 70 kg person). Considering the above, it should be noted that the upper daily limit for safely ingested caffeine intake is 400 mg [12]; far below the amount used in some of the clinical studies. Hence, caution should be advised when consuming caffeinated beverages and supplements to make certain this threshold is not exceeded. This is particularly important if caffeine is consumed later in the day, as this can impair sleep quality [16] and prove counterproductive. This applies to caffeine consumed in any form but may be more concerning if a component of manufactured caffeinated beverages that contain high amounts of sugar, which has been raised as a concern by many [17].

Caffeine effects

Caffeine is used for its many effects; most notably the effect on perceived energy, focus, reaction time, and mood [18]. In fact, "Caffeine has many positive actions on the brain. It can increase alertness and well-being, help concentration, improve mood and limit depression" [19]. These effects can be apparent in those engaged in sport activities [20], as well as those simply seeking performance improvement with practical items such as reaction time [21].

Aside from the subjective items noted above, caffeine is often used as a weight loss aid [22], as it appears to possess thermogenic effects [23]. That is, caffeine can increase metabolic rate [24], leading to more calories being burned throughout the day. In addition, some studies support the role of caffeine to decrease appetite [25], which may result in fewer calories being consumed and ensuing weight loss.

Related to weight loss, caffeine is known to impact lipolysis, or the breakdown of triglycerides (TAG) into fatty acids and glycerol. Lipolysis is necessary in order to allow for the utilization of lipid as a fuel source (i.e., lipid oxidation/combustion) [26]. Lipolysis allows for increased energy during times of need and also results in a loss of stored fat, leading to a reduction in body fat and weight over time. Caffeine appears to possess lipolytic/thermogenic effects due to its ability to both decrease the breakdown of cAMP, as well as increase cAMP production via β-adrenergic receptor independent and dependent mechanisms, respectively [27].

In terms of improved exercise performance, the lipolytic potential of caffeine (as discussed above) appears particularly beneficial during prolonged, aerobic exercise [15]. This effect may be partly related to an increased concentration of circulating fatty acids, but also a possible lowering of the threshold for exercise-induced beta endorphin and cortisol release [28]. The caffeine can also stimulate the CNS and directly impact skeletal muscle [29].

Collectively, caffeine has multiple potential benefits to the user, and these may be augmented by the addition of other bioactive ingredients. One such ingredient is L-theanine, which is discussed below.

L-Theanine described

L-theanine (N-ethyl-γ-glutamine) is an amino acid found in green tea (*Camellia sinensis*), and also in black tea, providing some of the tea's flavor [30]. L-theanine is also a bioactive compound with numerous health benefits [31] including antioxidant, anti-inflammatory, cardiovascular protective, neuroprotective effects, and immune regulatory effects. Due to the multiple beneficial functions, L-theanine has a great deal of application in the development of dietary supplements and functional foods. Besides occurring naturally in tea, L-theanine is produced synthetically, primarily due to increased interest in its reported health benefits and the fact that synthetically produced L-theanine can be delivered in higher quantities.

L-theanine was discovered in 1949 and a review of the scientific literature shows a high volume of published studies, including clinical trials, specific to the use of L-theanine. Chemically, L-theanine is a glutamic acid derivative with a unique structure. From a physiological perspective, it has been shown to cross the blood-brain barrier and exert various effects on neurotransmitters and brain activity—which is likely an explanation for the various cognitive and mood stimulating effects often observed with use. Specifically, L-theanine has gained a great deal of attention for its benefits in promoting relaxation, reducing stress and anxiety, and improving focus and cognitive performance.

L-Theanine metabolism and dosage

L-theanine is often delivered in a dosage ranging from 100-200 mg, although higher amounts have been used [32]. If used in conjunction with caffeine, the ratio is typically 2:1 (e.g., 200 mg L-theanine and 100 mg caffeine). L-theanine is fairly well absorbed in the intestines following ingestion, and has a reported bioavailability of around 50%, with peak concentration occurring at 50-60 minutes post ingestion.

L-theanine appears to behave like a glutamate reuptake inhibitor while also acting in the hippocampus as a competitive low-affinity glutamate receptor antagonist. It's also shown to have a neuroprotective effect by its action on the gamma aminobutyric acid (GABA)-A receptors [4], and has been shown to influence oscillatory brain activity in the alpha band (8-14 Hz) to aid attentional processing [33] and relaxes the mind without inducing drowsiness [34].

Animal studies suggest that L-theanine increases brain serotonin and dopamine levels, while exerting neuroprotective effects

possibly through its antagonistic effects on group 1 metabotrophic glutamate receptors [35]. Regarding its impact as a sleep aid, L-theanine appears to act via anxiolysis and not sedation [36]. L-theanine significantly increases activity in the alpha frequency band which indicates that it relaxes the mind without inducing drowsiness.

L-Theanine effects

As stated above, L-theanine has been well-studied and both scientific evidence and anecdotal reports of effectiveness exist to support its efficacy. The areas for which L-theanine has been reported to promote the most consistent effects are related to cognitive function, with effects for a variety of related issues also noted. These are discussed briefly below.

L-theanine has been shown in multiple studies to improve attention and reaction time in otherwise healthy men and women. For example, 100 mg/day of L-theanine taken for 12 weeks reduced the reaction time to attention tasks (Stroop test, Part 1), and increased the number of correct answers while decreasing the number of omission errors in working memory tasks in middle-aged and older men and women [37]. Similar findings have been noted for the intake of green tea [38], which can be at least partly attributed to the L-theanine content.

Other studies have noted a reduction in anxiety and stress following L-theanine use [39]. Published data indicates that L-theanine consumed at daily doses ranging from 200 to 400 mg, for periods of up to 8 weeks, are safe and induce anti-anxiolytic and anti-stress effects in both acute and chronic conditions [40]. Related to this, it has been reported that a dose of 250 mg per day of L-theanine for a period of 8 weeks is both safe and effective in improving symptoms of depression and anxiety, while also improving sleep quality and cognition in a sample of patients with major depressive disorder [41].

Although receiving less overall attention, the immunomodulatory effects of L-theanine have been noted. Both clinical and epidemiological studies have shown that L-theanine reduces immunosuppression caused by rigorous exercise, while also preventing colds and influenza by improving immune function [30]. In animals under stress conditions, L-theanine may prevent the damaging effects of reactive oxygen species and can be provided in the diet to help animals improve their performance, especially their immunity during stress conditions [42].

Even less well-studied is the impact of L-theanine on premenstrual syndrome (PMS)—a condition well-known to cause anxiety and mood swings. An early study showed that L-theanine (delivered as the product Suntheanine®) reduced the incidence of PMS_ specific mental, physical, and social aspect symptoms [43].

Discussion

Considering the impact of caffeine and L-theanine independently, it is logical to conclude that the two would be used in combination. As stated earlier, this is commonplace in the dietary supplement market, and the literature supports the co-ingestion of these ingredients-and in some cases, at very low dosages. Specifically, it has been reported that low doses of caffeine (50 mg) and L-theanine (100 mg) improve both speed and accuracy of performance during an attention-switching task, while reducing susceptibility to distracting information in a memory task in healthy subjects [5]. In a similar study using a low dose of caffeine (40 mg) and L-theanine (97 mg), it was reported that the combined treatment significantly improved accuracy during task switching and self-reported alertness and reduced self-reported tiredness [44]. In a separate study using the same dosages of the two ingredients, improved attention on a switch task was noted, while subjective alertness and intersensory attention were not improved significantly [45].

When using a higher dose of caffeine (150 mg) and L-theanine (250 mg), investigators noted that treatment improved Rapid Visual Information Processing accuracy and 'mental fatigue' ratings, as well as simple reaction time, numeric working memory reaction time, and sentence verification accuracy [46]. When used to treat boys with attention deficit hyperactivity disorder (ADHD) [47], the combination of caffeine (2 mg/kg) and L-theanine (2.5 mg/kg) was reported to improve total cognition composite and d-prime in a Go/NoGo task, with a trend for improvement of inhibitory control. The combination was associated with decreased task-related reactivity of a brain network associated with mind wandering. A similar effect for decreasing mind wandering was noted by Kahathuduwa and colleagues (2018) when using a combination of caffeine (160 mg) and L-theanine (200 mg) in healthy adult men [48].

Collectively, the literature supports the use of combined treatment of caffeine and L-theanine, highlighting the value of a much lower dose of caffeine as compared to when caffeine is ingested alone. Studies including the combination of ingredients provide reliable evidence showing that L-theanine and caffeine have beneficial effects on a number of outcomes, including sustained attention, memory, and the suppression of distraction [49]. Knowledge of L-theanine's efficacy may prove useful for those utilizing caffeine alone for the purposes of cognitive enhancement. This is especially true for those who have a sensitivity to caffeine [50] when consumed at higher dosages. That said, it should be noted that there are limited data currently available regarding caffeine + L-theanine use for other outcomes, whereas caffeine alone has been shown to be helpful (e.g., lipolysis, exercise performance) [51].

Conclusion and practical applications

Caffeine is the most commonly consumed psychoactive agent in the United States. L-theanine is consumed as a component within tea and is often included within dietary supplements targeting en-

hanced cognitive performance and mood. When used in isolation, both have a proven track record of success. When used in combination, similar outcomes are observed but the necessary effective dosage may be reduced considerably, in particular for caffeine. With this knowledge, those who desire the effects of caffeine but who may be sensitive to higher dosages may consider the combination of the two ingredients, while utilizing a lower dosage of each (e.g., 50-100 mg caffeine; 100-200 mg L-theanine). This combination may be helpful for improvements in certain aspects of cognitive performance and mood. Although, together they may not yield positive effects on other outcomes impacted by higher dose caffeine ingestion alone, such as exercise performance.

Future directions

A wealth of data is available with regards to caffeine use in isolation, with multiple noted effects. While not as many studies have focused on the use of L-theanine in human subjects, many do exist, with promising findings. Additional research is needed to investigate the combined effects of caffeine and L-theanine on health and performance measures, ideally involving both men and women ingesting different combinations of each ingredient. Outcomes specific to focus, cognition, and reaction time—with regards to both usual daily activities, as well as sport performance—would be welcome.

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Author Contributions

RJB and JQT were both responsible for the conception and writing of this manuscript. Both authors read and approved of the final manuscript.

Conflicts of Interest

JQT is an employee of Calerie Life. RJB has received research support and has been a consultant for several dietary supplement companies, including Calerie Life.

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