

Brain Senescence and Neuroprotective Dietary Components

Keiko Unno* and Minoru Hoshino

Laboratory of Bioorganic Chemistry, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan

Abstract: Senescence is an ageing process characterized by progressive and irreversible dysfunction of various physiological systems. Physiological senescence with advancing age is not a disease, but it affects the life-span and life-quality of elderly people. Brain functions such as cognition and motor skills, as with other organ systems, are impaired in almost all elderly people. Neuroprotective dietary components can play a key role in ensuring healthy ageing of the brain. Although the causative mechanisms of senescence are complex and not yet fully elucidated, enhanced oxidative stress is thought to be an important contributor. Dietary antioxidants from fruits and vegetables have preventative effects on oxidative stress. Catechin, a polyphenol found in green tea, has a potent antioxidative effect. Recently, catechin has been reported to protect against reduced ageing-related cognitive functions such as those associated with learning and memory, and ischemic brain damage. Catechin may act as a neuroprotective agent in progressive neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. The neuroprotective effects and putative mechanisms of action of catechin and other antioxidants are examined and discussed in this review.

Keywords: Antioxidant, brain, green tea catechin, learning & memory, oxidative damage, senescence.

INTRODUCTION

The proportion of elderly people in the population is increasing in many countries. Ageing is an important risk factor for diseases such as cancer, cardiovascular-related disorders, diabetes and dementia. Furthermore, almost all elderly people show brain atrophy and cognitive dysfunction, even if they exhibit no distinct pathology. Since the maximum longevity and number of cell divisions are fixed in each organism, the process of ageing is, to a large degree, programmed. However, the level of brain regression among age-matched people varies, suggesting that brain senescence may be prevented or delayed by improvements or alterations in life-style.

Although the factors and mechanisms underlying senescence and neurodegenerative disease involved are complex, and include both genetic and environmental factors, enhanced oxidative stress has been proposed to play a major role in both processes [for example, see 1-4]. The brain is highly susceptible to oxidative damage because it consumes a large amount of oxygen and generates an abundance of free radicals as normal products of cellular metabolism [5-7]. In aged organisms, the defense response against reactive oxygen species associated with oxidative damage may decline or become defective. Oxidative damage is thought to be a cause of age-related decline in learning and memory [8]. In addition, several conditions involving age-related brain dysfunction, such as Alzheimer's (AD) and Parkinson's disease (PD), involve oxidative damage. Thus, prevention of oxidative damage to the brain is likely to be beneficial for the maintenance of cognitive function.

Neuroprotective dietary components have an essential role in facilitating healthy ageing of the brain [9, 10]. Dietary antioxidants from fruits and vegetables have preventative effects on oxidative stress [11-16]. Green tea catechin (GT-catechin) is a mixture of plant polyphenols that have potent antioxidative and radical-scavenging activities [17-21]. In this respect, it is important to determine whether antioxidants derived from nutritional sources have preventive and/or therapeutic effects on declining learning and memory functions and neurodegenerative disorders. The effect of dietary supplements may occur directly in the brain. To understand the neuroprotective function of dietary antioxidants, we focused on the properties of GT-catechin, including its antioxidative and radical scavenging activities, distribution and metabolism, and alterations in brain senescence and neurodegenerative state. In addition, other dietary components that may be effective for altering brain senescence are described.

1. GREEN TEA CATECHINS

GT-catechin, a polyphenol, is the main component of green tea, and has a bitter and astringent taste. In Japanese green tea, the average content is about 10-20%, although this varies with season, location and growing condition. When green tea (5-10 g) is extracted with 100 ml of hot water, the content of catechins is about 60 mg, or ~30-40% of the dried extract. GT catechin consists mainly of (-)-epigallocatechin gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG) and (-)-epicatechin (EC; Fig. 1). The catechin content of black tea is lower, ranging from 3-10%, but it has a higher content of theaflavins and other polyphenols.

1.1. Antioxidative and Radical Scavenging Activities

GT-catechin has strong antioxidative and radical scavenging activities. Such activity is dependent on the position

*Address correspondence to this author at the Laboratory of Bioorganic Chemistry, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Shizuoka, Japan; Tel: +81-54-264-5731; Fax: +81-54-264-5909; E-mail: unno@u-shizuoka-ken.ac.jp

(*o*-, *m*-, *p*-) of the diphenol hydroxyl group. The compounds that have neighboring hydroxyl groups have higher antioxidative activity. When measured using an oxygen electrode [22], the antioxidative activity of EGCG is higher than those of other GT-catechins (EGCG>ECG>EGC>>EC), with the activity being dependent on the number of hydroxyl groups in the compound. Green tea solutions have antioxidative activity comparable to, or higher than, that of EGCG. The antioxidative activities of GT-catechin are affected by pH and metal ions. GT-catechin has peak activity at pH 6-12. Cu^{2+} and Mn^{2+} increased the antioxidative activity of EGCG, whilst Fe^{2+} has an inhibitory effect [23]. Iron preferentially binds to the gallate group of EGCG and ECG, with binding destabilizing the formation of the phenoxyl radical formed from the hydroxyl group in the gallo-catechin of EGCG and ECG.

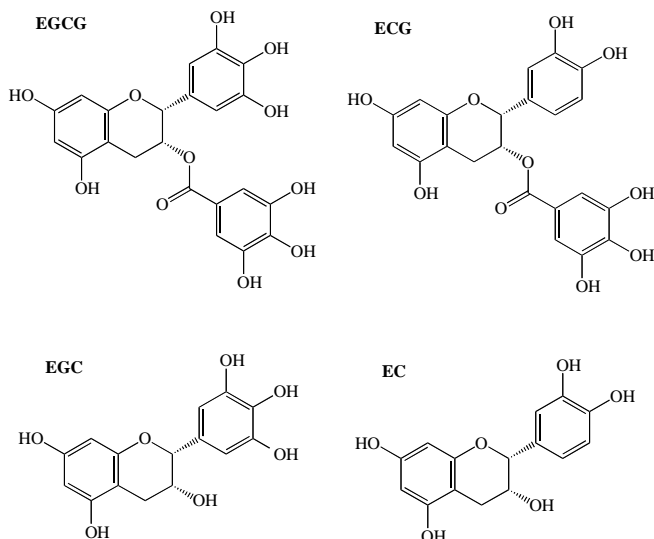


Fig. (1). Structure of green tea catechins.

The scavenging rates of GT-catechin are altered by free radicals in a complex reaction. For example, the reaction rates ($\text{M}^{-1}\text{s}^{-1}$) of GT-catechins are in the order of 10^9 with hydroxyl radical, 10^5 with superoxide anion, and 10^3 with 1,1-diphenyl-2-picrylhydrazyl (DPPH), respectively [24]. The reaction rate of EGCG with hydroxyl radical is 7 times higher than that of EC. One molecule of EGCG scavenges 14 molecules of DPPH [25]. When scavenging activity (1 g of dry weight eluted from water and dimethyl sulfoxide) is compared using a fluorescent probe and superoxide anion generator, the activity of green tea against DPPH is ~20-fold higher, and the activity against superoxide anion (O_2^-) ~20-30 times higher than those of blueberry and strawberry [26].

1.2. Distribution and Metabolism

EGCG administered orally is rapidly absorbed, and is distributed mainly into the liver, plasma and mucous membranes of the small intestine [27]. EGCG distributed in plasma has been calculated to be ~2% of consumed EGCG. Using chemiluminescence-detection HPLC, after 1 h administration, the level of EGCG in brain is detectable at a low level [27]. Using [^3H]-EGCG dosing in mice, after a 6 h interval, a second equal administration enhances the level of

radioactivity in blood, brain, liver (and in several other tissues), at 4-6 times above those after a single administration [28]. This suggests that frequent consumption of green tea enables the body to maintain a high-level of GT-catechin. Another study of metabolic fate in rats using [^3H] EGCG found that radioactivity peaked at 24 h in blood, brain and other tissues, with EGCG degradation products being conjugated with glucuronide in the intestine [29]. Therefore, while the level of GT-catechin in the brain may low after the initial administration of green tea, multiple administrations may increase these levels. Furthermore, the distribution of GT-catechin metabolites may be an important indicator of antioxidant activity. The glucuronide conjugates exhibit high antioxidative activity [30, 31]. Measurement of the antioxidative and physiological activity of other metabolites, such as those conjugated to sulfate, or methylated or hydrated may be a useful index of such activity. Further detailed analysis of the distribution of EGCG and its metabolites in brain would be helpful to clarify the potential neural effects of GT-catechin and its metabolites.

2. IMPROVEMENT OF BRAIN ATROPHY AND FUNCTION BY GT-CATECHIN

To investigate the complex mechanisms underlying brain senescence, a suitable animal model is required. We investigated the influence of GT-catechin intake on brain function, cerebral atrophy and oxidative damage in mice with accelerated senescence (SAMP10). SAMP10 is a useful mouse model of brain senescence, as such mice are an inbred strain having cerebral atrophy and decreased memory and learning abilities, due to neuronal loss in later life [32-34].

2.1. Cerebral Atrophy in Aged SAMP10 Mice

Experimental mice had free access to a normal diet (CE-2; Clea Co Ltd, Tokyo, Japan) and tap water containing 0.02% GT-catechin (Polyphenon 70S, Mitsui Norin Co Ltd, Tokyo, Japan) from the age of 1 month. Polyphenon 70S contains above 70% GT-catechin analyzed as below. The GT-catechin consists of 31.7% EGCG, 15.7% ECG, 10.0% EGC, 8.5% EC, 4.5% (-)-gallocatechin gallate, and 1.0% (-)-catechin gallate. The remaining portion consists of other catechins from green tea and no caffeine. Each mouse consumed 5-15 ml of 0.02% catechin water per day. The mean dose of GT-catechin was calculated to be ~35 mg/day/kg. The mean body weight of mice fed catechin water was not significantly different from age-matched controls. However, the cerebral weight of 12-month-old control mice was significantly lower than that of those at 6 months. Interestingly, the cerebral atrophy was significantly suppressed in 12-month-old mice that had been fed GT-catechin water [35].

2.2 Memory Acquisition and Retention Test

We also tested the effects of GT-catechin on memory acquisition and retention using a step-through passive-avoidance task on SAMP10 mice. When a mouse entered a dark chamber from an illuminated one, the door was closed and an electric foot shock delivered at 0.5 mA for 1 s. Acquisition of the avoidance response was judged successful if the mouse remained in the illuminated chamber for 300 s. The trial was repeated until the mouse satisfied the acquisi-

tion criterion within five trials. The time required for learning in 11-month-old control SAMP10 mice was significantly longer than that for younger animals. However, the learning time significantly improved in 11-month-old SAMP10 mice that had received GT-catechin water [35].

One month later, mice were further examined to see whether they would remain in the illuminated chamber for 300 s. Many of the 6-month-old mice succeeded in remembering the avoidance response, although some of the 12- and 15-month-old mice entered the dark chamber. Aged mice that had been fed GT-catechin had a significantly lower failure ratio compared to age-matched controls (Fig. 2) [36]. Thus, memory was better maintained in the aged SAMP10 mice given catechin water.

In humans, epidemiological studies show that a higher consumption of green tea is associated with a reduced prevalence of cognitive impairment [37]. In contrast, a weak or null relation between consumption of black or oolong tea or coffee and cognitive impairment has been described. These results from mice and human studies suggest that a higher consumption of green tea may attenuate brain senescence.

2.3. Oxidative Damage and Endogenous Antioxidative Activity

The level of oxidative damage in aged brain associated with suppression of brain senescence by consumption of GT-catechin was investigated in SAMP10 mice. Oxidative damage to DNA was quantitated by measuring levels of the marker 8-oxodoxyguanosine in the cerebrum. There was significantly more oxidative damage in 15-month-old mice than 2-month-old mice [36]. However, in age-matched SAMP10 mice fed GT-catechin water, the level of oxidative damage to DNA was suppressed. In addition, the level of serum antioxidant activity in SAMP10 mice was also re-

duced with ageing, being significantly lower in 15-month-old SAMP10 mice than in 2-month-old SAMP10 mice [36]. The levels in aged mice fed GT-catechin were significantly higher than controls. Various antioxidants in blood plasma, such as ascorbic acid, albumin, bilirubin, and uric acid, are supplied via the circulation to tissues, where they suppress oxidative damage. GT-catechin in plasma might be preferentially metabolized over other antioxidants, resulting in increased antioxidative activity, as was found in the serum of the mice fed GT-catechin. In humans, continuous intake of GT-catechin has been reported to increase plasma antioxidant activity [38].

To evaluate the cerebro-protective effect of GT-catechin in ischemia, 0.5% GT-catechin was given to rats in drinking water from 5 days prior to transient middle cerebral artery occlusion [39]. GT-catechin reduced the brain infarct area and volume, inducible nitric oxide synthase expression, infiltration of neutrophils and formation of peroxynitrite. This effect of GT-catechin was postulated to occur via the scavenging properties of oxygen radicals and inhibition of nuclear factors that are regulated by the intracellular redox-state. In aged rats in which oxidative stress was induced by chronic ethanol consumption, administration of GT-catechin protected lipid and proteins against oxidative modifications in the brain [40]. They showed that GT-catechin prevented changes in antioxidant enzymes and ethanol-induced antioxidant products, which were enhanced with ageing. In brain, GT-catechin (2 mg/kg) induced the activity of superoxide dismutase (SOD) and catalase [41]. The decreased activity of glutathion peroxidase was improved in cerebral cortex of aged SAMP10 mice fed GT-catechin water [42]. Furthermore, the neuroprotective activity of EGCG may directly exert its effects as a free radical scavenger in neurons, although EGCG significantly inhibited NF-kappa B activation in T cells [43]. These data suggest that antioxidative

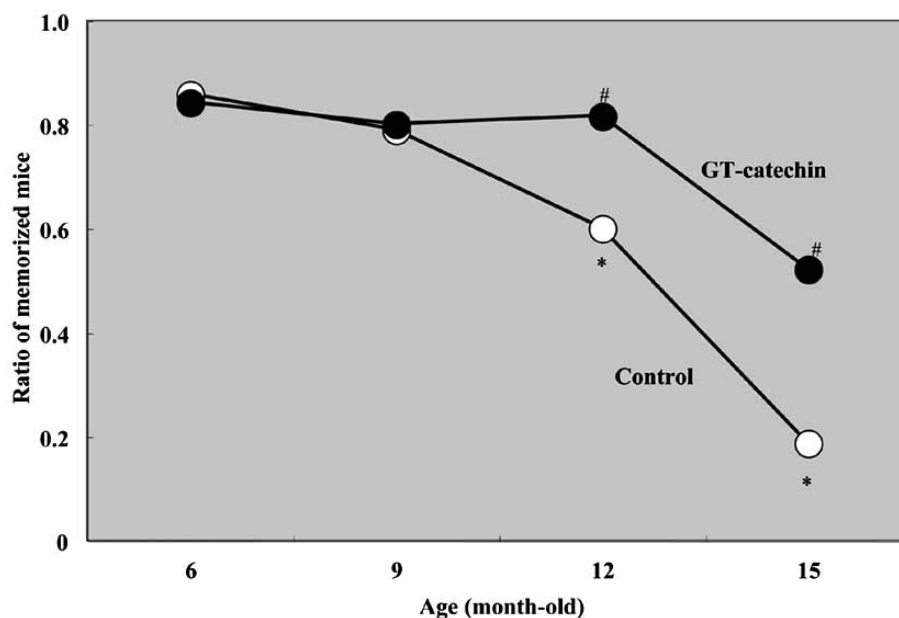


Fig. (2). GT-catechin consumption improves memory regression in aged mice.

GT-catechin consumption represents mean \pm SEM ($n = 15-23$). Asterisk (*) and sharp (#) represent significant difference between young control and age-matched control, respectively ($P < 0.05$, Fisher exact test).

activity of GT-catechin and enhanced levels of endogenous antioxidative enzymes and antioxidants may be critical for the suppression of brain senescence and injury. A recent study using the longest-living rodent, the naked mole-rat, suggested that maintenance of constant antioxidant defenses with age delayed aging in this species [44]. To maintain antioxidative defenses constantly, supplement of exogenous antioxidants such as GT-catechin might be a reasonable strategy.

3. EFFECT OF GT-CATECHIN AS A MODULATOR OF CELLULAR RESPONSE

Potent antioxidative activity does not appear to explain all of the effects of GT-catechin. EGCG possesses iron-chelating activity [45]. Metal ions accumulate in the brain with ageing and in several neurodegenerative diseases such as AD, PD and Wilson's diseases. For example, with hydrogen peroxide, redox-active iron (Fe^{2+} , iron (II)) has the potential to produce a highly reactive hydroxyl radical (Fenton reaction); implicating iron as a candidate mediating oxidative stress in AD and PD. In human neuroblastoma cells, EGCG modulates iron metabolism-related proteins such as amyloid precursor protein (APP) and transferrin receptor. Furthermore, EGCG reduced toxic β -amyloid ($\text{A}\beta$) peptide generation in Chinese hamster ovary cells overexpressing the APP 'Swedish' mutation. EGCG may also affect metal homeostasis in brain via metal-chelating and radical scavenging properties.

EGCG has been found to modulate protein kinase C and, as a consequence, to increase secretion of soluble amyloid precursor protein (sAPP) [46]. Furthermore, Rezaei-Zadeh et al. show that EGCG modulated APP cleavage and reduced cerebral amyloidosis in AD transgenic mice [47]. When EGCG was administered intraperitoneally (20 mg/kg, 60 days) or intracerebroventricularly to the transgenic mice, a reduction in cerebral detergent soluble $\text{A}\beta$ and elevated activity of alpha-secretase was found. Purified EGCG was more capable of reducing $\text{A}\beta$ generation *in vitro* than when it was present in a mixture in whole green tea extract. The oral dose level in humans and the effect of chronic administration of EGCG require investigation; with the possibility of effective prophylaxis for AD potentially being provided by EGCG supplementation.

A receptor that mediates the anticancer activity of EGCG has recently been identified [48]. The receptor, 67-kDa laminin receptor, has been expressed in a variety of tumor cells. In addition, a possible role for the receptor in suppressive EGCG effects on IgE-mediated allergic reaction has been suggested [49]. The receptor did not bind to other GT-catechin such as EGC and EC. Although it has not been clarified whether a specific receptor for GT-catechin is present in neurons or glial cells, these results suggest that GT-catechin-mediated effects may occur via various signal transduction mechanisms, via a specific receptor or target.

4. ANTIOXIDATIVE ACTIVITY OF FRUITS, VEGETABLES AND HERBS

Nutritional antioxidants, such as the polyphenols found in fruits and vegetables, can reverse age-related decline in neuronal signal transduction, cognitive and motor deficits.

One study determined both lipophilic and hydrophilic antioxidant activities of fruits, vegetables and other foods using the oxygen radical absorbance activity assay, with a fluorescent probe and peroxide radical generator [50]. Total antioxidant, lipophilic and hydrophilic antioxidant capacities, was found to be very high in cranberry, blueberry, plum, blackberry and raspberry. Furthermore, the total phenolic content of these foods and their contribution to total antioxidant capacity was evaluated.

In rats and mice fed a diet supplemented with spinach, strawberry or blueberry extracts, age-related deficits in neuronal and cognitive function were improved [51]. APP/presenilin-1 transgenic mice given a diet supplemented with 2% blueberry extract had increased cognitive performance in a Y-maze test, compared to mice given a control diet [52]. Using a bromodeoxyuridine assay, neurogenesis in the dentate gyrus was shown to be increased in aged rats fed a diet supplemented with blueberry extract [53]. Young rats exposed to oxidative stress using particles of high-energy and charge have been used as a model of accelerated ageing [54]. In these rats, a diet supplemented with 2% strawberry or blueberry extracts, resulted in improved spatial cognition in the water maze test. Blueberries contain high levels of proanthocyanidin (condensed tannin) and strawberries contain high levels of ellagitannins (hydrolysable tannins). The difference between polyphenols in these fruits may occur via their action in different brain regions.

Due to its strong antioxidative properties, the role of the herb garlic in prevention of age-related disease has been investigated [55, 56]. Garlic extract and its components showed a dose-related attenuation of reactive oxygen species activity and inhibition of brain damage caused by ischemia-reperfusion [57]. Importantly, garlic extract prevented brain atrophy and improved learning and memory in SAMP8 and SAMP10 mice [58, 59]. Recently, an ameliorative effect of garlic extract on amyloidogenicity and inflammation was reported using an AD double mutant mouse model [60].

In addition to the above, a number of studies have shown that fruits, vegetables and beverages have a beneficial effect on brain function. For example, beneficial effects of an apple-rich diet on SOD activity [61], grape seed extract on lipid peroxidation [62], and resveratrol, a red wine polyphenol, on ischemia-reperfusion injury [63], have been reported.

5. DIETARY RESTRICTION

Dietary restriction (DR) seems to be a little different from the intake of nutritional antioxidants, but the effect on brain may look like as a strategy for protection of brain from senescence. The beneficial effects of DR on brains have been supported by many reports [64-70]. Although the mechanisms of DR action remain unclear, one of the beneficial effects of DR on brain is thought to reduce in oxidative damage of brain proteins [71]. Poon *et al* showed that oxidative modification of proteins was decreased in all brain regions of aged rats restricted their foods when compared to those of the age-matched control. Based on proteomics analysis, they suggested that improved glutamate regulation, mitochondrial function and protein synthesis in aged brain by DR was, at least partially, due to the DR-mediated alteration of the oxidation or the expression of some proteins.

6. SUMMARY AND FUTURE DIRECTIONS

Senescence is an ageing process after maturity that is characterized by progressive and irreversible dysfunction of various physiological systems and the failure of homeostasis. Physiological senescence of the brain, which includes declining cognition and motor skills, affects the quality of life of many elderly people and represents an important socioeconomic problem. Much evidence has shown that various foods, such as fruits, vegetables, beverages and herbs can have potent antioxidative activities, that are beneficial for slowing brain regression associated with ageing. In particular, studies have shown that GT-catechin has excellent antioxidative properties. A GT-catechin dose of 35 mg/kg/day has antisenesence effects in SAMP10 mice; similar to that which would be achieved by a person drinking about 10 cups of green tea per day. If tea partly suppresses senescence, it represents a simple and beneficial anti-ageing method for many people. Blueberry, strawberry, and garlic also represent similar interesting simple interventions for improving brain function.

Multiple mechanisms are suggested to be involved in the preventative effect of GT-catechin. The most important target of GT-catechin in the brain likely occurs via an antioxidative process, although signal transduction, metal chelation or other related activities may also be involved. The investigations of GT-catechin metabolites and the detailed examination of their distribution in the brain would provide critical information on their mechanism of activity. Moreover, clarification of whether there is a critical target of GT-catechin, other than that associated with the antioxidative process, is an important field for further study. Recently, higher consumption of green tea was reported to associate with a lower prevalence of cognitive impairment by cross-sectional data from 1003 Japanese subjects aged above 70 years [37]. Epidemiological studies that span large populations will be important, since in both experimental animal models and humans the progression of senescence greatly differs among individuals. Dietary antioxidants promise to provide a key defense against senescence for health systems that must cope with an increasingly aging population.

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