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Review

Neuroprotective effects of theanine and its preventive effects on cognitive dysfunction

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ABSTRACT

Theanine (γ-glutamylethylamide) characteristically present in tea leaves (*Camellia sinensis*). It has a similar chemical structure to glutamate, which is a neurotransmitter related to memory. Theanine passes through the blood–brain barrier and has been shown to have a cerebroprotective effect and a preventive effect on neuronal cell death after transient cerebral ischemia. The neuroprotective effect is partly due to the antagonistic action of theanine on glutamate receptor subtype AMPA and kainate receptors, but the affinity is very low. Theanine also acted on glutamine (Gln) transporter strongly and inhibited the incorporation of extracellular Gln into neurons, which in turn suppressed the conversion of Gln to glutamate by glutaminase, a reaction required for condensation into synaptic vesicles to form a neurotransmitter pool responsible for subsequent exocytotic release upon stimuli. In an investigation of elderly persons with normal or slight cognitive dysfunction, volunteers who ingested powdered green tea containing a high theanine concentration (equivalent to 47.5 mg day^{-1} of theanine) showed significantly lower decline in cognitive function compared with that of the placebo group. This result suggested that theanine might have improved a slight cognitive dysfunction in elderly persons.

1. Introduction

There are estimated to be approximately 2 million dementia patients in Japan. Given the country's rapidly aging society, the number of dementia patients is likely to increase further in the near future. Such patients will become an enormous burden on care givers and a huge financial strain on society. The most common causes of dementia in the elderly include Alzheimer's disease, cerebrovascular disease, and dementia with Lewy bodies. Of these, Alzheimer's disease is the leading cause, followed by cerebrovascular disease, and their mixed dementia is also found in Japan.

It has been reported that cerebrovascular dementia [1] is associated with blood vessel disorders of the brain caused by cerebral infarction [2], diabetes [3], high blood pressure [4], cardiac vascular disease [5], etc. The Framingham study in the U.S.A. reported that stroke increased a subject's risk of dementia compared with that in age- and sex-matched controls. Primary and secondary prevention of stroke should significantly decrease the risk of dementia [6]. Other studies have also reported that stroke is a significant risk factor of cognitive impairment and dementia [7,8]. Glutamate can cause neuronal cell death by acting as a powerful neurotoxin in the central nervous system when its extracellular concentration is elevated because of cerebral ischemia such as stroke. In order to diminish glutamate toxicity, the extracellular concentration must be decreased, for example, by postsynaptic glutamate receptor antagonists in glutamatergic neurons [9,10]. However, although there are reports of neuroprotectants in stroke, such as *N*-methyl-D-aspartate (NMDA) receptor antagonists [11,12], all have been subject to side effects. Therefore, there is a need to develop useful medicines, preventive medical supplies, and/or neuroprotective supplements.

Kuriyama et al. [13] reported that high consumption of green tea (≥2 cups per day) is associated with lower prevalence of cognitive impairment in humans in epidemiology study of Tsurugaya project in Japan. An attractive quality ingredient of green tea leaves is theanine, which has an analogous chemical structure to glutamate and glutamine (Gln) (important neurotransmitters related to memory) (Fig. 1). There are several reports on the neuroprotective effects of theanine on ischemic neuronal cell death [14–16], and also on its action mechanisms [17,18] and metabolism [19,20]. Kataoka et al. [21] showed that long-term ingestion of a high concentration of theanine in powdered green tea suppressed the progression of cognitive dysfunction and suggested a preventive effect on dementia in the elderly.

2. Metabolism of theanine

Common-grade green tea leaves contain 0.2–2.4% (w/w) theanine [22]. Kitaoka et al. [23] reported that intestinal absorption of theanine and Gln was mediated by a common Na^+-coupled

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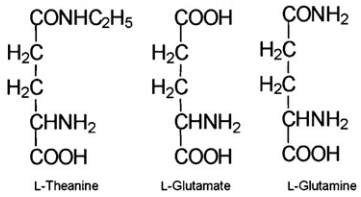

Fig. 1. Chemical structure of L-theanine (γ-glutamylethylamide), L-glutamate, and L-glutamine.

co-transporter in the brush-border membrane, the affinity of which was lower for theanine than for Gln. Unno et al. [19] showed that when 200 mg of theanine was orally administered to rats, the plasma concentrations of theanine and ethylamine reached their highest levels approximately 0.5 and 2 h after administration, respectively. Within the rat kidney, theanine is hydrolyzed to glutamate and ethylamine. Tsuge et al. [20] reported that theanine was hydrolyzed by phosphate-independent glutaminase in the kidney and proposed that the glutamyl moiety was transferred by means of a γ-glutamyl transpeptidase reaction to other peptides in vivo. In contrast, Yokogoshi et al. [24] reported that theanine was transported into the brain through the blood–brain barrier via a leucine-preferring transporter system. In this way, orally administered theanine was easily absorbed from the intestinal tract and partially transported into the brain through the blood–brain barrier.

3. Neuroprotective effect of theanine

3.1. Neuroprotective effect of theanine on delayed neuronal cell death after transient brain ischemia

Theanine has an inhibitory effect on the stimulation of the central nervous system by caffeine [25,26], a reduction effect on blood pressure [27], a relaxation effect [28], and an enhancing human γδ T lymphocyte function [29]. The chemical structure of L-theanine is a similar to that of glutamate, which is a very important neurotransmitter related to memory. The neuroprotective effects of L-theanine on delayed neuronal cell death following transient ischemia were elucidated using an animal model [14]. Transient forebrain ischemia was induced by bilateral occlusion of the common carotid arteries for 3 min in gerbils. Seven days after ischemia, pyramidal neurons in the hippocampal CA1 region degenerated or disappeared (Fig. 2b and e). No change in the number of CA1 pyramidal neurons was observed in the sham-operated group (Fig. 2a and d). On the other hand, most CA1 pyramidal neurons were preserved in animals that were administered 1 μL of 500 μM theanine solution 30 min before ischemia (Fig. 2c and f). Theanine pretreatment significantly inhibited ischemic neuronal cell death in the hippocampal CA1 field in a dose-dependent manner. Lowering the intraischemic brain temperature by 2 °C has been shown to significantly reduce the extent of ischemic neuronal damage [30]. MK801, an NMDA-type glutamate receptor antagonist, exerts protective effects when the brain temperature is lowered [31]. However, some NMDA-type glutamate receptor antagonists have been shown to exert their protective effects without a lowering of the brain temperature [32]. In the animal model described above cerebral ischemic experiments were performed during brain regulation at an ischemic insult temperature and continuous monitoring [33]. The tests were performed while maintaining the brain temperature at 37 °C; this suggests that the neuroprotective effect of theanine does not depend on lowering of the brain temperature but may be due to a direct effect on neurons [14]. Egashira et al. [34] reported that theanine significantly prevented impairment of spinal memory in rats subjected to repeated cerebral ischemia at 7 days after the second reperfusion. They further reported that theanine significantly inhibited the decrease in the number of surviving cells in the hippocampal CA1 field of the same rats [34]. These results indicate that theanine may prevent cerebrovascular disease by mitigating cognitive dysfunction through inhibition of ischemic neuronal cell death.

3.2. Neuroprotective effect of theanine on middle cerebral artery occlusion

Kakuda et al. [15] reported that theanine significantly prevented neuronal cell death in rats using an occluded middle cerebral artery (MCA) model similar to the clinical model described above. They further suggested a cerebral protective action of theanine. Theanine (125 μM, 250 μM, and 500 μM) was injected through the lateral ventricle 30 min before the onset of MCA occlusion under controlled body temperature (37 °C) and anesthesia. Focal cerebral ischemia was induced by temporary MCA occlusion for 1 h with a suture technique. After 24 h, the brains were removed, and infarct volumes were measured. The infarct volume was significantly reduced by treatment with 250 μM and 500 μM theanine in a dose-dependent manner. Egashira et al. [35] reported that theanine (1 mg kg^{-1}) was injected i.p. 3 h after occlusion or immediately before occlusion significantly decreased the size of cerebral infarcts 1 day after the occlusion. Thus, theanine has a neuroprotective effect on MCA occlusion, which is often observed clinically and might be clinically useful for preventing cerebral infarction.

4. Mechanisms underlying of the neuroprotective effects of theanine

4.1. The neuronal excitotoxin glutamate and neuronal cell death

The human brain is thought to contain approximately 100 billion neurons. These neurons form complicated neural networks from several thousands to several tens of thousands of synapses. It is thought that information entering the human body through vision, audition, gustation, olfaction, and/or tactile sense is transferred to the hippocampus, where it is consolidated and stored temporally as short-term memory. Potent information is finally fixed in the hemisphere as long-term potentiation (LTP). The memorized information is judged in an association cortex and is thought to be used functionally.

Glutamate is an important neurotransmitter concerned with memory and is present at a concentration of approximately 10 mM in the glutamatergic neurons. When electric information is transmitted to the synapse via an axon, glutamate is discharged in the synaptic cleft from synaptic vesicles in pre-synaptic terminals. Glutamate receptors in the post-synaptic membrane are activated, and information is transmitted as chemical information (Fig. 3). When the transfer of information is complete, glutamate is eliminated from the synaptic cleft and taken into glial cells and neurons by glutamate transporter [36,37]. A low extracellular glutamate concentration (<2 μM) is maintained to avoid excessive excitement [38]. This process is very short term. However, when the supply of oxygen and glucose (a nutrient source) stops because of cerebral infarction or cardiac arrest, the electric potential of the cell membrane depolarizes, glutamate is excessively released into the extracellular space, and glutamate receptors are excited in a disorderly manner [39]. There is a particularly vulnerable region in the brain [40,41], in which neuronal cell death occurs approximately 2 days after 5 min of cerebral ischemia [42]. Cerebral ischemia results in excessive stimulation of glutamate receptors and abundant flow of Ca^{2+} ions into neurons through NMDA receptors [43]. Such an excessive flow of Ca^{2+} ions into neurons results in excessive

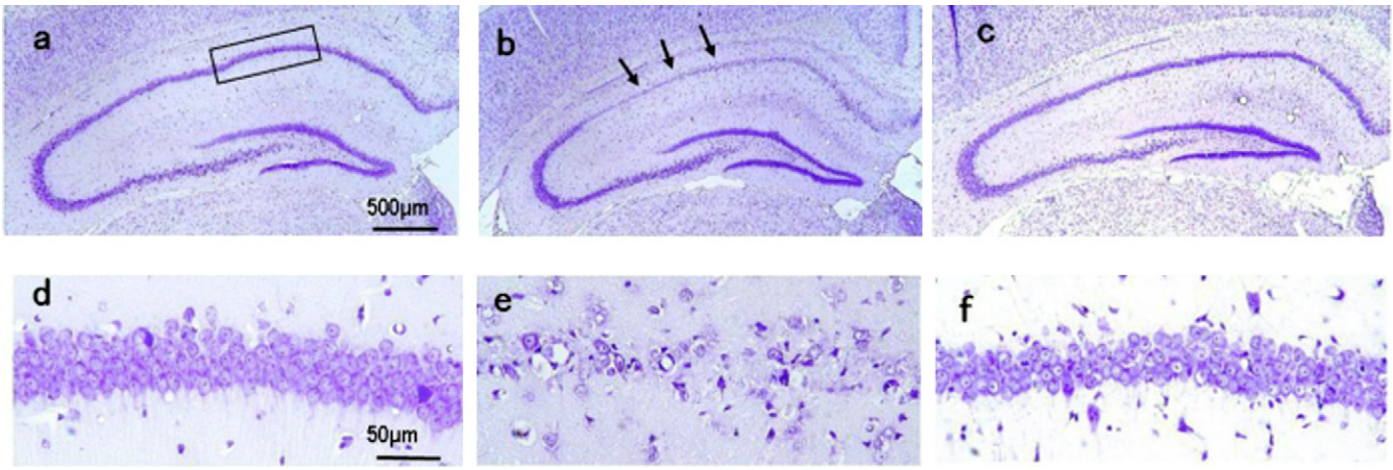

Fig. 2. Photograph showing the neuroprotective effects of theanine against ischemic delayed neuronal death in the gerbil hippocampus [14]. Brain sections were obtained 7 days after 3-min transient ischemia. (a and d) Animals were administered theanine solution 30 min before a sham-operation. (b and e) Animals were administered saline solution 30 min before ischemia. (c and f) Animals were administered 1 μL of 500 μM theanine 30 min before ischemia. Lower photographs show higher magnification of the CA1 field for each experimental group. The number of intact cells in the defined area was assessed. Ischemic neuronal destruction in the CA1 field was inhibited by theanine administration.

discharge of glutamate into the extracellular space and disorderly excitation of glutamate receptors. This serial process is called excitotoxicity. Likewise, glutamate is enormously important with respect to excitotoxicity but this process is very long-term, especially when compared to memory consolidation. The flow of Ca^{2+} ions into neurons activates various type of enzymes [44] and generates reactive oxygen species [45]. Such serial reactions are thought to cause neuronal cell death. Recently it has been suggested that this excitatory neuronal toxicity participates in neurodegenerative diseases such as Alzheimer's disease [46,47].

4.2. Antagonistic action of theanine on glutamate receptors

Theanine is a natural analog of glutamate (Fig. 1). Therefore, one of the mechanisms by which it exerts a neuroprotective effect on ischemic neuronal cell death is thought to be an antagonistic effect on ionotropic glutamate receptor subtypes, such as NMDA receptor, DL-α-amino-3-hydroxy-5-methylisoxazole-4-propioate (AMPA) receptor, and kainate receptor. Kakuda et al. [17] compared the inhibitory effects of theanine and glutamate on [^{3}H]AMPA, [^{3}H]kainate, and the NMDA glycine site antagonist [^{3}H]MDL 105,519 receptors. They found that theanine inhibited binding on AMPA, kainate, and NMDA receptor subtypes of radioactive ligands. However, although theanine bound the 3 receptors, the IC_{50} was 80- to 30,000-fold less than that of glutamate. Moreover, the binding activity of theanine on AMPA and kainate receptors was 10-fold higher than that on NMDA glycine receptor. The IC_{50} for the binding activity of theanine on AMPA receptor was approximately 10^{-5} M, which was 80-fold weaker than that of glutamate. Nevertheless, this activity might be pharmacologically significant. Sheardown et al. [48] reported that administration of an antagonist of AMPA receptor before and after ischemic loading resulted in pyramidal neuronal cell death in the hippocampal CAI region. Ischemic neuronal cell death is thought to involve not only NMDA receptors but also AMPA receptors. AMPA receptors regularly show high permeability to Na^+ ions but rarely show permeability to Ca^{2+} ions. However, the downregulation of *gluR2* gene expression and an increase in influx of Ca^{2+} ions through AMPA receptors in response to endogenous glutamate are likely to contribute to delayed neuronal cell death after global ischemia [49,50]. These results suggest that the antagonistic effect of theanine on AMPA receptors contributes to the prevention of neuronal cell death after cerebral ischemia.

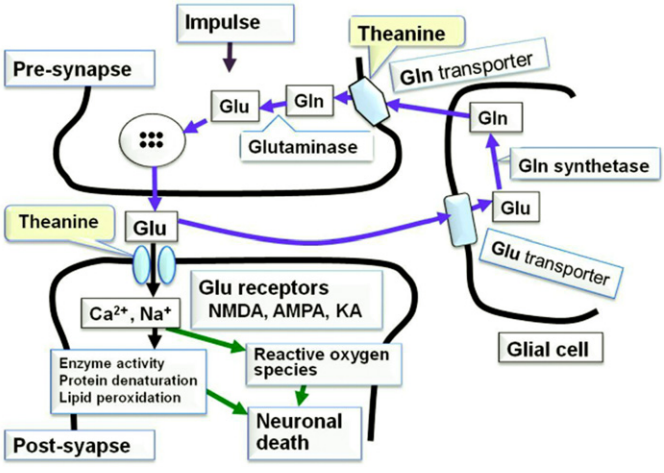

Fig. 3. Schematic representation. Theanine inhibits the incorporation of extracellular glutamine (Gln) into neurons. This suppresses the conversion of Gln to glutamate (Glu) by glutaminase, a reaction required for condensation into synaptic vesicles to form a neurotransmitter pool responsible for subsequent exocytotic release upon stimuli. Extracellular Glu is incorporated into adjacent astroglia through excitatory amino acid transporters (EAATs), whereas glutamine transporter (GlnT) mediates the import of extracellular Gln derived from synthesis by Gln synthetase enriched in astrocytes into neighboring neurons. Theanine also acted on Glu receptors [17], but the action of theanine on Gln transporter is stronger than that of Glu receptors.

4.3. Action of theanine on glutamine transporter

The mechanism by which theanine exerts a neuroprotective effect was initially thought to be solely due to the antagonistic effects of theanine on glutamate receptors (theanine is a structural analog of glutamate). However, as shown in Section 4.2, the affinity of theanine for ionotropic glutamate receptor subtypes is very low [17]. Kakuda et al. [18] studied the mechanism of action of theanine on a glutamate and Gln receptors. The brain was removed from the cranial cavity and homogenized for a short period, and the homogenate was centrifuged. The granule (synaptosome) of the nerve system postlude was broken off and the synaptosomal fraction obtained. In this study, [^{3}H]theanine was actively accumulated in a temperature-dependent and saturable manner in rat brain synaptosomal fractions. The accumulation of [^{3}H]theanine was

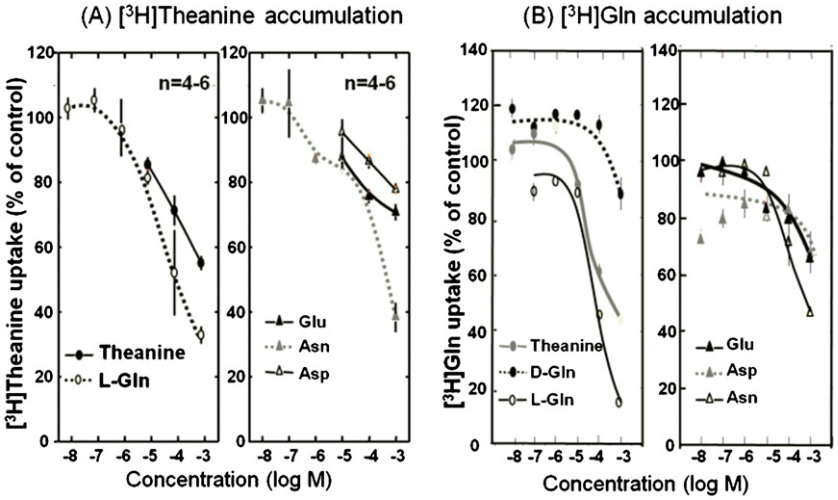

Fig. 4. Effect of structural analogs on accumulation of [^{3}H]theanine and [^{3}H]Gln in synaptosomal fractions [18]. Synaptosomal fractions were incubated with 1 μM [^{3}H]theanine (A) or 1 μM of [^{3}H]Gln (B) at 30 °C for 20 min in the presence or absence of a concentrations (10 nM to 1 mM) of L-theanine, L-Gln, D-Gln, Glu, aspartate (Asp) and asparagine (Asn). Values represent mean ± S.E. of 4–6 independent sets of experiments performed in triplicate.

markedly inhibited by Gln in a concentration-dependent manner (Fig. 4A left). Similarly, the accumulation of [^{3}H]Gln was inhibited by theanine in a concentration-dependent manner (Fig. 4B left). Kakuda et al. [18] then examined the accumulation of [^{3}H]Gln and [^{3}H]theanine in primary cultured neurons and astrocytes prepared from rat cerebral cortex, in place of synaptosomal fraction. They found that the accumulation of [^{3}H]Gln and [^{3}H]theanine increased almost linearly with incubation time, up to 20 min. Cultured neurons and astrocytes were incubated with [^{3}H]Gln in the presence or absence or a range of theanine concentrations (0.1–10 mM). In both cell cultures, addition of theanine induced a significant decrease in [^{3}H]Gln accumulation in a concentration-dependent manner (Fig. 5A and B). Cortex neurons were incubated for 3 days in the presence or the absence of 10 mM theanine, followed by collection of the culture medium for determination of glutamate. Sustained exposure to theanine resulted in a slight but statistically significant decrease in extracellular glutamate level in the cultured neurons (Fig. 5C). These results indicate that the exocytotic release of glutamate is suppressed by theanine. Glutamate released into the extracellular space is largely taken up into astrocytes via glutamate transporter and is synthesized into Gln by glutamine synthetase. This Gln is released into the extracellular space, where it is again taken up into glutamatergic neurons via Gln transporter and is hydrolyzed by means of the phosphate-activated glutaminase [51]. The glutamate is pooled in synaptic vesicles, thus forming a neurotransmitter pool in nerve terminals [51–53].

The prevailing view is that Gln exported to the extracellular space is taken up through Gln transporter expressed by neurons to fuel the glutamate/Gln cycle required for the neurotransmitter pool of glutamate at the nerve terminals in glutamatergic neurons. Theanine could at least partly alter extracellular Gln levels under the delicate control of Gln transporter expressed by astrocytes adjacent to the glutamatergic synapses in a particular pathological situation such as brain ischemia. This mechanism of action of theanine is thought to contribute to its protective effect on neuronal cell death by alleviating the action of the neuronal excitotoxin glutamate. Interestingly, Walton et al. [54] have suggested that alterations in glutamate neurotransmission and glutamate/Gln cycling contribute to Alzheimer's disease pathology and are probably major players in the propagation of neuronal destruction.

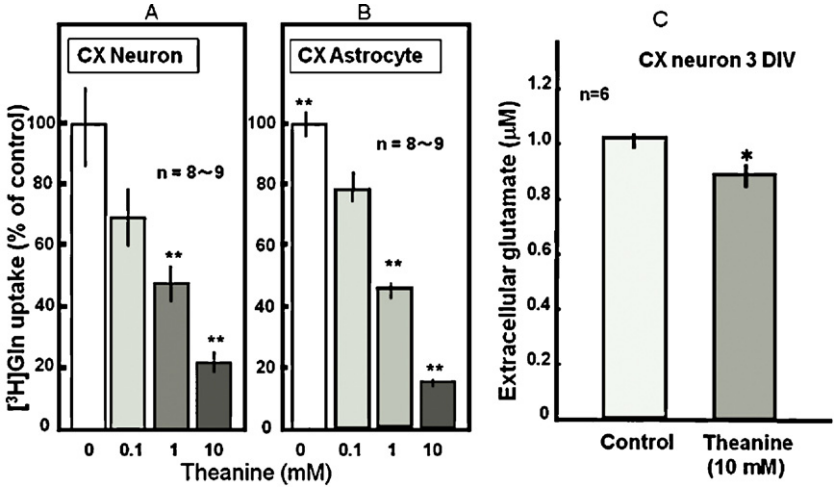

Fig. 5. Effects of theanine on [^{3}H]Gln accumulation and glutamate efflux [18]. (A and B) Cortex neurons and astrocytes were incubated with 1 μM [^{3}H]Gln at 30 °C for 20 min in the presence of a range of theanine concentrations (0.1–10 mM). (C) Cortex neurons were cultured for 3 days in the presence or absence of 10 mM theanine, followed by collection of the culture medium for determination of glutamate. Values represent mean ± S.E. of the separate measurements indicated. *$P < 0.05$ and **$P < 0.01$ indicate significant difference from control values obtained in the absence of theanine.

4.4. Similarity of action mechanisms of theanine and memantine for Alzheimer's disease

Recently, memantine [55,56] has been approved as a curative pharmaceutical for Alzheimer's disease. Memantine is an uncompetitive glutamate receptor subtype NMDA receptor antagonist [56] and has a preventive effect on glutamate toxicity. Although, theanine also inhibits glutamate toxicity by acting on glutamate receptor subtype AMPA, kainate receptor, and NMDA receptor, its affinity is very low. It has been suggested that theanine at least partly alters extracellular Gln levels under the delicate control of Gln transporter expressed by neurons to fuel the glutamate/Gln cycle required for the neurotransmitter pool of glutamate at the nerve terminals in glutamatergic neurons. Moreover, this may contribute to the neuroprotective action of theanine on cerebral ischemia. These views suggest that theanine is useful as a curative pharmaceutical for Alzheimer's disease because of its preventive effects on glutamate toxicity.

4.5. Action of theanine on neurogenesis

The production of neurons is largely confined to the prenatal period in most regions of the mammalian brain. However, neurogenesis occurs in a limited region such as the hippocampal dentate gyrus [57,58]. Several developments finally established neurogenesis in the adult rodent, including the introduction of the thymidine analog bromodeoxyuridine (BrdU), a marker of DNA synthesis that labels proliferating cells and their progeny [59,60]. In the 1960s, studies were conducted using the newly introduced methods of ^{3}H-thymidine autoradiography, in which ^{3}H-thymidine is taken up by cells undergoing DNA synthesis in preparation for mitosis, and can thus be used as a marker for proliferating cells and their progeny. Exposure to stressful experience decreased the number of new neurons in the dentate gyrus. Exposure to predator odor in adult rats and to social stress in tree shrews and marmots inhibited the proliferation of granule cell precursors in the dentate gyrus [61].

Abe et al. [62] investigated the effect of theanine on neurogenesis in the hippocampal dentate gyrus. When mice were exposed to psychosocial stressful conditions, the number of clusters of BrdU-positive cells decreased. However, when theanine was administered mice before and after stress exposure, the number of clusters of BrdU-positive cells was restored. These results suggested that theanine promotes neurogenesis. Abe et al. [62] also reported an increase in the reduction ability of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT), an index of cell proliferation ability and survival ratio, following exposure of rat cerebral cortex nerve system precursor cells to theanine. This suggests that theanine enhances the proliferative ability of nerve system precursor cells. These results further indicate that theanine can be used as part of neuronal regeneration therapy in neuron-denaturalized disease, such as Alzheimer's disease.

4.6. Summary of mechanisms

The mechanisms of underlying of neuroprotective effects of theanine were summarized as follows. (1) Possible post-synaptic receptor antagonist action is rather weak (Fig. 3). (2) Possible presynaptic action to reduce glutamate release into the synaptic cleft by acting glutamine transporter is strong (Fig. 3). (3) Possible effect on neurogenesis either to promote cell proliferation and/or to promote cell survival is suggested, but this action mechanism need study more.

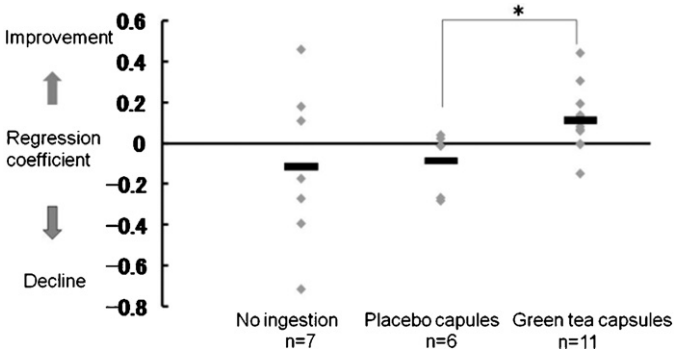

Fig. 6. Regression coefficients of HDS-R scores over 12 months for individual subjects in 3 groups (no ingestion, placebo capsules, and PGTH-theanine capsules) [21]. Regression coefficient for each subject (●) and average regression coefficient for each group (—). *$P < 0.05$ vs. placebo capsules (Student's t-test).

5. Preventive effects of theanine on cognitive dysfunction in aged person

Given the neuroprotective effects of theanine on neuronal cell death after cerebral ischemia such as stroke, the preventive effects of theanine on vascular dementia in aged persons were investigated. Kataoka et al. [21] reported that the cognitive dysfunction of aged volunteers improved following consumption of powdered green tea containing a high theanine concentration (PGTH-theanine). The effects of long-term ingestion of PGTH-theanine on cognitive dysfunction was studied in 29 volunteers (average age, 85 years), each with a score of >20 on the Hasegawa's Dementia Scale-Revised (HDS-R) score [63]. Green tea leaves containing 2.33% (w/w) of theanine and 7.95% (w/w) of catechins were used. The green tea leaves were powdered like a Matscha tea (using tea ceremony), mixed with cornstarch at a ratio of 1:5, and encapsulated in size-2 capsules, each containing 170 mg of PGTH-theanine. As a placebo, cornstarch containing 25% (w/w) low-grade powdered green tea (to match the color) was used. The volunteers were instructed to take 4 capsules, 3 times per day, after breakfast, lunch, and dinner, for 12 months. Thus, a total of 12 capsules (2040 mg day^{-1} of PGTH-theanine, equivalent to 47.5 mg day^{-1} theanine and caffeine 64.8 mg day^{-1}) were ingested. The HDS-R score was examined for all 3 groups, every month, and changes in cognitive dysfunction were analyzed. Compared to the placebo group, the PGTH-theanine group had a significantly higher HDS-R score from the 7th month, except in the 11th month. For each group, the mean HDS-R score gradient during the 12-month test period was examined by plotting the mean HDS-R score for each month.

The gradients of the non-intake and placebo groups had negative values (−0.087 and −0.116, respectively). In contrast, the gradient of the PGTH-theanine group had a positive value of (0.119). The HDS-R score gradient was also calculated for each volunteer for the 12-month test period, and the mean value in each group was plotted. The mean value in the PGTH-theanine group was significantly higher than that in the placebo group (Fig. 6). The results suggest that decline in the HDS-R scores of aged volunteers was prevented following ingestion of PGTH-theanine over a prolonged period. This, in turn, suggests a preventive effect of PGTH-theanine on senile dementia which is caused by ischemia with cerebrovascular accidents such as stroke. On the other hand, Yamada et al. reported that theanine-fed rats showed improved recognition, and that theanine affected learning and memory [64]. This report showed that theanine related to memory. From these results, slight improvement of cognitive dysfunction in part of aged persons might be suggested by long term ingestion of theanine, but we need study more in detail.

The PGTH-theanine used in this study contained 2.33% (w/w) of theanine, which is more than twice concentration of theanine contained in regular green tea. The volunteers ingested 2040 mg day^{-1} of PGTH-theanine (equivalent to 47.5 mg day^{-1} of theanine). This is higher than the theanine intake from regular green tea. On the other hand, the consumption of powdered green tea at a tea ceremony is approximately 1000 mg per person, and the theanine intake a single cup of common powdered green tea is estimated to be approximately 35 mg. Therefore, 47.5 mg day^{-1} of theanine used in this study is higher concentration than that of regular ingestion.

The PGTH-theanine used in this study contained 7.95% (w/w) of catechins, resulting in a catechin consumption of approximately 162.1 mg day^{-1}. Given that regular green tea leaves contain approximately 15% (w/w) of catechins, a catechin ingestion of approximately 200 mg per cup is common. Therefore, the ingestion of catechins from the PGTH-theanine used in this study was slightly lower than from regular green tea. However, the PGTH-theanine was ingested periodically 3 times per day for 12 months. Thus, it is likely that the preventive effects of lowering the HDS-R score can be attributed not only to theanine but also to the synergistic action of catechins. It has been reported that a substantial proportion of ingested catechins is absorbed via the intestines [65,66], with a small amount detected in the brain [66,67]. Although it is questionable weather phenolic compounds such as catechins pass through the blood–brain barrier, the protective effects of catechins against neuronal damage after ischemia have been documented [68–70]. On the other hand, Unno et al. reported that catechins had a radical scavenging effect [71]. Reactive oxygen species are increased by MCA occlusion in the rat and by various types of central nerve pathological conditions [72]. Thus, the radical scavenging activity of catechins might be useful for preventing neuronal cell death. Kuriyama et al. [13] reported that a higher consumption of green tea was associated with a lower prevalence of cognitive impairment in humans in Tsurugaya project. This agrees with the findings of Kataoka et al. [21] that ingestion of PGTH-theanine or high theanine over a prolonged period may have a preventive effect on senile dementia.

6. Conclusion

Orally administered theanine, an ingredient of green tea leaves, is easily absorbed via the intestines and a small amount is transported to the brain through the blood–brain barrier. The theanine acts directly on the central nervous system and shows neuroprotective effects by inhibiting neuronal cell death after cerebral ischemia such as stroke. Although these neuroprotective effects were partly due to the antagonistic action of theanine on ionotropic glutamate receptor subtype AMPA and kainate receptor, the affinity was very low. It is thought that theanine can partly alter extracellular Gln levels under the control of Gln transporter expressed by astrocytes adjacent to glutamatergic synapses in a particular pathological situation such as brain ischemia. The action of theanine on Gln transporter is stronger than that on glutamate receptors. Theanine was also shown to have a promoting effect on neurogenesis. Decline in the HDS-R scores of aged volunteers was prevented following ingestion of PGTH-theanine every day for 12 months. The effects of theanine were very mild compared with those of pharmaceuticals, and daily consumption led to very few side effects. Thus, there is potential for theanine to be used not only for acute therapy clinically but also for the prevention of cognitive dysfunction and/or dementia. Green tea contains more than 10% (w/w) of catechins, which are expected to exert synergistic effects. Eight years ago, Kakuda reviewed the biological activity of theanine, an ingredient of green tea [73], and thereafter many studies of as reviewed herein have elucidated the neuroprotective effects of theanine.

The chemical content of tea leaves varies considerably according to variety and/or cultivation method. In Japan, the functionalities of tea chemical compounds have recently been elucidated and developed for foods for specified health uses (FOSHU). It is anticipated that In the future, theanine will find further application as a FOSHU and pharmaceuticals for preventing cognitive dysfunction and/or dementia.

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