Neuroprotective attributes of L-theanine, a bioactive amino acid of tea, and its potential role in Parkinson's disease therapeutics

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A B S T R A C T

Meta-analyses of tea consumption and reduced risk of Parkinson's disease have thrown light in the pathway of exploring beneficial properties of tea components. On the basis of dry mass, a typical black or green tea beverage contains approximately 6% of free amino acids, which impart high quality, taste and distinctive aroma to the tea infusion. L-theanine (chemically known as γ-glutamylethylamide) is a non-proteinogenic amino acid of tea that takes part in the biosynthesis of its polyphenols. Recently discovered neuroprotective effects of L-theanine can be attributed to its structural analogy with glutamate, the principal excitatory neurotransmitter in brain. This unique amino acid also bears a potential to ameliorate the pathophysiological changes associated with Parkinson's disease as it displays antioxidant and anti-inflammatory properties, improves motor behavioral abnormalities, increases dopamine availability and may cause a favorable downshift in neurodegeneration due to glutamate excitotoxicity. To gain an explicit understanding of the role of L-theanine, this review article is the first one to focus on its mechanism of neuromodulatory action and to critically evaluate the possibilities of employing this bioactive amide in the forage of anti-Parkinsonian medication. We also hypothesize the idea of L-theanine being a potent natural agent against L-DOPA induced dyskinesia, since long-term reliance on dopamine replacement therapy is linked with elevation in glutamate receptor activity.

1. Introduction

Tea, derived from *Camellia sinensis*, holds immense popularity in different regions of the world and is currently ranked as one of the most frequently consumed beverages (Khan and Mukhtar, 2013). According to the process of manufacture, tea can be categorized into three types: Green tea is unfermented, where the oxidation is prevented by steaming the fresh leaves; Oolong tea is semi-fermented, in which the leaves are partially fermented before drying; black or red tea is almost entirely fermented prior to steaming and drying (Cabrera et al., 2006). Among all the tea types, black tea and green tea are the ones that are being extensively studied to unveil their bioactive constituents along with their perspective medicinal properties (Cabrera et al., 2006; Kakuda, 2002; Schimidt et al., 2017). Flavonoids form the principal composition of tea leaves, comprising of around 35–37% of the dry weight. Theaflavins and thearubigins, catechins, alkaloids, and polyamines together

with both proteinic as well as non-proteinic amino acids constitute a significant bulk of the essential bioactive components (Jain et al., 2013). The proportion of these discrete phytoconstituents in tea infusions depends on the variety of tea plant, the climatic conditions, time of harvest, as well as their geographical area of growth (Lin et al., 2003; Vuong et al., 2011).

L-theanine (γ-glutamylethylamide) is a non-protein amino acid abundantly present in tea. The compound was first isolated towards the end of the 1940s by Sakato (Sakato, 1949). Similar to other amino acids in nature, L-theanine is a chiral species. Although synthetic theanine is normally prepared as a racemic mixture of L- and D-forms, it occurs in nature predominantly as L-(S) enantiomer (K. Helen Ekborg-Ott et al., 1997). The amino acid accounts for about 10–30 g/kg of the dry leaf weight. Common-grade green tea leaves comprises of 0.2–2.4% (w/w), whereas, on an average, a standard 200 ml cup of black tea contains around 25 mg of L-theanine (Keenan et al., 2011). In addition to other

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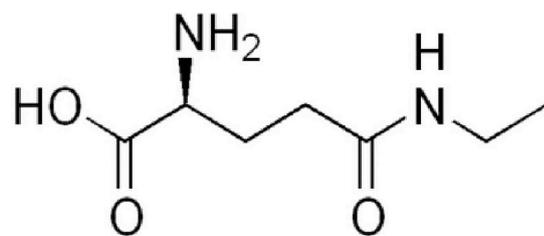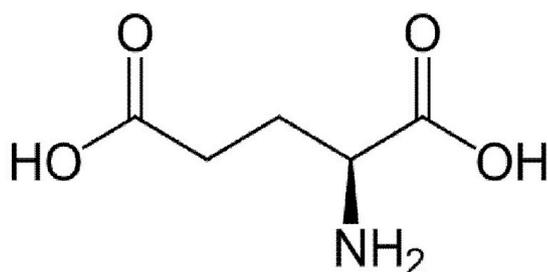 *E-mail address:* anupomborahh@gmail.com (A. Borah).

L-THEANINE

L-GLUTAMIC ACID
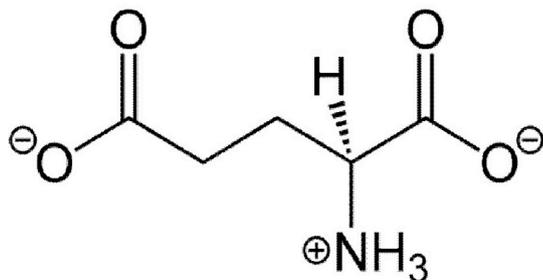
GLUTAMATE

Fig. 1. The chemical structures of L-theanine, glutamic acid and glutamate.

amino acids, L-theanine is involved in producing the distinctive aroma and taste of tea, specifically regarded as the 'umami taste'. Thus, the theanine content in tea leaves can be correlated with its high quality and price (Vuong et al., 2011).

Accumulating shreds of evidence revealed that regular consumption of green tea (≥ 2 cups per day) is associated with lower prevalence of Parkinson's disease (PD) and cognitive impairment in humans as well as in experimental animals (Kuriyama et al., 2006). L-theanine, the unique ingredient of tea leaves, is also a natural analog of glutamate and

glutamine (Fig. 1), the important neurotransmitters related to long-term potentiation (LTP), memory and cognition (Di et al., 2010). Also, there are numerous supporting reports on the benefits of L-theanine against neuronal cell death due to ischemia, the mechanisms involved in its action and its effectiveness in restoring neuronal activities (Egashira et al., 2004; Kakuda et al., 2000; Zukhurova et al., 2013). Long-term ingestion of L-theanine in powdered green tea manages stress, improves focus or attention and exerts a preventive effect on dementia in elderly stages of life (Gomez-Ramirez et al., 2009; Kahathuduwa et al., 2018; Kakuda, 2011; Ogawa et al., 2018; Takeda et al., 2011).

Parkinson's disease is a progressive neurodegenerative disorder, with a prevalence of 1%–2% in the population aged over 65 years (DeMaagd and Philip, 2015). The main pathological characteristic of PD is the death of neurons in substantia nigra *pars compacta* region of basal ganglia in brain. Lesser amount of dopamine is available for neurotransmission in the *corpus striatum*, thus leading to motor-related problems and culminating morbidities overtime (Alexander, 2004). Neuronal death is accelerated by increased level of extracellular glutamate and over-activation of its receptors. By virtue of its inhibitory potential towards glutamate receptors, L-theanine should be able to regulate excitotoxicity of neurons and attenuate their rapid degeneration (Kakuda et al., 2002). Increase in dopamine and other neurotransmitters by L-theanine administration and its protective effects against motor behavioral abnormalities may also serve as a ray of hope for its beneficial role in PD (Thangarajan et al., 2014; Yokogoshi and Terashima, 2000). Thus, the aim of this comprehensive review is to assemble the evidence of neuroprotective ability possessed by L-theanine and to elucidate its possible therapeutic efficacy in the treatment of PD.

2. Biochemistry and synthesis of L-theanine

L-Theanine is chemically named by the International Union of Pure and Applied Chemistry (IUPAC) as 2-amino-4-(ethylcarbamoyl) butyric acid. It is also termed as 5-*N* ethylglutamine, γ-glutamyl-L-ethylamide, γ-ethylamino-L-glutamic acid and γ-L-glu-ethylamide (Deng et al., 2010, 2008; Vuong et al., 2011). The unique amino acid exists as a zwitterionic species and is a colorless crystalline solid with a melting point ranging within 214–216 °C (Vuong et al., 2011). Bearing a molecular weight of 174.2 g/mol, L-theanine exhibits higher solubility in water as compared to the catechins. During infusion, it does not react with any other chemical component, which makes its separation easier (Ho et al., 2009).

Almost a decade ago, the presence of natural L-theanine was falsely considered to be limited within the *Camellia* genus, mostly the tea-producing plants - *Camellia sinensis* var. *sinensis* and *C. sinensis* var. *assamica* as well as some closely related species such as *C. japonica* and *C. sasanqua*. But later on, L-theanine was also encountered in basidiomycete mushroom, *Xerocomus badius,* from where it can be now be extracted in massive quantities by the technique of submerged fermentation (Li et al., 2008). Theanine synthase enzyme acts upon glutamic acid and ethylamine, forming L-theanine (Fig. 2), which may be hydrolyzed back to its original constituents in the growing leaves under the influence of sunlight and temperature (Deng et al., 2008). But for commercial synthesis, theanine synthetase could not be a preferable choice since the quantity of L-theanine produced by this process is

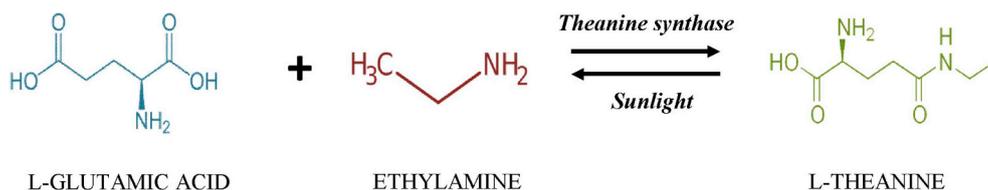**L-GLUTAMIC ACID**   **ETHYLAMINE**   **L-THEANINE**

Fig. 2. Biosynthesis of L-theanine in tea plants. Theanine synthase enzyme acts upon L-glutamic acid and ethylamine, forming L-theanine, which may be hydrolyzed back to its original constituents in the growing leaves under the influence of sunlight and temperature.

considerably less (Zhang et al., 2010). Biosynthesis of L-theanine in matured tea plants mostly takes place in the roots and is transferred to the growing parts through the phloem. These principal components are responsible for giving rise to both L-theanine and catechins. The amount of sunlight exposure to the growing tea plants determines the quantity of the amino acid formed in tea plants. More amount of sunlight produces more catechins, whereas the plants grown in sufficient shades produce more of L-theanine (Vuong et al., 2011).

3. Bioavailability and metabolism of L-theanine

The plasma concentration of L-theanine reaches its highest level at approximately 0.5 h after ingestion when 200 mg of the compound is orally administered to rat (Unno et al., 1999). L-theanine level experiences a peak plasma concentration of 26.5 μmol/L at 0.8 h, following an oral intake of 250 ml tea by human volunteers (Scheid et al., 2012). Kitaoka et al. reported that intestinal absorption of L-theanine and glutamine is mediated by a common sodium-coupled co-transporter in the brush-border membrane (Kitaoka et al., 1996). For uptake of the amino acids within the rat kidney, L-theanine is hydrolyzed by phosphate-independent glutaminase enzyme to glutamate and ethylamine. In this way, orally administered L-theanine is efficiently absorbed from the intestinal tract and conveyed to the brain across the blood brain barrier (BBB) (Kakuda, 2011).

L-theanine passes through the BBB and exerts a cerebroprotective and a preventive effect on neuronal cell death. Its psychoactive properties are documented by a number of successful experimental outcomes (Gomez-Ramirez et al., 2009; Kimura et al., 2007; Thangarajan et al., 2014). The BBB crossing capability of L-theanine was confirmed by continuous electropharmacogram record of intra-cerebral field potentials in freely moving rats. Resultant motion was increased in the first hour of L-theanine administration, but a subsequent decrease was observed during further accumulation of L-theanine in plasma concentration (Dimpfel et al., 2007). Further evidence suggests the transport of ^{14}C-labeled L-theanine through the BBB after its intra-peritoneal injection in mice and an elevation of its intra-cerebral levels of GABA within 30 min of the injection (Kimura and Murata, 1971).

In general, each circulating amino acid is competitively taken in the brain *via* a high-affinity transport system, while the efflux of these amino acids from brain back into plasma is driven in a huge part by a sodium-dependent active transport system (Smith, 2000). Within an hour of oral administration, an elevation in L-theanine level in brain continues to increase for a further 4 h, and gradually decrease to negligible levels in the following 19 h. Yamada et al. supported the idea of L-theanine crossing the BBB and acting as an agonist or an antagonist of multiple receptors (Yamada et al., 2005). The amino acid overcomes this barrier probably through leucine-preferring transport system in a competitive manner relative to large neutral amino acids. Interestingly, the ethyl base of L-theanine increases its lipophilicity, assisting its faster and easy passage through the BBB (Kimura and Murata, 1971; Yokogoshi et al., 1998a,b). L-theanine also interacts with the glutamine transporter and inhibits its neural incorporation (Kakuda, 2011).

4. Neuroprotective effects of L-theanine

4.1. L-theanine imparts anti-stress and relaxation

L-theanine exerts anxiolytic effects under resting conditions (Ogawa et al., 2018). In humans, L-theanine influences resting state oscillatory brain activity in the alpha band (8–14 Hz) and is therefore capable of facilitating long-lasting attention during the time span of a difficult task (Gomez-Ramirez et al., 2009). This resting state alpha-oscillatory activity was significantly improved as revealed through posterior magneto-encephalography. These findings support the anti-stress effects of L-theanine (White et al., 2016). Post 1 h of consuming an L-theanine based nutrient drink by 34 individuals of 18–40 years; the subjective as

well as cortisol response to a multitasking cognitive stressor was significantly lowered. A high level of corticosterone in the blood indicates stress, whereas, the administration of 0.3% theanine decreases serum corticosterone level (Takeda et al., 2012). The traditional use of green tea as a relaxing agent is supported by experimental evidence demonstrating a calming or relaxing effect of L-theanine. Only in models of anticipatory anxiety, the amino acid failed to display any acute anxiolytic effects (Lu et al., 2004).

In a comparison between L-theanine and its structural analog, glutamine, the former was found to be more effective in lowering blood pressure in spontaneously hypertensive rats, when administered at 1500–2000 mg/kg (Yokogoshi et al., 1995). L-theanine intake also results in a reduced heart rate and salivary immunoglobulin A, in responses to an acute stress-generating task (Kimura et al., 2007). It improves concentration and learning ability by its anti-anxiety and anti-depressant properties (Shen et al., 2018). Ingestion of L-theanine effectively manages psychosocial stress in experimental mice (Unno et al., 2013). Also, the amino acid can evidently demonstrate a pronounced effect on attention performance and reaction time response in normal healthy subjects who are prone to high anxiety levels (Higashiyama et al., 2011).

4.2. L-theanine influences memory and cognition

L-theanine has an impact on mood, cognition as well as human brain functions (Mancini et al., 2017). Apart from inducing anxiolytic effects, the amino acid can effectively improve learning and hippocampal activity, which has been proposed to be mediated by changes in glutamate and methionine levels in the brain (Ogawa et al., 2018; Yokogoshi and Terashima, 2000). Its intake reduces NMDA (N-methyl-D-aspartate) receptor-dependent CA1 hippocampal LTP, but increases NMDA-receptor independent CA1 LTP. Thus, L-theanine owns the ability to induce LTP in hippocampus, but NMDA receptor-independent (Takeda et al., 2011). *In vivo* dendate gyrus LTP was also induced in L-theanine-administered rats. Object recognition memory could be maintained in rats treated 48 h after the training. It is inferred that the intake of L-theanine is advantageous to the development of hippocampal function after weaning. In addition, the improvement in BDNF (Brain-derived neurotrophic factors) and NGF (Nerve growth factors) can also be observed post L-theanine treatment (Tamano et al., 2014). Park et al. demonstrated that green tea extract and L-theanine together improves memory significantly in test subjects (Park et al., 2011). In addition, an experimental regime administering treatment capsules of 360 mg of green tea extracts and 60 mg of L-theanine showed considerable benefits. Not only did its administration exhibit a reversal of cognitive impairments and oxidative damage induced by chronic restraint stress, but it also reversed the abnormal level of catecholamines in the brain and serum (Tian et al., 2013). Recently, Nguyen and his team also indicated that theanine is capable of attenuating memory impairment in *Klotho* gene depleted mice (Nguyen et al., 2019).

4.3. L-theanine regulates brain neurotransmitter level

L-theanine is capable of influencing dopamine, serotonin, glycine and GABA concentration and increases the nerve growth factor mRNA levels in cerebral cortex and hippocampus. L-theanine administration causes remarkable elevations in dopamine concentrations, especially in the striatum, hypothalamus, and hippocampus (Yokogoshi and Terashima, 2000). Also, excess dopamine-induced neurotoxicity was significantly attenuated by L-theanine in neuron-astrocyte co-cultures, but not in neuronal culture alone (Takeshima et al., 2016).

L-theanine elevates the tryptophan content in brain, whereas, intracerebral GABA level is also improved after an injection (i.p) of 7.5 mM/kg of the amino acid (Shinozaki and Ishida, 1978). According to Egashira et al., the neuroprotective effect of L-theanine is mediated at least in part by GABA$_A$ receptors (Egashira et al., 2007). It thus

affects inhibitory neurotransmission and regulates brain development in infant rats, since inhibitory neurotransmission is required for the brain to mature. L-theanine may inhibit excitatory neurotransmission and cause inhibitory neurotransmission specifically *via* glycine receptors (Yamada et al., 2005). Although some reports opine that it induces serotonin degradation and reduces serotonin synthesis, a few have proved the opposite to be true (Li et al., 2016; Shen et al., 2018; Yokogoshi et al., 1998a,b; Yokogoshi and Terashima, 2000). So, the direct effects of L-theanine administration on serotonin level still need to be deciphered. Furthermore, 10 mM of L-theanine can sufficiently regulate glutamate-glutamine cycle since it inhibits glutamine transport in neurons and astroglia in rat brains (Kakuda et al., 2008). It is also capable of decreasing the levels of nor-epinephrine (Yamada et al., 2007). Perfusion of theanine in brain prevents aspartic acid release and increases glycine release, in addition to exhibiting inhibitory actions in AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors (Yamada et al., 2009).

4.4. L-theanine exerts protective effects against cerebral ischemic injury

In spite of several advancements made in treatment modalities for ischemic stroke, it still remains a major cause of deaths in industrialized nations. Treatment with anti-coagulators exhibiting thrombolytic effects is not sufficient for the reversion of healthy cells on reperfusion (Cook and Tymianski, 2011). A large number of reports suggest that even low doses of L-theanine, as much as 1 and 4 mg/kg are capable of substantially reducing the size of cerebral infarcts. Repeated intrastriatal injections of L-theanine during reperfusion prevents brain injury and reduces infarct volume following middle cerebral artery occlusion in mice (Egashira et al., 2004). Administration of L-theanine improves the total neurological status of test subjects, while it also acts as a savior against neuronal death of hippocampal CA1 neurons in transient forebrain ischemia (Kakuda et al., 2000; Zukhurova et al., 2013). The protective effect of L-theanine on cerebral ischemia-reperfusion injury in rats has been associated with its influence on amino acid neurotransmitters and the increased mRNA expression of BDNF and Bcl-2, which regulate neuronal death and survival (Shen et al., 2011).

5. Prospective role of L-theanine in PD pathophysiology

Neurodegenerative diseases exert a significant social and economic burden to the affected population of the world. On top of that, there is no effective treatment for the common neurodegenerative disorders. Currently marketed therapeutic drugs against PD are basically symptom-oriented with multiple side effects, which increase in a dose dependent manner (Kulisevsky et al., 2018). Although the clinical diagnosis of PD relies on the presence of bradykinesia, shaking, stiffness, and other motor abnormalities, the disease is associated with many other non-motor symptoms that accentuate the overall disability (Perlmutter, 2009). Apart from neuronal death due to excitotoxicity, the loss of dopaminergic neurons in the substantia nigra *pars compacta* of basal ganglia leading to striatal dopamine deficiency may be associated with oxidative stress, neuroinflammation, intracellular accumulation of protein and mitochondrial dysfunction. These include some of the major neuropathological hallmarks of PD (Poewe et al., 2017).

Oxidative stress is thought to play an important role in dopaminergic neurotoxicity (Hwang, 2013). Various interruptions in the electron transport chain of mitochondria leads to acute over-production of reactive oxygen species (Chen et al., 2003). In both idiopathic and genetic cases of PD, oxidative stress is considered to be the common underlying mechanism which leads to cellular dysfunction and death (Jenner, 2003). Chronic neuroinflammation is also one of the distinctive features of PD pathophysiology and studies related to human PD patients and experimental animals have suggested that activation of glial cells (astrocytes and microglia in particular) as well as increase in pro-inflammatory factors are observable in the brain. The inflammatory processes have been suggested as promising targets for PD and even other neurodegenerative diseases (Wang et al., 2015).

L-theanine is an anti-psychotic and anti-depressant drug which can also attenuate neurodegeneration and may act against movement-related disorders (Fig. 3). Compiling reports on its neuroprotective effects drive an enthusiasm for exploring its role as a natural anti-Parkinsonian agent (Table 1).

5.1. Management of oxidative stress

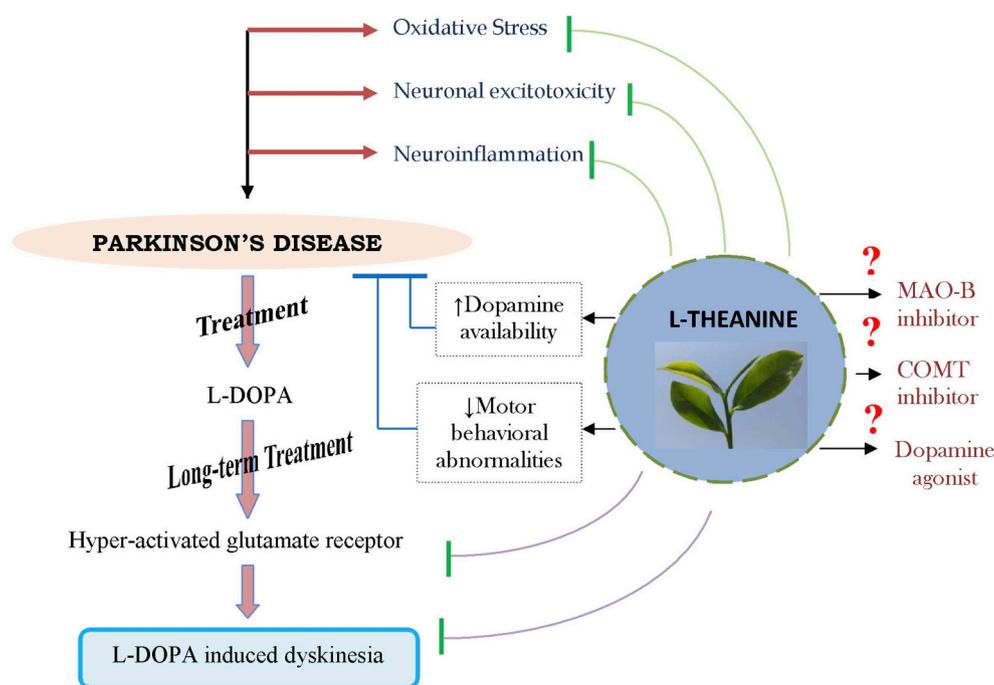L-theanine is considered as a safe compound whose repeated oral

Fig. 3. **Probable mechanism of action of L-theanine with relevance to Parkinson's disease pathology**. Persistent L-DOPA treatment is associated with over-activation of glutamate receptors which is implicated as an important cause behind dyskinesia. Apart from the known anti-oxidative and anti-inflammatory properties of L-theanine, it bears a significant potential to ameliorate L-DOPA induced dyskinesia and neuronal excitotoxicity due to its uncompetitive antagonistic action towards glutamate receptors. A salient property of L-theanine is its ability to diminish motor behavioral abnormalities and up-regulate striatal dopamine levels, which may be due to its unrevealed MAO-B or COMT inhibitory action or dopamine receptor activation.

Table 1
Role of L-theanine in ameliorating the cardinal pathophysiological changes in Parkinson's disease.

Parkinson's disease pathophysiology	Beneficial impact of L-Theanine	Reference
Anti-oxidative effects	1) 100 and 200 mg of L-theanine administered 1 h before 3-nitropropionic acid results in an increase in antioxidant molecules, superoxide dismutase and glutathione as well as substantial up-regulation in catalase and succinate dehydrogenase activity.	Thangarajan et al. (2014)
	2) 500 μM of L-theanine efficiently diminishes the level of HO-1 and ERK1/2 phosphorylation.	Cho et al. (2008)
	3) Significant increase in glutathione level in both astrocytes and glial conditioned medium and striatum of mice at 4 mg/kg L-theanine dosage for 14 days.	Takeshima et al. (2016)
	4) Excessive dopamine induced quinoprotein formation is attenuated by L-theanine (500 μM) in mesencephalic neuron-rich cultures.	Takeshima et al. (2016)
	5) 10 mmol (1.74 g)/kg once a day of L-theanine intake induces the mRNA expression of PLC-β1 and γ1 anti-stress molecules in primary cultured rat cerebral cortical neurons.	Nishida et al. (2008)
	6) Oral administration of 200 mg/kg L-theanine increases the over-all status of antioxidants, decreases lipid peroxidase, TBARS and nitric oxide.	Nishida et al. (2008)
	7) L-theanine prevents polychlorinated biphenyl induced oxidative damage in brain.	Nishida et al. (2008)
Anti-inflammatory effects	1) High dose of L-theanine (400 mg/kg) reduces the expression of overall inflammatory cytokines.	Li et al. (2016)
	2) 100 & 200 mg/kg oral L-theanine intake improves immunity by altering T_H2/T_H1 cytokine balance and their expression.	Thangarajan et al. (2014)
Restoration of altered neurotransmitter level	1) L-theanine increases dopamine concentration in striatum, hippocampus and hypothalamus.	Yokogoshi and Terashima (2000)
	2) Administration of L-theanine elevates GABA level by influencing $GABA_A$ receptors.	Shinozaki and Ishida (1978)
	3) Improvement in tryptophan and glycine concentration and alteration in serotonin synthesis and metabolism is also visualized following L-theanine treatment.	Yokogoshi and Terashima (2000)
	4) 0.1–10 mM L-theanine stabilizes the glutamate-glutamine neurotransmitter pool and influences long-term potentiation in cultured neurons.	Kakuda et al. (2008)
	5) L-theanine perfusion prevents aspartic acid release.	Yamada et al. (2009)
Motor behavioral improvement	1) L-theanine (100 & 200 mg/kg) treatment successfully reduces motor behavioral symptoms as observed in Morris water maze, open field test, and forced-swim test and rotarod activities in Huntington's disease model.	Thangarajan et al. (2014)
	2) Rearing behavior can be significantly improved in 0.3% L-theanine-administered rats.	Takeda et al. (2011)
	3) Exploratory activity is influenced by L-theanine intake, which indicates neurogenesis in hippocampus leading to improved memory and cognition.	Ogawa et al. (2018)
Other potential anti-Parkinsonian properties	1) L-theanine is structurally similar to glutamate because of which it serves as a glutamate receptor antagonist. It can thus protect neuronal damage against excessive glutamate-induced cellular excitotoxicity, which is one of the major pathophysiological changes associated with Parkinson's disease.	Hypothesis needs to be tested
	2) Changes in glutamate receptor activity are also involved in L-DOPA induced dyskinesia. L-theanine holds an ability to attenuate the complicacy associated with dyskinesia and may prove to be a useful alternative to amantadine.	Hypothesis needs to be tested

administration reduces oxidation levels in the brain, especially the cerebral cortex, by increasing the expression of phospholipase C-β1 and -γ1 (Nishida et al., 2008). As a response to oxidative-stress, phospholipase C mediates survival signaling by protein kinase C-dependent phosphorylation of Bcl-2 and inhibition of caspase-3, thereby inhibiting apoptosis of neuronal cells (Bai et al., 2002).

Besides, L-theanine can effectively reduce thiobarbiturate reactive substances to a huge extent, indicating its favorable action against cellular oxidative burden (Nishida et al., 2008). Oral administration of L-theanine (200 mg/kg) increases the status of antioxidants and diminishes the levels of lipid peroxidase as well as nitric oxide. The amino acid can even regulate the expression of inflammatory cytokines and is capable of altering T_H2/T_H1 cytokine balance and their expression in rat hearts (Li et al., 2016; Thangarajan et al., 2014). Higher levels of glutathione in striatum are observed after an oral administration of 4 mg/kg of L-theanine. Thus, it is an effective neuroprotectant against oxidative-stress-induced neuronal damage and neuroinflammatory conditions (Takeshima et al., 2016).

In 3-nitropropionic acid induced Huntington's disease model, intraperitoneal injections of L-theanine at 100 and 200 mg/kg significantly attenuated oxidative stress and also restored glutathione, superoxide dismutase as well as catalase levels. It successfully improved succinate dehydrogenase (Mitochondrial Complex II) activity and histopathological analysis of striatum confirmed that L-theanine can diminish the overall neuronal damage (Thangarajan et al., 2014). Even against the two well-known PD-related neurotoxicants - rotenone and dieldrin, 500 μM of L-theanine protects from cytotoxicity as demonstrated in SH-SY5Y cell culture, specifically by attenuating the action of heme oxygenase 1, which is an oxidative stress-induced enzyme for the degradation of heme. It further minimizes the phosphorylation of ERK1/2 normally found to be involved in the initiation of neuroinflammatory cascades. The overall treatment with L-theanine also up-regulates the levels of BDNF and glial cell-derived neurotrophic factor (GDNF), both necessary for neuronal growth and survival (Cho et al., 2008).

5.2. Motor behavioral improvement and restoration of dopamine level

L-theanine (100 and 200 mg/kg) treatment significantly attenuates the impairment in motor behavioral symptoms as revealed through Morris water maze, open field test, forced swim test and rotarod activities in Huntington's disease model (Thangarajan et al., 2014). Whereas, in a separate set of experiment performed by Takeda et al. (2011), newborn rats fed with 0.3% L-theanine significantly improved rearing behavior. The ability to recognize novel object and exploratory activity is increased by L-theanine intake, which suggests its facilitation of neurogenesis in hippocampus to boost memory. Behavioral tests performed by Ogawa et al., also supported that L-theanine exerts anxiolytic activity and initiates hippocampal regeneration (Ogawa et al., 2018).

L-theanine perfusion into the brain striatum causes rapid release of DA from dopaminergic neurons and an increase of DA in a dose-dependent manner can be observed after the direct administration of L-theanine into brain striatum by microinjection (Yamada et al., 2005; Yokogoshi et al., 1998a,b). The mechanism of this dopamine release caused by L-theanine is different from glutamate transporter blockers or glutamic acid.

5.3. Prevention of glutamate excitotoxicity and neuronal death

Glutamate is an important neurotransmitter associated with synaptic plasticity, which is an essential property of the brain for memory and learning. It is usually present in glutamatergic neurons in a concentration of around 10 mM, where it efficiently performs synaptic neurotransmission (Moussawi et al., 2011; Olney, 1990). But when nutrient supply is terminated because of cerebral infarction or cardiac arrest, the membrane electric potential starts to get depolarized uncontrollably and glutamate is excessively released into the extracellular space. This, in turn, excites the glutamate receptors resulting in a phenomenon called 'neuronal excitotoxicity'. Excitotoxicity is the pathological process by which neurons are damaged by the over-activation of glutamate receptors such as the NMDA receptor and AMPA (Gupta et al., 2013).

Being structurally similar to glutamate and glutamine, the mechanism of neuroprotection by L-theanine lies in its inhibition of substrate-binding in AMPA (IC_{50} = 24.6 ± 0.9 μM), kainate (IC_{50} = 41.5 ± 7.6 μM) and NMDA-glycine (IC_{50} = 0.011 ± 0.002 μM) receptors (Fig. 4). However, the inhibitory concentration of L-theanine was found to be 80 to 30,000-fold less than that of L-glutamic acid. L-theanine is capable of binding to all the three glutamate receptors subtypes and cause favorable down-regulation of glutamate excitotoxicity (Kakuda et al., 2002). L-theanine (10 μM) also binds and influences group I metabotropic receptors (mGluRs) (Nagasawa et al., 2004). It is capable of regulating overall glutamate

synthesis and inhibits transportation of glutamine in neurons and glial cells, thus directly affecting the glutamatergic pool (Kakuda et al., 2008). Most importantly, L-theanine displays the capacity to inhibit neuronal death by excitotoxicity and promote dopaminergic neuronal survival in PD.

6. Implications of L-theanine as a beneficial agent against L-DOPA induced dyskinesia

L-DOPA (L-3,4-dihydroxyphenylalanine) is the amino-acid precursor of the neurotransmitter dopamine and is currently considered as the most effective drug available for symptomatic treatment of PD. However, it is affiliated with multiple side-effects which are evident mostly after a particular duration of treatment (Borah and Mohanakumar, 2010; 2007; Thanvi et al., 2007). Dyskinesia is commonly observed in Parkinsonian patients treated with L-DOPA. The exact mechanism underlying L-DOPA induced dyskinesia (LID) is still not entirely comprehensible, but the recent line of evidence revealed excessive striatal glutamate release as one of the pathophysiological changes involved with it (Nevalainen et al., 2013). Significant alterations in both dopaminergic and non-dopaminergic neurotransmission are observed in the basal ganglia during LID, because of which a recent strategy is to indirectly stabilize dopaminergic signaling by targeting non-dopaminergic neurotransmitter systems, including glutamate (Morin and Di Paolo, 2014).

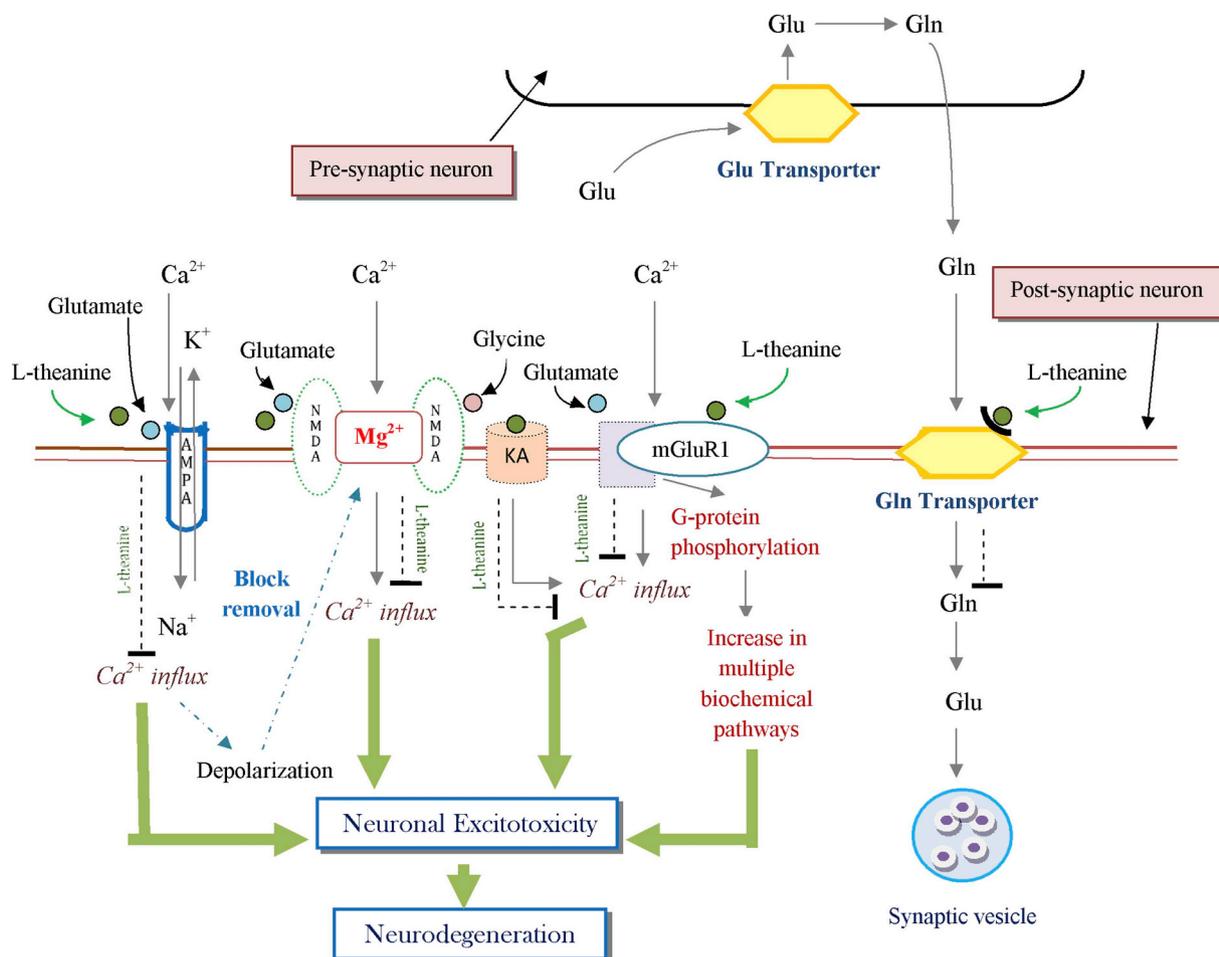Changes in glutamate receptor status have been implicated in LID

Fig. 4. Antagonistic effect of L-theanine on glutamate receptors and its inhibitory role on glutamine receptors. L-theanine selectively inhibits the binding of glutamate to ionotropic receptors (KA, AMPA and NMDA) and metabotropic receptor type I, thereby reducing the influx of calcium ions due to over-activation of glutamate receptors. Excessive entry of calcium into the neuron causes enhanced oxidative stress through mitochondrial dysfunctions. Mitochondrial dysfunctions result in cytochrome *c* release and caspases activation leading to cell death. L-theanine also prevents the assimilation of extracellular glutamine (Gln) into neurons by partially blocking the Gln receptors, thus lowering the conversion of Gln to glutamate (Glu) within the neurons.

(Calon et al., 2003). Long-term L-DOPA administration alters the status of the striatal NR2B subunit of NMDA receptors by its up-regulation, as observed in dyskinetic MPTP (1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine) primates (Calon et al., 2000). In 6-hydroxydopamine lesioned rats exhibiting PD-like symptoms, the receptor-binding studies have also demonstrated a significant increase in NR2B subunit expression after regular intake of L-DOPA (Mellone et al., 2015). Even over-activation of metabotropic glutamate receptor type 5 in animals with dyskinesia suggests a causal link between induction of persistent dyskinesia and glutamatergic storm (Mela et al., 2007).

These experimental outcomes indicate that the antagonistic effect of L-theanine on glutamate receptors might be a beneficial treatment strategy against LID, since the blockage of receptor activity by several existing antagonists of NMDA and AMPA receptors display favorable anti-dyskinetic effects in PD patients and in animal subjects (Calon et al., 2003; Morin and Di Paolo, 2014). Also, no cost-effective drug is yet available for the treatment of LID, apart from minimum benefits rendered by amantadine. However its usefulness of amantadine in PD is limited because of its side-effects in central nervous system (Meissner et al., 2011). Thus, ionotropic and metabotropic receptors form interesting targets to reduce LID and the complications associated with it.

7. Conclusion and future perspectives

L-theanine is a unique natural amino acid whose potential medicinal benefits have long been underrated, since it engrosses a relatively smaller proportion of bioactive components in tea plants as compared to that of polyphenols. It also possesses an ability to modify the neurological status through its stress-relieving effect, improvement of attention, mood and cognition. The virtuousness of this non-protein amino acid may be extended to its capacity to decrease neurodegeneration and improve neuronal survivability as authenticated by numerous experimental results. The current findings initiate an impulse to assess its worth in Parkinson's disease therapeutics since L-theanine displays protective actions against a multitude of parameters related to the pathophysiological changes observed in neurodegenerative disorders. Future research demands a lucid understanding of its mechanism of neuromodulation, its safety profile, appropriate dosage, its biokinetics and the process of its elimination from our body. Being a structural analog of glutamate, L-theanine may serve as one of the amino acid neurotransmitters in brain and may regulate the consequences of glutamatergic upsurge in the neuronal niche. Increase in dopamine level and minimization of motor behavioral symptoms by L-theanine may be due to its unrecognized dopamine receptor agonistic effects or monoamine oxidase-B or catechol-o-methyltransferase inhibitory properties vested in it, which needs to be experimentally established. Despite visible advancements in clinical trials with synthetic drugs, their long-term intake relates to undesirable side-effects which mostly end up being disastrous for PD patients. Thus, there is an urgent need to recruit natural components like L-theanine as alternatives for medications that are available over-the-counter.

Conflicts of interest

The authors declare no conflict of interest to publish this manuscript.

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