The application of L-theanine for patients with mental health conditions - a review

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Abstract

L-theanine is an amino-acid found in green tea (Camellia sinensis), a beverage consumed by people all around the world. Its chemical structure is similar to L-glutamic acid. L-theanine acts as an antagonist of AMPA and kainate receptors as well as partial co-agonist of the NMDA receptors. The application may be associated with several health benefits, such as improvements in cognition, reduction of stress and anxiety-like symptoms. Although the dosage of L-theanine in green tea, which is around 20 mg per tea, is not very likely to have meaningful impact on mental health, supplementation of doses 200-400 mg/day has shown some promising advantages.

Despite some evidence towards beneficial impact of L-theanine on mental health, longer-term and larger cohort clinical studies are required in order to justify its application for patients suffering from such diseases as anxiety, depression, bipolar disorder, schizophrenia and sleep disorders. What is more, it is more possible to act as a therapy augmentation in particular cases, rather than conventional therapy replacement.

Introduction

L-theanine is distributed in various parts of the tea plants. It is produced in the roots and later relocated to the shoots [1]. L-theanine has been a recent topic of study because of its interesting properties and acting mechanisms on people's brain. It has been found to easily cross the blood-brain barrier within 30 minutes (Yokogoshi et al., 1998a, Yokogoshi et al., 1998b) [2].

In a study published in Japan and reviewed in English, L-theanine has been proven to significantly increase alpha frequency waves of the electroencephalogram (EEG) within parietal and occipital sites, as opposed to placebo[3]. L-theanine binds to glutamate receptors, i.e. AMPA, kainate, NMDA [4]. As a result, the binding of glutamic acid to its receptors is blocked. Due to these specific activities, L-theanine demonstrates various desirable manners, in which it impacts human brain and mental health. Mainly, AMPA receptor antagonism results in antiepielptic action. Kainic acid may be the cause of epileptic seizure. Therefore, the blockage of kainic acid through kainate receptor antagonism leads to antiepileptic action, as well. Co-agonism of NMDA receptors inhibits excessive activation of glutamate receptors in the brain. Thus, it blocks excitotoxicity and neuronal damage [5,6,7].

In studies performed on rodents, L-theanine has been found to act as a neuroprotective and cognitive-enhancing agent. It modulates monoamine levels as well as glutamine and glycine neurotransmission. L-theanine also influences synaptic plasticity of hippocampus and improves cognition in stressed rats. It showed antidepressant and anxiolytic properties associated with the increase in the level of brain-derived neurotrophic factor (BDNF) in the hippocampus, which was observed in Wistar Kyoto rats [8].

In human studies, L-theanine has also been found to exhibit advantageous effects on mental state. These are the result of the action on the glutamate receptors as well as the modulation of alpha brain activity and involve mainly antidepressant and anxiolytic effect. It

also shows some properties of enhancing sleep quality due to its relaxing agent features. According to Steptoe et al. (2007), L-theanine reduces blood cortisol levels in response to stress [9,10,11]. Studies examining bipolar disorder and schizophrenia indicate both of these disorders may be caused by glutaminergic dysregulation [12,13].

3. The application of L-theanine in mental health conditions

3.1 Anxiety

Partial or complete irresponsiveness to antidepressants as well as addictive aspects of anxiolytic agents used in the treatment of Generalized Anxiety Disorder (GAD) is prevalent in clinical settings. That is why, adjunctive recommendations may be required. Doses of 400mg to 800mg have been found safe and effective in inducing anxiolytic effects in chronic and acute conditions. These findings were supported by psychometric tools, which included HARS (Hamilton Anxiety Rating Scale), PSQI (Pittsburgh Sleep Quality Index), PANSS (Positive and Negative Syndrome Scale) and Tension Anxiety Scores [15]. In a study performed of 36 participants by White et al. (2016), no significant changes in cortisol levels were observed within one hour after consumption of L-theanine. However, significant decline in cortisol levels occurred after three hours, which may suggest anxiolytic action. What is more, alpha waves were found to be increased in a group who received treatment, but this was not correlated with anti-stress effect [16]. On the other hand, a study performed on 46 patients by Sarris et al. (2018) showed that the application of L-theanine in doses of 450mg to 900mg is not more significant than placebo. However, in the same study, patients who received L-theanine turned out to have better self-reported sleep quality than placebo group [17].

3.2 Depression

One of the patophysiological mechanism of depression, which is more commonly mentioned, is the dysregulation of the hypothalamic-pituitary- adrenal (HPA) axis [18]. A study performed by Wang et al. demonstrated that rats, which were given L-theanine and later subjected to stress, showed significantly reduced levels of ACTH and cortisol levels compared to control group [19]. Another common patophysiological hypothesis of depression is monoamine hypothesis. It states that depression is a result of dysregulated levels of neurotransmitters, such as serotonin (5-HT), dopamine (DA) and norepinephrine (NE). A study, in which participants were given 2mg/kg of L- theanine, the

levels of 5-HT, DA and NE were found to be significantly increased in areas of prefrontal cortex, nucleus accumbens and hippocampus [20]. Nevertheless, according to comprehensive review performed by Moncrieff et al. in 2022, the monoamine hypothesis is still uncertain and there is no one- sided conclusion that depression is caused by low level of serotonin (5-HT) [21].

3.3 Bipolar disorder

Bipolar disorder is a disease in which both depressive and manic episodes occur interchangeably. The interest in the role of metabotrobic glutamate receptors (mGluRs) in the neuropathology of bipolar disorder has been recently increasing [22]. The therapy in bipolar disorder involves mainly the application of anticonvulsant drugs and lithium, which are called mood stabilizers. In chronic cases of bipolar disorder, lithium up-regulates glutamate uptake and acts as a stabilizing agent [24]. Anticonvulsant drugs work by, inter alia, the blockage of excitatory glutamate receptors [25]. Therefore, the pharmacology of mood-stabilizing drugs closely resembles the one of L-theanine by protecting glutamate receptors from over-excitation.

3.4 Schizophrenia

Schizophrenia is a disease believed to be caused mainly by abnormalities in dopamine levels in a brain. Thats is why, antipsychotic drugs used to tread the disorder aim at reversing the anomalies. Despite the fact that these medications have high level of efficacy, a lot of patients are not cured completely. Recently, a focus has been made on potential impact of glutaminergic abnormalities in patients' brains on schizophrenia neuropathology. Emerging literature has suggested that aiming at meoabotrobic glutamate receptors can provide an alternative approach to implement more effective therapy in the treatment of schizophrenia [26]. A study, which showed the efficacy of adjunctive L-theanine, which targets glutaminergic receptors, was performed on 80 patient chronically treated for schizophrenia. First group received only an anti-psychotic risperidone (6mg/day) and the second risperidone plus L-theanine (400mg/day). The patients were assessed with the usage of Positive and Negative Syndrome Scale (PANSS) and Hamilton Depression Rating Scale (HDRS). Eventually, sixty participant were analyzed and reduction rates in total scores of PANSS turned out to be significantly greater in the L-theanine group. Therefore, it was concluded that L-theanine adjunct to anti-psychotic risperidone outperformed risperidone alone in a safe and tolerable way [27].

3.5 Sleep disorders

The most common sleep disorder is insomnia and it involves difficulty falling asleep or staying asleep. It is often associated with underlying mental health disorders, such as anxiety or depression. While most cases of insomnia are associated with other mental health problem, which should be treated traditionally with antidepressant medicines or sleeping pills, it can also be a result of unhealthy lifestyle or excessive caffeine consumption. Coffee is the most popular psychoactive substance consumed by people all around the world and it has been proven to negatively influence total sleep time, sleep efficiency and perceived sleep quality. Coffeine consumption also results in electroencephalographic (EEG) slow-wave reduction as well as increase in wakefulness and arousals [28] . L-theanine has been found to act antagonistically to coffeine and result in significant reversal of decrease in slow-wave sleep caused by coffeine [29]. Therefore, L-theanine can be advised to ameliorate sleep duration in individuals consuming excessive amounts of coffeine. A study performed on animals by Dasdelen et al. (2022) depicted L- theanine as well as Mg-L-theanine (a novel complex of L-theanine with magnesium) induced slow-brain waves, regulated brain electrical activity and increased GABA neurotransmitter and receptor level. It was concluded that L- theanine reverses the impact of caffeine on sleep disturbance [30].

4. Discussion

There is no denying that the usage of L-theanine as a supplement has a number of advanatages as well as disadvantages. The main advantage is that it is a natural substance found in tea and the risk of allergic reactions is extremely low. What is more, it is easily available for patients. Since patients often have problems with compliance with suggested medical drugs regimen, it can be tried as an alternative. As both animal and human studies depicted, it has been found effective in some of mild to moderate symptoms of mental health disorders. It can also be considered an effective adjunctive treatment for patients suffering from more serious and chronic conditions, such as schizophrenia. For instance, the addition of L-theanine to standard antipsychotic drugs has been suggested to be efficacious. Moreover, it targets the same receptors as some of medical drugs used in psychiatry, such as anticonvulsant drugs, which also suggests its effectiveness. There has been recently many ethiopathology theories of mental health disorders and in most cases there is no theory that is completely proven, for example serotonin deficiency theory

in depression. That is why, new substances are worth investigating.

However, it is a novel substance in studies examining its effectiveness in mental health disorders. Thus, its pharmacology is relatively unidentified, so interactions with standard therapy are unknown. It also should not be used as substitute for routine and proven medications. Moreover, its supplementation can delay implementation of standard therapy. Since it was proven in some

studies that L-theanine usage is capable of incresing serotonin levels, using L- theanine together with antidepressant drugs can cause serotonin syndrome - a life-threatening conditions. The doses used in studies were quite various, so the exact dose which can advised for patients is unknown.

5. Conclusion

All things considered, the research in the application of L-theanine in treatment alone or as an adjacent therapy is in no way conclusive. More studies should be performed to examine its pharmacology, effectiveness and interactions. It constitutes a promising alternative as an adjunctive therapy for mental health conditions or an individual treatment in the case of mild symptoms. L-theanine should never be considered as a substitute for a standard and scientifically-proven therapy.

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