

Daily consumption of green tea catechin delays memory regression in aged mice

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Abstract Almost all elderly people show brain atrophy and cognitive dysfunction, even if they are saved from illness, such as cardiac disease, malignancy and diabetes. Prevention or delay of brain senescence would therefore enhance the quality of life for older persons. Because oxidative stress has been implicated in brain senescence, we investigated the effects of green tea catechin (GT-catechin), a potential antioxidant, in senescence-accelerated (SAMP10) mice. The mouse is a model of brain senescence with short life span, cerebral atrophy and cognitive dysfunction. Mice were fed water containing 0.02% GT-catechin from 1- to 15-month-old. The mean

dose was about 35 mg/kg/day. We found that daily consumption of GT-catechin prevented memory regression and DNA oxidative damage in these mice. GT-catechin did not prolong the lifetime of SAMP10 mice, but it did delay brain senescence. These findings suggest that continued intake of GT-catechin might promote healthy ageing of the brain in older persons.

Keywords Brain · Oxidative damage · Senescence · SAMP10 · Green tea catechin · Atrophy · Learning · Memory

Introduction

The proportion of elderly people has been increasing in many countries. Physiological senescence, which includes declining cognition and motor skills, is not a disease but affects the quality of life of many elderly people. The atrophy of forebrain and hippocampus observed with ageing (Lye et al. 2004; Meguro et al. 2001; Rusinek et al. 2003; Ylikoski et al. 2000) may underlie impairments of learning and memory. Prevention of brain atrophy might therefore protect against the progressive degeneration of brain function. However, few animal models are available for the study of brain atrophy. The short life span of normal mice and rats (2–3 years) precludes significant brain atrophy.

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A mouse model with accelerated senescence, SAMP10, has short life span and neuronal loss in later life and is therefore useful for the study of cerebral atrophy and the resulting brain dysfunction (Shimada 1999; Shimada et al. 2002, 2003). Atrophy in the rhinencephalon and frontal cortex of SAMP10 mice occurs in a pattern with sufficient similarity to that in ageing human beings for it to be a suitable model for examining brain ageing and antisenesescence effects.

There are very different levels of brain regression among age-matched people. Although there are various complex influences, such as genetic background and environmental conditions (Arnaiz et al. 2004; Fernandez et al. 2004; Kachiwala et al. 2005), enhanced oxidative stress has been proposed to play a major role in senescence and in neurodegenerative diseases (for example, see Mariani et al. 2005; Navarro and Boveris 2004; Wang et al. 2005). The brain is highly susceptible to oxidative damage and generates an abundance of free radicals as normal products of cellular metabolism (Sanz et al. 2005; Serrano et al. 2004). Neuroprotective dietary components have an essential role in facilitating healthy ageing of the brain (Devi and Kiran 2004; Joseph et al. 2005). Dietary antioxidants from fruits and vegetables have preventative effects on oxidative stress (Bastianetto and Quirion 2002; Esposito et al. 2002; Galli et al. 2002; McDaniel et al. 2003; Schmitt-Schillig et al. 2005; Youdim et al. 2002). Green tea catechin (GT-catechin) is a mixture of plant polyphenols that have potent antioxidative and radical-scavenging activities (Kashima 1999; Kimura et al. 2002; Levites et al. 2001; Nanjo et al. 1999; Skrzydlewska et al. 2002; Suzuki et al. 2004; Terao 1999). GT catechin consists mainly of (–)-epigallocatechin gallate (EGCG), (–)-epigallocatechin (EGC), (–)-epicatechin gallate (ECG), and other catechins. In this study, we investigated the influence of GT-catechin intake on brain function and oxidative damage in SAMP10 mice.

Methods

Animals

All experimental protocols were approved by the University of Shizuoka Laboratory Animal Care

Advisory Committee. Male SAMP10/TaSlc (SAMP10) mice were purchased from Japan SLC Co. Ltd (Shizuoka, Japan) and bred under conventional conditions in a temperature- and humidity-controlled room with a 12-h light/dark cycle. SAMP10 is a senescence-prone inbred strain. Experimental mice had free access to a normal diet (CE-2; Clea Co. Ltd, Tokyo, Japan) and tap water containing 0.02% Polyphenon 70S (Mitsui Norin Co. Ltd, Tokyo, Japan) from the age of 1 month. Polyphenon 70S contains about 70% GT-catechin and no caffeine. The GT-catechin consists of 31.7% EGCG, 15.7% EGC, 10.0% ECG, 8.5% (–)-epicatechin, 4.5% (–)-gallocatechin gallate, and 1.0% (–)-catechin gallate. The remaining portion consists of other catechins from green tea. Catechin water was freshly prepared every third day. Control mice were given a normal diet and tap water without catechin.

Brain and blood samples

SAMP10 mice tasked both memory acquisition and retention tests were killed under ether and their brains were removed immediately. The whole brain and the cerebrum were weighed. Blood samples from the carotid artery and jugular vein were kept at room temperature for 30 min. Serum was obtained by centrifugation in a collection tube with gel/clot activator (Capiject, Terumo Medical Corporation, Somerset, NJ, USA) at 1200 g for 10 min. The brain and serum samples were immediately frozen in liquid N₂ and stored at –80 °C until the measurements were made.

Measurement of oxidative damage in DNA

The cerebrum was used for measurement of oxidative DNA damage. DNA was extracted under argon gas atmosphere as described by Kaneko et al. (1997). The DNA fraction was treated with nuclease P1 in 20 mM acetate buffer (pH 4.8) at 37 °C for 30 min and subsequently treated with alkaline phosphatase in 50 mM Tris-HCl (pH 7.4) at 37 °C for 1 h. The reaction mixture was filtered with Ultrafree-C3LGC (Millipore, Bedford, MA, USA). The nucleoside fraction was analysed by high-performance liquid chromatography with an ODS column. The ratio

of the peak area of 8-oxodG against that of deoxyguanosine (dG) was obtained. The amount of 8-oxodG was determined, and used as a measure of oxidative damage to DNA.

Memory acquisition test

A step-through passive avoidance task was carried out using mice of 8- and 14-month-old as described previously (Unno et al. 2004). In brief, when a mouse entered the dark chamber from the light one, the door was closed and an electric foot-shock was delivered at 0.5 mA for 1 s. Acquisition of the avoidance response was judged successful if the mouse remained in the light chamber for 300 s. The trial was repeated until the mouse satisfied the acquisition criterion within five trials. To estimate the difference between the mice that immediately entered the dark chamber and the mice that hesitated for almost 300 s, both the trial number and the time spent in the light chamber were recorded. For each trial, the time spent in the light chamber was subtracted from 300 s; this result from successive trials was summed for each mouse to give a measure of the time required for learning (learning time).

Memory retention test

This test was carried out as described previously (Unno et al. 2004). In briefly, mice underwent the second passive avoidance test on the next day after the first acquisition test described above. After 2 days of trials (maximum 10 trials), many mice retained the avoidance response for several months. One month later, mice of 9- and 15-month-old were again examined to see whether they would remain in the light chamber for 300 s. The number of mice that had satisfied the acquisition criterion (300 s) was recorded. After these memory acquisition and retention tests, each mouse was killed and its cerebral weight was measured.

Antioxidative activity in serum

Antioxidative activity in serum of 2–15 months mice was measured using the ferric reducing ability (FRAP) assay described by Benzie and

Strain (1996) and Erdogan et al. (2002), with some modifications. In brief, working FRAP reagent was prepared by mixing 10 volumes of 0.3 M acetate buffer (pH 3.6), one volume of 10 mM 2,4,6-tripyridyl-*s*-triazine (TPTZ) in 40 mM HCl, and one volume of 20 mM FeCl₃·6H₂O. Freshly prepared working FRAP reagent (750 µl) was mixed with 25 µl serum at room temperature. Exactly 10 min later, the absorbance at 593 nm was determined. Aqueous solutions of 100–1000 µM FeSO₄·7H₂O were used for calibration, with the 1.0 FRAP value defined as the absorbance equivalent to 1.0 mM FeSO₄·7H₂O.

Statistical analyses

Data are expressed as mean ± SEM. The effect of GT-catechin intake was determined by one-way analysis of variance followed by the Bonferroni *t*-test for multiple comparisons. The Fisher exact test was used to compare the effects of GT-catechin intake on memory retention and mortality.

Results

Effect of GT-catechin consumption on brain atrophy

Each mouse consumed between 5 and 15 ml of 0.02% catechin water per day. The mean dose of GT-catechin was therefore calculated to be about 35 mg/kg/day. The mean body weights of control mice of 2–15 months were compared with those of mice that were fed catechin water. The body weights were not significantly different from age-matched control (Table 1). As the brain atrophy was observed in aged mice, the cerebral weights

Table 1 Body weight of each aged SAMP10 mice

Age (month-old)	Body weight (g)	
	Control	GT-catechin
2	29.8 ± 0.3 (35)	28.6 ± 0.6 (7)
6	36.4 ± 0.7 (26)	35.3 ± 0.9 (24)
9	37.2 ± 0.9 (29)	38.0 ± 0.9 (24)
12	37.6 ± 0.9 (51)	39.5 ± 0.9 (52)
15	36.7 ± 0.7 (20)	39.8 ± 1.3 (22)

Each value represents mean ± SEM (n = 7–52)

of mice fed GT-catechin were compared with those of young and age-matched control mice. The cerebral weight significantly decreased in aged SAMP10 mice (Fig. 1). No effect was observed in 15-month-old mice that were fed GT-catechin water.

Suppression of DNA oxidative damage by GT-catechin consumption

The level of 8-oxodG in cerebrum was measured in SAMP10 mice ($n = 7–11$). That was represented as the molecule of 8-oxodG to 100,000 molecules of dG. The level in 15-month-old mice was significantly higher than that in 2-month-old mice (Table 2). However, in age-matched SAMP10 mice that were fed GT-catechin water the level was clearly suppressed. Oxidative damage in DNA was suppressed in aged mice that were fed GT-catechin water.

Improvement of brain function by GT-catechin

The learning time for the passive avoidance task was measured using 8- and 14-month-old mice ($n = 18–21$). That was 1.9 times longer than that of 8-month-old ones (990.2 ± 81.0 , 520.7 ± 66.2 ,

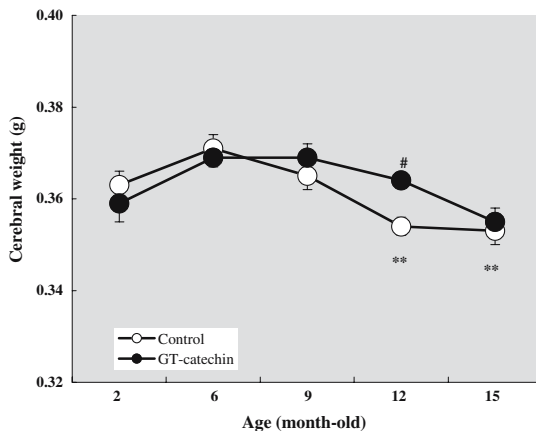


Fig. 1 Effect of GT-catechin consumption on brain atrophy in aged SAMP10. Each value represents mean \pm SEM ($n = 5–52$). Asterisk (*) and sharp (#) represent significant difference with control of 6-month-old and age-matched control, respectively (** $p < 0.0001$, # $p < 0.001$, Bonferroni t -test)

Table 2 Effect of GT-catechin intake on DNA oxidative damage

Age (Month-old)	8-oxodG/10 ⁵ dG	
	Control	GT-catechin
2	0.133 \pm 0.007 ($n = 18$)	0.135 \pm 0.008 ($n = 7$)
15	0.163 \pm 0.008* ($n = 9$)	0.122 \pm 0.008# ($n = 11$)

Each value represents mean \pm SEM. Asterisk (*) and sharp (#) represent significant difference with the young control and age-matched control, respectively (* $p < 0.05$, # $p < 0.05$, Bonferroni t -test)

respectively). No effect on learning time was observed in 14-month-old SAMP10 mice that were fed GT-catechin (995.2 ± 75.2).

One month after the passive avoidance task, mice were tested to determine whether they could remember the task. Control mice of 15-month-old retained less avoidance memory than that of 9-month-old (Table 3). The reduction of memory was significantly suppressed in age-matched mice that were fed GT-catechin water.

Antioxidative activity in serum

The levels of antioxidative activity in serum were measured in 2- to 15-month-old SAMP10 mice ($n = 5–18$). The levels were reduced with ageing and were significantly lower in 15-month-old SAMP10 mice than in 2-month-old SAMP10 mice (Fig. 2). The levels in aged mice that were fed GT-catechin were significantly higher in the mice that were fed GT-catechin than control.

Table 3 Improvement of memory regression by GT-catechin intake

Age (month old)	Avoidance ratio (memory)	
	Control	GT-catechin
9	0.789 ($n = 19$)	0.800 ($n = 15$)
15	0.187*** ($n = 16$)	0.522# ($n = 23$)

Asterisk (*) and sharp (#) represent significant difference with the young control and age-matched control, respectively (*** $p < 0.0005$, # $p < 0.05$, Fisher exact test)

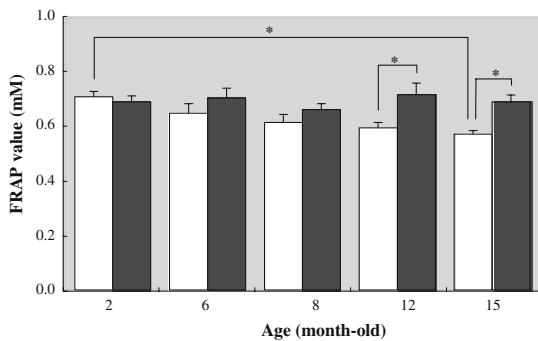


Fig. 2 Effect of GT-catechin on antioxidant power (FRAP) in the serum of SAMP10 mice. The antioxidative activity was measured using the FRAP assay in the mice that were fed GT-catechin (filled column) and in control mice (open column). Each value represents mean \pm SEM ($n = 4\text{--}18$). Asterisks represent significant differences ($*p < 0.05$, Bonferroni t -test)

Mortality of SAMP10

SAMP10 mice died sporadically after 5 month of age and almost all mice died before they were 18 months old. The maximum lifespan was 24-months. The mortality of SAMP10 mice was 33.3% at 15 months in both experimental animals and control ($n = 30$ and 36 , respectively).

Discussion

In the aged mice that were fed GT-catechin, senescence of brain function was delayed. The oxidative damage in DNA was apparently suppressed (Table 2), and memory was significantly retained in the 15-month-old mice that were fed catechin water (Table 3). Brain atrophy was significantly suppressed in 12-month-old of SAMP10 mice with GT-catechin feeding (Unno et al. 2004), although there was no effect was observed on the atrophy at 15-months of age. Neurons of mice with GT-catechin feeding might be less damaged than those of control mice, even if their numbers of neurons were similarly decreased. Lu et al. (2004) investigated gene regulation and DNA damage in the ageing human brain and proposed that protection of the genome early in adult life might influence the rate of subsequent functional decline and the vulnerability of the brain to age-related neurodegenerative diseases.

SAMP10 mice aged 15-months were earlier than average longevity (50% mortality). In the age-matched mice with GT-catechin feeding memory was significantly retained, suggesting that the continued consumption of GT-catechin is a potent strategy for suppression and delay of ageing early in adult life.

The antioxidative activity in serum was decreased with ageing in SAMP10 mice (Fig. 2). Various antioxidants in blood plasma, such as ascorbic acid, albumin, bilirubin, and uric acid, are supplied via the circulation to the tissues, where they suppress oxidative damage. GT-catechin incorporated into blood plasma is likely to be consumed instead of other antioxidants, resulting in raised antioxidative activity, as was found in the serum of the mice that were fed GT-catechin in this study. In addition, GT-catechin has been reported to distribute to brain (Nakagawa and Miyazawa 1997). GT-catechin and other antioxidants in the brain are believed to reduce oxidative damage. The changes in FRAP value were moderate in aged SAMP10 with GT-catechin feeding (Fig. 2). Accumulated effect however seemed to be significant for decreasing of oxidative damage, because the serum with increased antioxidative activity was always supplied in the brain. Antioxidative enzymes also act to reduce oxidative stress in the brain, and the improving effect of GT-catechin on an antioxidative enzyme was found (data not shown). GT-catechin intake for long term may have an important influence by improving oxidation–reduction balance.

Promoted apoptosis may be an important mechanism driving mammalian ageing (Kujoth et al. 2005). EGCG suppresses apoptosis in some types of cultured neurons (Choi et al. 2001; Koh et al. 2004). It is needed to investigate whether the suppressive effect of GT-catechin on brain atrophy is caused, in part, by inhibition of apoptosis. Moreover, EGCG has been reported to modulate amyloid precursor protein cleavage and reduce cerebral amyloidosis in Alzheimer transgenic mice (Rezai-Zadeh et al. 2005), so GT-catechin might also protect brain cells via mechanisms other than suppression of apoptosis.

The question remains as to whether oxidative stress in ageing and neurodegeneration is a primary cause or merely a downstream consequence

of the associated neuronal cell loss (Andersen 2004). Oxidative damage in DNA was significantly increased in SAMP10 of 15-month-old (Table 2), however, brain atrophy and dysfunction were observed in younger mice. Oxidized DNA might not be an important trigger of oxidative damage that would be related to brain atrophy and dysfunction. It remains to be interpreted how GT-catechin improve the memory, it at least appears likely that the daily consumption of GT-catechin inhibits oxidative stress and is capable of breaking the cycle of cell death that causes brain atrophy and dysfunction. The dose of GT-catechin (35 mg/kg/day) that showed an antisenescence effect in this study would be achieved by a person drinking between 1 and 2 l of green tea per day. As dose-dependency was not observed in 0.02–0.2% of GT-catechin on brain atrophy and dysfunction (data not shown), high dose would not be needed. It remains to examine whether lower level of GT-catechin is sufficient for delay of senescence. The findings of this study suggest that GT-catechin consumption would be associated with improvements in quality of life rather than an increase in longevity, a prospect that would be consistent with the expectations of healthy ageing held by most elderly people.

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