Green Tea Suppresses Brain Aging

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Contributor: Keiko Unno

Epidemiological studies have demonstrated that the intake of green tea is effective in reducing the risk of dementia. The most important component of green tea is epigallocatechin gallate (EGCG). Both EGCG and epigallocatechin (EGC) have been suggested to cross the blood–brain barrier to reach the brain parenchyma, but EGCG has been found to be more effective than EGC in promoting neuronal differentiation.

Keywords: arginine ; brain aging ; catechin ; epigallocatechin gallate ; green tea ; stress reduction ; theanine

1. Introduction

Since the aging population is growing worldwide, the prevention of brain aging is a universal problem. In Japan, in particular, the number of elderly people is increasing rapidly, with the highest percentage of elderly people in the world. According to data collected in 2012 by a research group from the Ministry of Health, Labor and Welfare of Japan, over 70% of women aged 95 years and over suffer from dementia. Similarly, over 50% of men aged 95 years and over suffer from dementia. Besides genetic factors, dementia is greatly affected by brain aging, environmental factors, and lifestyle-related factors. Improving these aspects and mitigating age-related changes are believed to help to delay the onset of dementia. With age, various changes, such as arteriosclerosis, climacteric disorder, diabetes, hyperlipidemia, kidney disease, hypertension, obesity, and poor memory, commonly occur. However, these age-related changes have reportedly been improved or counteracted in people who followed advice pertaining to exercise and diet [1]. Ingesting green tea is one such recommendation. In fact, green tea consumption has been epidemiologically shown to be inversely associated with both male and female heart disease mortality and male cerebrovascular and respiratory mortality [2]. In addition, there are accumulating reports that the ingestion of green tea is effective in preventing dementia [3][4][5][6][7]. In order to elucidate the effect of green tea, studies mainly focusing on the antioxidant effect of epigallocatechin gallate (EGCG) have been conducted in vivo and in vitro [8][9][10][11]. The effects of EGCG are often strong, but the effects of green tea cannot always be explained by the effects of EGCG alone. It is also necessary to investigate the interactions among other green tea components, such as caffeine, theanine, and arginine. In addition, the involvement of green tea metabolites must be studied too. Detailed studies have been conducted on the metabolites of green tea catechins [12][13][14], and research on their biological effects has been undertaken in recent years [15][16][17][18][19][20][21]. It should be noted that the metabolites produced by the gut microbiota have important effects on our health.

Theanine, the most abundant free amino acid in green tea, has been found to relieve stress and have a relaxing effect [22][23][24][25][26]. In addition, arginine, which is the second most abundant free amino acid in Japanese green tea, has an anti-stress effect similar to theanine [27][28]. However, since the stress-reducing effects of theanine and arginine are counteracted by EGCG and caffeine, the composition ratio of these components is important for the anti-stress effect of green tea [27][29]. Stress is deeply involved in the development and progression of many diseases, such as asthma, hypertension, peptic ulcers, obesity, and diabetes. The brain is also subjected to significant stress. Even healthy people undergo atrophy in the brain when they are repeatedly subjected to intense stress—for example, as a result of bereavement, job loss, accidents, or major natural disasters [30][31][32]. It has also been reported that brain atrophy occurs in abused children [33][34][35]. Furthermore, many people are more stressed than before due to the current coronavirus pandemic [36][37]. The stress-reducing effect of theanine and green tea is thought to contribute to the maintenance of mental health and the control of brain aging in many people.

In order to clarify the functionality of foods, we must examine the interactions among food components and the actions of metabolic decomposition products. In this review, we focus on the effects of green tea components—catechins, EGCG metabolites, theanine, and arginine—on brain function. In addition, we explain the anti-stress and anti-depressant effects of several types of green tea.

2. Catechins

The relationship between the intake of green tea catechins and lifespan was investigated using senescence-accelerated model mice, SAMP10/TaSlc (SAMP10), with a short lifespan. The median survival time (MST) was significantly prolonged when 1 mg/kg (equivalent to one cup of green tea per day in humans) was taken daily [38]. Even when 5 to 60 mg/kg of green tea catechins was taken, MST was prolonged, although not significantly, when compared with mice consuming no green tea catechins [38]. It thus seems important to drink several cups of green tea at least daily, but not to consume large amounts of catechins.

Green tea intake has been reported to prevent cognitive decline [3][4][39][40]. In experiments using SAMP10, we found that the daily ingestion of green tea catechins suppressed brain dysfunction in aged mice [41][42]. To clarify the effect of green tea catechins on the suppression of cognitive impairment with aging, the effect of the start time of green tea catechins intake was investigated in aged SAMP10 mice. Six- or nine-month-old SAMP10 mice began drinking water containing green tea catechins until they were 11 months old [43]. In SAMP10 mice, six and nine months of age are considered an adult and middle-aged, respectively. Mice that received green tea catechins from 6 to 11 months had significantly higher memory acquisition capacity, as examined by the passive avoidance trials, than control mice of the same age who did not consume green tea catechins. Consuming green tea catechins from 9 to 11 months also tended to improve learning ability. The daily ingestion of green tea catechins has been suggested to suppress brain dysfunction with aging. Additionally, even if ingestion started from middle age, this appeared to be more beneficial than not consuming it at all.

Next, the dose-dependency of the effect of green tea catechins on cognitive function was examined. A significant effect on memory acquisition was observed at 1 mg/kg or more of green tea catechins, as assessed by the passive avoidance test, and the most effective dose was observed to be 15 mg/kg [38]. Long-term memory retention was significantly higher in mice consuming green tea catechins daily at 60 mg/kg. Spatial working memory measured using a Y-maze was significantly increased in mice that ingested green tea catechins at 30 mg/kg and over [38]. In other words, green tea catechins' suppression of cognitive decline was dose-dependent, with a minimum required dose of 1 mg/kg in mice (equivalent to one cup of green tea in humans).

Since the transfer of catechins to the brain parenchyma is restricted by the BBB, the amount of catechins in the brain is considered to be lower than that in the periphery. The concentration-dependent effect of green tea catechins on cognitive function was observed in mice, but it was suggested that a daily intake of 1 mg/kg or more of green tea catechins suppresses age-related cognitive decline [38]. Epidemiological studies have also reported that a daily intake of one or several cups of green tea reduces the risk of dementia [3][4][44][39][40]. The quantity of catechins contained in green tea is generally around 70 mg/100 mL when eluted with hot water from tea leaves, and 30–50 mg/100 mL in commercially available bottles of green tea. Based on the BBB permeability of catechins, as discussed in Section 2.4 , the concentration of EGCG and its degradation products will presumably promote the differentiation of nerve cells when several cups of green tea, or approximately one bottle of catechins, are consumed. This may reduce the age-related decline in cognitive function.

3. Theanine and Arginine

The average survival time of SAMP10 mice was 17.6 ± 1.2 months under normal group housing conditions, which decreased significantly under confrontational housing conditions to 13.6 ± 1.5 months (**Figure 1**) [45]. Survival was reduced by three quarters due to stress loading. However, mice drinking water containing theanine (6 mg/kg) under the same stress-loading conditions showed a similar survival time to group-housed mice (17.9 ± 1.4 months). The longevity of group-housed mice was not prolonged by theanine intake, indicating that theanine suppresses the shortening of survival time by reducing stress. On the other hand, no shortening of lifespan due to stress load was observed in ddY mice. Individual differences in susceptibility to stress are well known, but it is not yet fully understood what causes these differences. SAMP10 and ddY mice may be suitable laboratory animals to assess differences in stress sensitivity.

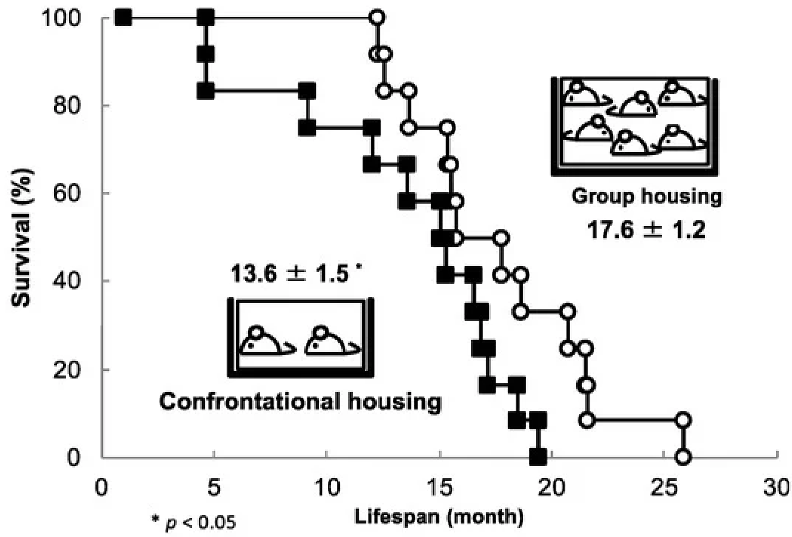

Figure 1. The effect of confrontational housing on the lifespan of SAMP10 mice. Mice were housed alone for one month before confrontational housing conditions were induced. Mice that died early were observed, and the maximum survival time was approximately 20 months (closed square). In contrast, group-housed control mice began to die at around 12 months of age, with a maximum survival time of 26 months (open circles) (n = 12) [45].

Both theanine and arginine have a stress-reducing effect, but there are differences in the major genes that they each target. Since many changes occur in organisms in response to stress loading, it is possible that there are various targets in stress reduction.

The relationship between stress and brain aging described in this section can be summarized as follows (**Figure 2**). In stress-vulnerable mice (SAMP10), brain atrophy was observed at least one month after stress loading, which then further progressed with aging, resulting in aging promotion (decreased brain function and shortened lifespan). On the other hand, in stress-resilient mice (ddY), the degree of atrophy in the brain due to the stress load was not significant; furthermore, this atrophy was recovered, and no effect on brain function or longevity was observed.

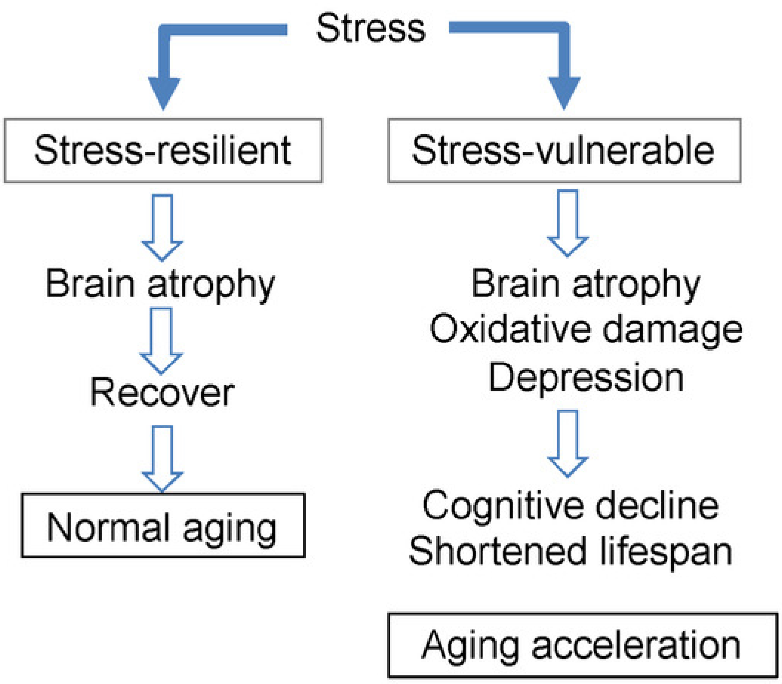

Figure 2. The relationship between stress and brain aging.

In SAMP10 mice given theanine, stress-induced atrophy in the brain subsequently recovered, though not completely. No atrophy was observed in ddY mice receiving theanine. In addition, mice ingesting theanine and arginine exhibited suppressed cognitive decline and lifespan shortening. Stress seems to cause neuroinflammation, oxidative stress, imbalances in excitation/suppression, and the suppression of neurogenesis in the brain. Although some of theanine and arginine's target genes have been identified in the early stages of stress loading, further research is needed to elucidate the effects of theanine and arginine on complex biological stress responses. Nevertheless, for those who are vulnerable to stress, theanine and arginine are probably essential substances.

4. Function of Green Tea

Green tea (Camellia sinensis (L.) O. Kuntze) is an unfermented tea that remains green via the rapid inactivation of enzymes during heating, such as polyphenol oxidase, and the prevented oxidation of the components. There are two main types of green tea [46]. One is Sencha, which is made from ordinary tea leaves and is rich in catechins. The other includes Gyokuro and Tencha, which are deprived of sunlight for approximately 20 days before harvesting. Shaded tea leaves have a high content of theanine because their metabolization into catechins is suppressed. The theanine content is higher in higher-grade green tea. Matcha tea is made by grinding Tencha into a fine powder with a stone mill. Catechins, caffeine, and amino acids containing theanine provide the taste components of astringency, bitterness, and umami, respectively. In addition, the balance of these ingredients affects the functionality of the tea.

The elution of caffeine and EGCG depends on the water temperature—their elution degree decreases in cold water—but amino acids and EGC are less affected by water temperature [47]. Therefore, low-caffeine green tea eluted with cold water has low levels of caffeine and EGCG and relatively high levels of theanine, arginine, and EGC. The mean value of each component of green tea used in clinical studies with participants in their 80s–90s is shown in **Table 1** .

Table 1. The content of caffeine, catechins, and amino acids in a solution of green tea.

Green Tea	Caffeine (mg/L)	Catechins (mg/L)								
		EGCG	EGC	ECG	EC	CG	(+) C	Total		
Standard	120	117	73.2	26.5	43.9	0.41	5.47	266		
Low -caffeine	37.2	64.7	145	10.7	53.8	0.26	4.13	278		
Green tea		Free amino acids (mg/L)								
	Theanine	Glu	Arg	Asp	Gln	Ser	Ala	Asn	GABA	Total
Standard	36.0	9.12	7.28	7.44	5.34	2.99	0.90	0.76	0.47	70.4
Low -caffeine	85.2	18.2	21.6	12.9	15.8	5.73	2.16	1.21	1.51	164

Low-caffeine green tea (20 g) was steeped in 2000 mL room-temperature water. Standard green tea (10 g) was steeped in 2000 mL boiling water. EGCG, (−) epigallocatechin gallate; EGC, (−) epigallocatechin; ECG, (−) epicatechin gallate; EC, (−) epicatechin; CG, (−) catechin gallate; (+) C, (+) catechin; Glu, glutamic acid; Arg, arginine; Asp, aspartic acid; Gln, glutamine; Ser, serine; Ala, alanine; Asn, asparagine; GABA, γ-amino butyric acid.

When a green tea plant is completely shaded for approximately two weeks, its levels of amino acids can be increased six- to seven-fold as compared with ordinary Sencha. The green tea produced in this way is called shaded white leaf tea (SWLT), and it is gaining interest as a green tea with a strong umami taste [48]. In SWLT, the theanine level is increased around 5-fold, and the arginine around 13-fold, compared to normal Sencha (**Table 2**); its CE/TA ratio is 1.12, thus suggesting a stress-reducing effect. However, no significant stress-reducing effect of this variety was observed in a clinical study [49].

Table 2. The caffeine, catechin, and amino acid contents in the eluate of SWLT and Sencha.

Tea	Caffeine (mg/L)	Catechins (mg/L)							
		EGCG	EGC	ECG	EC	GC	CG	(+) C	
SWLT	209.8	150.4	135.2	24.6	41.0	5.0	2.8	3.4	
Sencha	112.0	134.2	229.0	21.0	46.6	13.6	4.6	2.0	
Tea		Free amino acids (mg/L)							
	Theanine	Arg	Gln	Asn	Asp	Glu	Ser	GABA	Total
SWLT	140.2	69.9	51.7	33.8	33.5	19.3	12.6	0	361.0
Sencha	28.8	5.4	3.9	0.7	5.5	6.9	2.2	0	53.5

Shaded white leaf tea (SWLT) and Sencha green tea (3 g) were steeped in 500 mL room-temperature water for 3 h.

On the other hand, depressive behavior was significantly suppressed in mice ingesting SWLT for one month [49]. Depression is the most common mental illness, and stress is a major risk factor for it. Stress loads initially cause excitement, but chronic stress leads to depression. Therefore, in the context of long-term stress, a green tea that not only reduces stress but also alleviates depression is necessary. The intake of green tea has been reported to prevent depression, suggesting the involvement of caffeine and catechins [50]. For example, caffeine and EGCG have been reported to increase the expression of glutamate, a major excitatory neurotransmitter in the brain, while inhibiting GABA, an inhibitory neurotransmitter [51][52]. Balancing excitement and depression in the brain is considered to be very important for maintaining physical and mental health. In the near future, it will be possible to produce green tea with a CE/TA ratio suitable for improving depression in humans.

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