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Review Article

Health Benefits of Theanine in Green Tea: A Review

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Abstract

Theanine is an amide exclusively present in tea and some fungi, and is an important bioactive component of tea. The bioactive effects of theanine include antitumour, anti-diabetic, antihypertensive, anti-stress activities, and the ability to improve cardiovascular and cerebrovascular diseases. It also has protective effect on nerve cells against damage induced by environmental neurotoxins as well as on liver from injury induced by excessive alcohol intake. The bioactive functions of theanine as well as its pharmacokinetics are presented in this review.

Keywords: *Theanine, Pharmacokinetics, Pharmacology, Bioactive properties*

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INTRODUCTION

Theanine, also known as L-γ-glutamylethylamide or 5-N-ethyl-glutamine (Figure 1), is a specific amide found in the tea plant (*Camellia sinensis*), the basidiomycete (*Boletus badius*) and Guayusa tea (*Ilex guayusa*). It is synthesized from glutamine and ethylamine in the tea root and then transferred to the leaf where it accumulates [1]. Theanine is one of the important components related to taste, and to the healthy function of tea.

The developments of pharmacological and physiological technologies have made the study of theanine bioactivities possible. These studies discovered many novel physiological effects of green tea theanine on human health. Advances in pharmacokinetics, pharmacological and physiological functions of theanine are reviewed and summarized in this paper.

PHARMACOKINETICS OF THEANINE

Theanine is non-toxic for humans and animals. Some tests carried out on rats showed that theanine is non-toxic when up to a dose of 4.0 g/kg per day having no adverse effects on behaviour, food intake, body weight, mortality, morbidity, indicators of haematology, urine parameters, and histopathological characteristics in the tested animal [1].

Theanine is a chiral chemical compound with L-theanine and D–theanine isomers. In tea leaves, only L-theanine is present; however, both L-theanine and D–theanine are present in synthetic theanine products, and there are significant differences in the physiological responses to L-theanine versus D-theanine. First, L-theanine is more easily absorbed by animals than D-theanine. When Sprague-Dawley (SD) rats are fed the same dose of D-theanine or L-theanine, the plasma L-theanine level is about three times

that of D-theanine. When SD rats are fed with a mixture of both L-theanine (0.5 g/kg per day) and D-theanine (0.5 g/kg per day), the plasma L-theanine level is much higher than that of D-theanine. Secondly, there is a mutual antagonism between L-theanine and D-theanine. D-theanine inhibits the absorption of L-theanine when L-theanine and D-theanine are orally co-administered, and vice versa [2]. Thirdly, the absorbed D-theanine is more easily excreted from urine than L-theanine, although both L-theanine and D-theanine are partially lost through this route. However, the urine D-theanine concentration was 10–15 fold higher than that of L-theanine when an equal dose was administered either as an oral or peritoneal injection to rats [2,3]. Fourth, degradation occurs more quickly in plasma D-theanine than in plasma L-theanine. Both D-theanine and L-theanine are partially degraded into ethylamine and glutamic acid, which is catalysed by a phosphate-independent glutaminase in the kidney, but plasma D-theanine is more easily and more quickly degraded than L-theanine [3-5]. These observations explain why L-theanine extracted from leaves has better physiological functions than a synthetic theanine mixture containing both L-theanine and D-theanine.

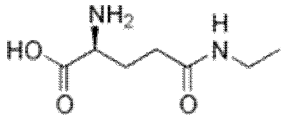

Figure 1: Molecular structure of theanine

PHYSIOLOGICAL AND PHARMACOLOGICAL FUNCTIONS OF THEANINE

Anti-tumour effects

There have been many studies showing that theanine has both *in vivo* and *in vitro* anti-tumour effects [6-11]. The anti-tumour mechanism of theanine includes the following.

(1). A theanine-enhanced effect on anticancer drugs. Theanine inhibits biosynthesis of the glutamate transport protein and intracellular glutathione (GSH), resulting in less glutathione-doxorubicin conjugate (GS-DOX) of the multi-drug resistance-associated protein-5/GS-X (MRP5/GS-X) pump, and less intercellular transport of doxorubicin (DOX), which is beneficial in enhancement of the used drug anti-tumour effect [6,7]. Theanine also enhances anti-tumour effects of cisplatin on mouse M5076 cells [7,8], and it stimulates the anti-tumour efficacy of irinotecan hydrochloride. When irinotecan hydrochloride is used alone, it has no anti-tumour efficacy. But when combined with theanine, it shows significant suppressive effects on tumours [8].

(2). Theanine relieves the toxic side effects induced by some anticancer drugs. Theanine decreases the activity of enzyme glutathione peroxidase and lipid peroxidation levels induced by the drug DOX, resulting in less super oxidative stress [9,10].

(3). Theanine also has hypercholesterolemia activity. Sustained high level of serum cholesterol can result in atherosclerosis. Dietary theanine supplementation significantly suppresses hypercholesterolemia in rats suffered with hepatoma [7], by increasing bile acid excretion into the faeces, which promotes cholesterol elimination from the animal body.

(4). Theanine derivatives inhibit tumour growth by targeting epidermal growth factor receptor/vascular endothelial growth factor receptor-Akt/nuclear factor-kappa B (EGFR/VEGFR-Akt/NF-kappa B) signalling pathways, which involve some of the most important pathways in controlling the survival and proliferation of cells. Theanine derivatives such as ethyl 6-fluorocoumarin-3-carboxylyl L-theanine (TFC) and ethyl 6-nitrocoumarin-3-carboxylyl L-theanine (TNC) effectively inhibit the cell growth of lung cancer *in vitro*, *ex vivo*, and *in vivo*, by targeting these pathways [11].

Neuroprotection

Theanine protects against nerve damage and improves neurological function by reducing cerebral infarction, to protect mice brain from cerebral ischaemia [12], and to prevent brain injury mediated by glutamate receptor agonist [13]. Theanine also inhibits cerebral cortical neuron involvement in delayed neuronal death (DND), and can serve a neuroprotective role by regulating the level of metabotropic glutamate receptor subgroup I (group I mGluR) by stimulating the expression of phospholipase C-β1 (PLC-β1) and phospholipase C-γ1 (PLC-γ1) [14]. The neuroprotective activity of L-theanine is related to its ability to decrease the efficacy of neurotoxin-induced neurotoxicity and oxidative stress. Theanine shows neuroprotective efficacy against Parkinson's disease (PD)- and Alzheimer’s disease (AD)-related neurotoxin damages. It decreases DNA fragmentation as well as nerve cell (SH-SY5Y) apoptosis induced

by neurotoxins by inhibiting the upregulation of haeme oxygenase. It also suppresses the downregulation of phosphorylation of extracellular signal regulated kinase 1/2 (ERK 1/2), brain-derived neurotrophic factor (BDNF), and glial cell-derived neurotrophic factor (GDNF) [15]. It inhibits the decrease in activity of catalase (CAT), superoxide dismutase (SOD), and succinate dehydrogenase (SDH), decreases the concentrations of reduced glutathione (GSH), and decreases the oxidative damage of neuronal cells [16-18]. In summary, L-theanine has a neuroprotective efficacy against PD- or AD-related neurotoxin damages, and can be used as an agent for preventing PD or AD.

Improvement of memory

Theanine enhances cognitive functions through increasing the concentration of brain neurotransmitters such as dopamine, 5-hydroxytryptamine (5-TH), glycine and GABA (γ-aminobutyric acid). In addition, it stimulates the expression level of nerve growth factor (NGF) mRNA of cerebral cortex and hippocampus, reverses abnormal levels of corticosterone in the serum and abnormal levels of catecholamines in brain and serum, and promotes the maturity of nervus centralis during the neural maturation period, which is beneficial to the development of the brain function [19,20]. Theanine improves learning and memory ability by eliminating acquired memory disorders, relieving oxidative stress, and improving the α-wave patterns of brainwaves [21-23]. The water maze test showed that appropriate dosages of theanine decreases the mistake number and shortens the time for mice to escape the maze [21]. The step down test showed that rats treated intragastrically with theanine have a significantly longer latency period, with fewer mistakes than the normal saline group (control). These changes showed dose-dependent responses [21-23]. In brain tissue homogenates, theanine significantly increases the activities of cholinesterase (AchE) and SOD, resulting in a reduction in malondialdehyde (MDA) levels [22]. Theanine also stimulates striatal dopamine release, which improves the brain α-waves [24], enhancing attention and memory in subjects suffering mild cognitive function impairment [25].

Anti-diabetic effects

Abnormal metabolism of zinc is considered to be associated with some metabolic disorders, including complications of diabetes. Zinc plays an important role in protecting the heart of diabetic myocardial patients from oxidative stress, and zinc supplementation is an important treatment in preventing cardiac-oxidative-damage and delaying diabetic cardiomyopathy. The theanine-zinc compound is a zinc complex that has a significant *in vivo* hypoglycaemic effect on KK-Ay mice [26]. This theanine-zinc complex is clinically recommended as a zinc supplement to prevent diabetes [27].

Hypotensive activity

L-theanine can block the binding between L-glutamic acid and glutamate receptors in brain. It not only has anti-stress effects, by suppressing cortical neuron excitation, but also reduces anxiety and attenuates blood pressure raises in high stress response adults [28]. An injection of theanine into spontaneous hypertensive rats (SHR) causes a significant hypotensive effect [29,30]. The hypotensive activity of tryptophan is related to its effect in raising the level of 5-HT (an angiotensin). However, theanine plays a role in hypotensive effects by regulating the peripheral nerves and vascular system, instead of increasing 5-HT levels [31]. It is reported that theanine accumulates in the tested animal brain, which is accompanied by a significant reduction in the levels of brain 5-HT and its metabolite 5-hydroxyindoleacetic acid (5HIAA) [31].

Anti-fatigue effects

Theanine alleviates physical fatigue by raising the concentrations of dopamine (DA) and hepatic glycogen, and decreasing the concentrations of 5-HT and serum urea. Weight loading swimming experiments on mice confirmed that intragastric administration with theanine (0.70 g/kg per day) for 30 days significantly prolongs the load swimming time, which is accompanied by a decrease in 5-HT, serum urea, and lactate levels, and an increase in DA and hepatic glycogen levels [32-34].

Anti-depressant effects

There are numerous studies reporting that L-theanine has anti-anxiety and antidepressant effects. Theanine intake after weaning prevents mice from stress-induced impairments of hippocampal long-term potentiation (LTP) and improves recognition memory [35]. The antidepressant mechanism of theanine involves its reduction in heart rate and decrease in salivary immunoglobulin A (s-IgA) responses to an acute stress task. The reduction in heart rate and s-IgA is thought to be mediated by

attenuating the sympathetic nerve activation or suppressing the excitation of cortical neuron [35,36]. Theanine also induces hippocampal BDNF, which is partially attributable to the agonistic action of L-theanine on the N-methyl-D-aspartate (NMDA) receptor. A study reported that a subchronic administration of L-theanine increases expression of BDNF protein in the hippocampus. L-theanine used in *in vitro* cortical neurons significantly increases the intracellular Ca^{2+} concentration, but this increase is suppressed by competitive and non-competitive NMDA receptor antagonists [37]. Theanine also prevents transient decrease in 5-bromo-2'-deoxyuridine (BrdU) incorporation into the hippocampal DG (dentate gyrus). The transient decline in BrdU incorporation in the hippocampal DG is positively correlated with behavioural abnormalities in adult mice. Oral administration of theanine alleviates behavioural abnormalities, together with inhibition of the transient decrease in the incorporation of BrdU in the hippocampal DG in the adult mice with severe traumatic stress [38]. Theanine also decreases the level of salivary α-amylase activity (sAA). The sAA is an indicator of activity of sympathetic nervous system. Stressful conditions increase the level of sAA, but theanine intake significantly suppresses the sAA increase induced by anxiety [39]. Theanine regulates expression of some genes. Post-traumatic stress disorder (PTSD) is considered to be characterized by the happening of some traumatic event, during which some genes are up-regulated while other genes are down-regulated. Expressions of three hippocampus genes and five amygdala genes were significantly different ($p < 0.05$) between the PTSD-stressed groups that received either L-theanine, midazolam, saline, or midazolam + L-theanine [40]. The central monoaminergic neurotransmitter system mediates the anti-depressant effect of L-theanine[41].

Protective effects on the cardiovascular system

Tea consumption improves vascular function and decreases the risk of cardiovascular disease. The protective efficacy of theanine involves lowering serum cholesterol [42], enhancing artery vasodilation and production of nitric oxide [43], and protecting brain from cerebral ischaemic injury [44,45]. Serum cholesterol is an important risk of coronary heart disease (CHD), so lowering cholesterol levels reduces the risk of cardiovascular and cerebrovascular diseases. When compared to controls, feeding mice with a diet with 0.028 % theanine for 16 weeks significantly decreased the levels of abdominal adipose, liver cholesterol, serum neutral fat, and cholesterol [42].

Endothelial nitric oxide is a crucial regulator of the vascular functions in endothelium. L-theanine administration activates ERK/ endothelial nitric oxide synthase (ERK/eNOS), resulting in an increase in NO production and artery vasodilation [43]. Theanine protects brain from cerebral ischaemic injury by decreasing the harmful effects of free radical metabolism induced by cerebral ischaemia injury in rats [44]. Theanine also suppresses changes in cerebral ultrastructure, serum interleukin-8 (IL-8), and neuron specific enolase (NSE) during cerebral ischaemia damages [45]. Finally, an epidemiological study has reported that drinking tea might decrease the risk of stroke [46].

Alleviation of liver injury induced by alcohol

Excessive uptake of alcohol causes liver injury, accompanied by an increase in levels of free radicals and lipid peroxide (LPO), and a decline in the activity of glutathione peroxidase [47]. Theanine increases activities of aldehyde dehydrogenase and alcohol dehydrogenase, accompanied by a decline in cytochrome P450 CYP 2E1 [47], which decrease alcohol-induced liver injuries.

The liver is sensitive to unpredictable and chronic mild stress (UCMS). However, theanine (2 mg and 4 mg/kg body weight per day) improves the hepatic indices by increasing the GSH level, raising the activities of CAT and SOD, but decreasing the MDA level in the liver. Moreover, theanine administration significantly ameliorates hepatic function and decreases the level of tumour necrosis factor-αin the liver [48]. Theanine protects mice against carbon tetrachloride (CCl_4)-induced acute liver injury by suppressing metabolic activation of CCl_4 and preventing CCl_4-induced reduction of the antioxidant capacity in the liver, to decrease inflammatory responses and hepatocyte apoptosis [49]. L-theanine protects hepatic Lo2 cells against the apoptosis induced by hydrogen peroxide through its inhibiting effect on hydrogen peroxide-activated p38 mitogen-activated protein kinase [50]. Theanine prevents acute hepatic damages caused by DOX, an antitumour agent, by inhibiting the activities of alanine aminotransferase and aspartate aminotrans-ferase and suppressing the hepatic expression of the apoptosis regulator Bax, mediated by DOX [51].

Improving immunity

Older patients are more easily infected with the influenza virus, because of their decreased immune responses. Co-administration of L-theanine with L-cystine enhances levels of serum IgG and antigen-specific IgM [52]. In addition, oral administration with L-theanine and L-cystine before vaccination can enhance the immune response to influenza vaccine in elderly persons with low haemoglobin [53]. Oral administration of L-cystine and L-theanine during the perioperative period alleviates post-gastrectomy inflammation and promotes recovery after surgery [54]. Supplementation of L-cystine and L-theanine significantly suppresses the exercise-induced fluctuation of blood immunocompetent cells, and helps to reduce alterations of the immune response by both attenuating the rise of neutrophil count and reducing the lymphocyte count caused by extreme endurance exercise [55-57].

CONCLUSION

Theanine is an amide in tea and some fungi and has anti-tumour, anti-diabetes, anti-hypertension, and anti-stress effects, decreases cardiovascular disease, and decreases cerebrovascular malformation. Theanine inhibits nerve cell damages induced by environment neurotoxins and protects the liver from damages caused by superfluous alcohol. A non-toxic dose of theanine in rats is as high as 4.0 g/kg per day, which provides useful reference for development of drugs and foods containing the compound.

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