A Systematic Review on the Effects of L-theanine and Caffeine Combination on Human Mood and Cognition

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Abstract: Caffeine is one of the most widely ingested psychoactive drugs in the world. However, this central nervous system stimulant has raised concerns because of its inauspicious effects on health that come with its overconsumption. Recent scientific advancements have allowed for the theoretical regulation of these side effects through the combination of caffeine and L-theanine, an amino acid that promotes relaxation and improves mental function. This mini-review aims to extend current knowledge by synthesizing both beneficial and detrimental effects of the administration of the combination of caffeine and L-theanine to the human brain and cognition. Information was extensively reviewed, analyzed, and compiled from a sample of 50 works of literature published from 2014 to 2020 in the DLSU Library Databases, as well as referenced studies excluded from the given timeframe that contain highly relevant information that help structuralize the review. Dosage was found to be important in attaining benefits on mood and cognition such as suppressed anxiety and stress, positive mental state, neurochemically fostered changes in neurotransmitter systems, improved accuracy, improved semantic and recognition memory, and heightened mental alertness. On the other hand, L-theanine was found to reduce arousal more than it regulates elevated emotions caused by caffeine while some literature found that induced cognitive effects were only independent for each substance. In summary, existing studies support the hypothesis that the combination benefits human mood and cognition. As such, future research may gear towards a build-up on knowledge and innovations on the topic.

Key Words: L-theanine; caffeine; human cognition; mood

1. INTRODUCTION

1.1. Background of the Study

Caffeine is one of the most widely ingested psychoactive drugs worldwide. It is an alkaloid found in various plants synthetically manufactured for incorporation into beverages and supplements (Turnbull et al., 2017). The chemical structure of caffeine is very similar to that of adenosine, one of the breakdown products of the high-energy molecule adenosine triphosphate. The longer a person is awake, the higher the adenosine levels present in neurons which eventually attach to adenosine receptors causing sleepiness. Due to similarities, caffeine has the ability to block these receptors and counteract adenosine activities such as release of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) which inhibits arousal and wakefulness, and reduction of dopamine activity, which accounts for the feeling of pleasure, motivation, and enthusiasm, norepinephrine, which is associated with treating mood disorders, and glutamate, which is responsible for learning and memory (Ribeiro & Sebastião, 2010). On the other hand, too many caffeine molecules blocking adenosine receptors may cause excitotoxicity or neuronal death processes (Simone et al., 2014), one of caffeine's inauspicious effects on health that come with its overconsumption.

Beverages such as tea have been popularly associated with relaxation due to an amino acid called L-theanine. It has beneficial bioactivities including "anti-cerebral ischemia-reperfusion injury, stress-reducing, antitumor, anti-aging, and anti-anxiety activities" (Saeed et al., 2017, p. 1261). Williams et al. (2016) claimed that L-theanine has generally proven to provide advantageous effects to cognitive functions including improved sleep quality and increased alertness. The chemical structure of L-theanine is very similar to that of glutamate, an excitatory neurotransmitter which, in excess, can lead to neuronal damage. Therefore, L-theanine can bind to glutamate receptors to antagonize fast synaptic transmission and agonize synaptic plasticity for learning and memory mechanisms (Adhikary & Mandal, 2017; Yamada et al., 2005). L-theanine also has the ability to elevate inhibitory neurotransmitters like serotonin and GABA, which causes a calming

effect, and reduces levels of excitatory brain chemicals linked to stress and anxiety. Most importantly, L-theanine enhances alpha brain waves which promote wakeful relaxation or relaxation without sedation (Dramard et al., 2018).

The presence of L-theanine in tea was found to help regulate the stimulation caused by caffeine, creating a synergistic effect that promotes different health benefits and minimizes health risks from its caffeine constituent (Dodd et al., 2015). This mini-review discusses both supporting and opposing findings of existing studies exploring the effects and benefits of the combination of caffeine and L-theanine, with the goal of synthesizing recent advancements regarding the understanding of this topic. Ultimately, the review aims to extend current knowledge on the topic by highlighting both beneficial and detrimental effects of L-theanine and caffeine administration on the human brain and cognition.

1.2. Research Objectives

This review aims to investigate the effects of caffeine, L-theanine, and their combination on human cognition by summarizing and evaluating the literature on the aforementioned topics. Furthermore, it aims to show relationships between studies discussing unclear and conflicting ideas. With this, the specific objectives are:

1.2.1 To provide an overview of current knowledge regarding the combination of caffeine and L-theanine on human cognition

1.2.2 To compare and contrast the findings of recent studies about the relationship of caffeine, L-theanine, and human cognition

1.2.3 To address whether or not the combination of caffeine and L-theanine is beneficial to human mood and cognition

1.3. Scope and Limitations

This mini-review focused on synthesizing the different effects of the combination of caffeine and L-theanine on different biological mechanisms of the human brain and cognition. Separate findings exploring effects of the combination were originally integrated into a single study and used in supporting other data and interpretations in the sample. Additionally, referenced studies outside the given timeframe containing highly relevant findings necessary to the review were mentioned.

The conclusions derived from this review were solely based on primary interpretations made in the sample studies and no further interpretations unsupported by published findings were made. Overall, this review provides a comprehensive chemistry-based categorical synthesis emphasizing common findings and contradictions present among recent studies on the topic.

1.4. Significance of the Study

Understanding the chemical structure of caffeine in combination with L-theanine creates a more detailed view of their impact on the human brain and cognition. Since L-theanine regulates the jolting effect of caffeine, enhances concentration, and increases relaxation without drowsiness, there is a heightened potential of how these components may help better obtain desired effects with minimal to no risks. Thus, this review will help achieve a better perspective on the combination of caffeine and L-theanine in terms of its chemical attribution to human mood and cognition.

2. METHODOLOGY

This review was conducted using the DLSU Library Databases and other electronic databases including Google Scholar, PubMed, and ProQuest Online. The search focused on different types of literature (original research, peer-reviewed articles, systematic reviews, etc.) published from 2014 to 2020. The keywords used in the search include L-theanine, theanine, caffeine, combination of caffeine and L-theanine, human cognition, human brain, and chemistry. Literature found in the initial search were further assessed whereas studies emphasizing relevant disciplines were included in the final sample. These disciplines include chemistry as the major discipline and biology and psychology as minor disciplines. A total of 50 works of literature were included and reviewed in the final sample.

3. RESULTS AND DISCUSSION

By itself, caffeine is thought to act as a central nervous system stimulant and has positive effects on cognitive and psychomotor functioning such as enhanced alertness, vigilance, reaction time, and memory function in both young and older adults (Waer et al., 2020). Contrarily, L-theanine is found to have an impact on mood, cognition, and human brain functions (Mancini et al., 2017).

Their combination has mostly been linked to the improvement of human cognitive function and mental clarity (Einother et al., 2010; Kahathuduwa et al., 2016; Haskell et al., 2008). However, there are also findings claiming that while it benefits the consumer, the effects are merely additive in that the effects are the same when the components are administered separately in similar dosages (Kahathuduwa et al., 2016). Saeed et al. (2017) also suggests that L-theanine inhibits the activation impact of caffeine on the problems of sleep.

Overall, the combination has both positive and negative effects, as well as promotional avenues that have yet to be extensively explored.

3.1. Beneficial effects of L-theanine and caffeine combination on the human brain and cognition

3.1.1 Mood

According to a study by Giles et al. (2017), "under emotional arousal, caffeine and theanine exert opposite effects on certain attentional processes, but when consumed together, they counteract the effects of each other". Moreover, a study by Unno et al. (2017) found that the combination of the substances was effective for the specific suppression of anxiety which is linked to stress. Additionally, several articles and reviews further imply that the combination of these substances seem to enhance overall mood and have a positive effect on the subjects' mental state. Similarly, Zaragoza et al. (2017) suggests the combination of caffeine and L-theanine have neurochemically fostered changes in neurotransmitter systems which include dopamine and serotonin that are responsible for pleasure, as well as stabilization of mood and happiness respectively.

3.1.2 Cognition

Reaction time, memory-retaining capacity, mental alertness, and attention were among the measures used to gauge the effectiveness of caffeine and L-theanine combination in cognition. Several studies including those conducted by Dodd et al. (2015), Einother et al. (2010), Camfield et al. (2014), and Giles et al. (2016) stated the effects of the combination in comparison to the effects of placebo. In summary, the studies concluded that there were relatively more beneficial effects on cognitive performance when consuming the combination than placebo.

Most studies highlight the importance of dosage when administering the substances together when analyzing their effect on cognition. Existing studies show that the highest dosage administered was 250mg L-theanine and 150mg caffeine, resulting in increased speed in accomplishing tasks as well as improvements in semantic memory and heightened alertness (Haskell et al., 2008). Dodd et al. (2015) revealed a 100mg:50mg combination improved accuracy, memory, and increased speed in attention-focused tasks, while Giles et al. (2016) cited the effectiveness of a 90-100mg:35-50mg and 50-100mg:75-100mg ratio in improving mental alertness and recognition memory. A 2.5mg/kg:2.0 mg/kg ratio also improved sustained attention and overall cognition acutely.

3.2. Toxicological effects of L-theanine and caffeine combination on the human brain and cognition

3.2.1 Mood

A study by Giles et al. (2016) tested the induction of negative emotions (e.g. anger, tension, etc.) in a psychologically aroused state wherein data showed participants had higher anger, confusion, vigor, tension, depression, and total mood disturbance rates 60-120 minutes following the administration of caffeine and L-theanine together and separately. Caffeine drives these mood effects; and although L-theanine may regulate these elevated emotions, it controls behavior less, obtains less relevant responses, and only reduces arousal in a stressful situation. On the contrary, according to Dekker et al. (2017), the combination was stated to have no definite impact on mood.

3.2.2 Cognition

Various data from studies and experiments on the effects of caffeine and L-theanine combination and its impact on cognition have been accumulated over the last few decades. Despite most studies claiming positive results of substances counteracting the effects of the other, there are some research specifying how cognitive benefits of the substances are independent of each other. According to Kelly et al. (2008, as cited in Giles et al., 2016), caffeine is mainly responsible for any beneficial determinants regarding attention, while L-theanine alone did not have any notable effects. Caffeine may also enhance cognitive performance, though in the long run may have consequences like impaired cognition (Giles et al., 2016). L-theanine was also found to inhibit caffeine and its activation effect on sleep problems (Saeed et al., 2017). Future studies have yet to assess the aforementioned, for most current studies state more favorable and significant effects for the substances combined.

3.3. Promotional avenues and commercialization aspects of the administration of L-theanine and caffeine combination

3.3.1 Vehicle of Administration

Tea, the main natural source of caffeine and L-theanine, is by far the most mentioned beverage across the reviewed studies. Since these components are known to have separate positive effects on human cognition and brain function, a variety of effective vehicles for their combination have been examined. A study by D'Cunha et al. (2020) suggests the ideal medium wherein effects may be optimally achieved is in pure encapsulated form, which induces better effects compared integration into food matrices. Dekker et al. (2017) mention its commercial

availability as a dietary supplement which "supports weight management, improves resting energy and mood states such as alertness, fatigue, and focus". This study also acknowledges the current advertisement of these supplements as a "cognition and mood-enhancing substance". However, there is a lack of a standardized dosage specialized according to certain soft biometric traits like body weight which may maximize effects on human cognition (D'Cunha et al., 2020). When the caffeine dose is higher than 75 mg per serving, the ability of L-theanine to decrease blood pressure becomes harder to accomplish (Dekker, et al., 2017). In relation to this, Giles et al. (2016) found that a 35-50mg to 90-100mg ratio of caffeine and L-theanine in tea exert similar benefits as having opposite concentrations which proves promising as a standardized dosage.

Several studies consistently show sensitivity of the combination to flavorings and other additional components for nutritional value which is perceived to improve sales. For instance, bitter matcha powder requires additional flavoring when used in products, limiting its functionality due to interference (Dekker et al., 2017). In fact, Antonio, et al. (2019) found that its anhydrous form is more capable of delivering enhanced endurance as opposed to its combination with other ingredients.

Baking is also accountable for a 19% decrease in total catechin content including epigallocatechin-3-gallate or EGCG which is the most abundant in tea, and epigallocatechin or EGC, both of which suppress cognitive dysfunction and improve memory functions and adaptive behavior, increase brain waves, and reduce stress. In combination, caffeine and EGCG suppress anti-stress effects of L-theanine while EGC and arginine retain these effects (Nakagawa et al., 2009). Therefore, more catechins improves stress reduction since it retains this effect of L-theanine by antagonizing caffeine's.

Furushima et al. (2018) confirm that "differences in the quantities and ratios of green tea components affect the efficiency of its stress-reducing action" and suggest that more catechin improves stress reduction. It was also found that a caffeine and epigallocatechin gallate to theanine and arginine (CE/TA) molar ratio of two or less is crucial in overcoming the disadvantage of adding other ingredients and cooking (Furushima et al., 2019), therefore keeping the combination functional when used in food or beverages. Further research is needed to establish effects relative to the vehicle in which it is administered. Domain-specific concentration ratios of caffeine and L-theanine may also be established by adjusting within the standard range.

3.3.2 Domain-specific Uses

Three studies examined the potential of the combination in the clinical setting as a therapeutic agent for ADHD patients and an antidepressant. Blume, et al. (2019) report that the combination may serve as a pharmacological and dose-sparing agent or adjuvant to manage ADHD-associated cognitive deficits, complementing other current medications while Ayaz, et al. (2020) states its potential as a neuroprotective agent, playing a role in saving ischemic neurons in the brain from irreversible injury. A variant called Shaded White Tea Leaf (SWLT) was also found to have antidepressant effects due to its higher levels of caffeine and L-theanine (Furushima et al., 2020).

Zaragoza et al. (2019) focused on the commercialization of the combination in sports, suggesting that "supplementation with caffeine, theanine, and tyrosine could potentially hold ergogenic value for athletes in sports requiring rapid accurate movements," and elaborating that athletes desiring maximized cognitive performance without altered mental state during training and competition could benefit from lower doses of caffeine within the combination.

4. CONCLUSIONS

The majority of existing studies conclude that the combination of caffeine and L-theanine gives rise to a number of benefits such as improvements in memory, alertness, switch tasks, speed, accuracy, and attention. These findings imply that the pair create a synergistic effect, giving off more nutritional advantages than when administered alone.

While some disadvantageous outcomes were recorded for the individual intake of these substances, their combination has favorable effects on mood and cognition, with only limited sources claiming negative effects when administered together. Although no toxicological effects have been precisely detected, additional research is still essential to better understand both short and long-term effects of the combination.

Consequently, more evidence is still necessary before its widespread application to clinical practice. Studies elaborating on the chemistry behind various concentration ratios and corresponding effects are necessary to support its potential as a pharmacological agent and allow development for further domain-specific specializations. Ultimately, this review may allow for future research to gear towards a build-up on knowledge and innovations on the topic.

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