Alzheimer’s Disease

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Many observational and clinical studies have shown that consumption of diets rich in plant polyphenols have beneficial effects on various diseases such as cancer, obesity, diabetes, cardiovascular diseases, and neurodegenerative diseases (NDDs). Animal and cellular studies have indicated that these polyphenolic compounds contribute to such effects. The representative polyphenols are epigallocatechin-3-O-gallate in tea, chlorogenic acids in coffee, resveratrol in wine, and curcumin in curry. The results of human studies have suggested the beneficial effects of consumption of these foods on NDDs, espacially Alzheimer's disease and cellular animal experiments have provided molecular basis to indicate contribution of these representative polyphenols to these effects. This article provides updated information on the effects of these foods and their polyphenols on Alzheimer's disease with discussions on mechanistic aspects of their actions mainly based on the findings derived from basic experiments.

polyphenols NDD ROS

1. Introduction

The pathological hallmark of Alzheimer’s disease (AD) is the extracellular accumulation of amyloid plaques composed of fibrous amyloid. The proposed mechanisms for AD include microglia-triggered inflammation, over-activation of glutamate receptors, increased intracellular calcium levels, excessive generation of reactive oxygen species (ROS) and nitric oxide species, mitochondrial dysfunction, and synaptic dysfunction and loss [1]. Senile plaques are composed of β-amyloid (Aβ) peptides derived from β-amyloid precursor protein (APP) through sequential cleavages by β- and γ-secretase [2]. Accumulated deposition of the abnormal fibrous Aβ and phosphorylated tau (p-tau) proteins is one of the most characteristic features of AD that is associated with inflammation [3], elevated expression of pro-apoptotic proteins [1], and oxidative stress [4], which leads to neuronal cell dysfunction and death in the cerebral cortex [5]. Therefore, agents that suppress the formation of these biomarkers are thought to be useful for the prevention of AD [6]. APP can be cleaved by α-secretase within the Aβ domain to release soluble form of APPα (sAPPα) and preclude Aβ generation [7]. Agents that enhance α-secretase would have therapeutic potential in the treatment of AD.

2. Effects of Tea/EGCG on AD

2.1. Human Studies of Tea/EGCG on AD

Some studies have indicated that tea consumption is inversely associated with the risk of AD. For example, a cross-sectional survey of 2015 subjects aged 65 or older in Zhejiang province, China, found that the age-gender-standardized prevalence rates of dementia, AD, and vascular dementia were 13.0, 6.9, and 0.5%, respectively. Being elderly, low educational level, heavy smoking, heavy alcohol consumption, diabetes, and stroke were associated with dementia, whereas tea consumption was associated with a low prevalence of AD and severe cognitive impairment [8].

In contrast, several studies failed to show any beneficial effect of green tea on AD. For example, a cohort study on 2622 participants aged ≥75 with follow-up for over 10 years showed that higher green tea intake was not associated with incident AD or memory decline [9]. Kim et al. [10] conducted a meta-analysis of 20 studies that included a total of 31,479 subjects and found that caffeine intake from coffee or tea was not associated with the risk of cognitive disorders. These authors listed five different studies in which tea consumption was not associated with the risk of AD.

While the existing evidence precludes a definite conclusion as to whether tea drinking can be preventive from AD, further research including longer-term longitudinal studies and randomized controlled trials (RCT) is warranted to shed light on this topic. Biological markers of tea consumption and AD should be employed in future research to better delineate the underlying mechanisms of tea's benefits on cognition [11].

2.2. Basic Studies of Tea/EGCG on AD

In an AD model mice experiment using 3% d-galactose at a dose of 150 mg/kg body weight once daily for 6 weeks, or a dose of 2 mg/kg/day or 6 mg/kg/day of EGCG for 4 weeks, EGCG supplementation significantly reduced the accumulation of Aβ and reduced neuronal injury in the hippocampus [12]. Similarly, in the TgCRND8 transgenic AD mouse model, which expresses multiple APP mutations, oral administration of EGCG at 50 mg/kg/day for 4 months exerted beneficial effects on cognition and significantly reduced soluble $A\beta_{1–42}$ levels in the cortex and hippocampus, compared to untreated mice [13]. In an experiment using the APPSw transgenic AD mouse model, both intraperitoneally injected EGCG (20 mg/kg) and orally given EGCG (50 mg/kg) suppressed *p*-tau isoforms [14]. The finding demonstrates that EGCG downregulates tau protein, showing a potential to prevent and treat AD.

In a study using $A\beta_{1–42}$-induced SH-SY5Y cells and APP/PS1 transgenic mice, Du et al. [15] found that EGCG prevented $A\beta_{1–42}$-induced toxicity, increased cell viability, and inhibited neuronal apoptosis in the cortex of APP/PS1 transgenic mice, together with attenuation of endoplasmic reticulum (ER) abnormal ultrastructural swelling and downregulation of ER-stress-associated proteins. These results suggest that EGCG may attenuate the neurotoxicity in AD through inhibition of ER-stress-associated neuronal apoptosis. In a cellular experiment using neuroblastoma N2a cells, Zhang et al. [16] demonstrated that $A\beta_{1–42}$ reduced the protein and gene expression levels of PPAR-γ coactivator-1α (PGC-1α) [16]. Overexpression of PGC-1α attenuated cell death and activation of caspase-3 induced by $A\beta_{1–42}$ and reduced the levels of proinflammatory cytokines via inhibition of the transportation of nuclear factor (NF)-κB p65 from cytoplasm to nucleus and IκBα degradation induced by $A\beta_{1–42}$ [16].

In a study using AD transgenic mouse model known as senescence-accelerated mouse prone 8 (SAMP8), long-term oral consumption of EGCG (15 mg/kg) improved memory function in the Y-maze and Morris water-maze tests. EGCG reduced the $A\beta_{1–42}$ and β-secretase levels in the frontal cortex and hippocampus and prevented the hyperphosphorylation of tau [17]. Ramis et al. [18] found that old rats given (+)-catechin or Polyphenon E, a standardized GTC formulation [19] showed a significant improvement in visuo-spatial working and episodic memory. Both treatments also cancelled the age-associated reduction in the neuroinflammation via increasing sirtuin-1 (SIRT1) expression in the hippocampus.

A recent meta-analysis of 17 preclinical studies using animal AD models found that EGCG had favorable effects in AD with shorter escape latency (standardized mean difference (SMD): −9.24, CI: −12.05, −6.42) and decreased $A\beta_{42}$ level (standardized difference (SD): −25.74, 50% confidence interval (CI): −42.36, −9.11) [20]. These preclinical studies have proposed regulation of α-, β-, γ-secretase activity, inhibition of tau phosphorylation, anti-oxidation, anti-inflammation, anti-apoptosis, and inhibition of acetylcholinesterase (AchE) activity as the main neuroprotective mechanisms. In an experiment employing mice which received intracerebroventricular injection of 0.5 μg $A\beta_{1–42}$, Lee et al. [21] found that EGCG dose-dependently reduced the $A\beta_{1–42}$-induced memory dysfunction. EGCG attenuated $A\beta_{1–42}$-induced decrease in brain α-secretase and increases in both brain β- and γ-secretase activities. In addition, EGCG was found to inhibit the activation of extracellular signal-regulated kinase and NF-κB in the $A\beta_{1–42}$-injected mouse brains, and $A\beta_{1–42}$-induced apoptotic neuronal cell death in the brain. Furthermore, EGCG inhibited the fibrillization of Aβ in vitro with a half maximal inhibitory concentration of 7.5 mg/L. These results suggest that EGCG's beneficial effects on AD.

In an experiment employing human SH-SY5Y neuroblastoma and rat pheochromocytoma PC12 cells, Levites et al. [22] presented the data to show that EGCG enhanced the α-secretase-mediated release of the non-amyloidogenic sAPPα into the condition media of these cells. An inhibition or down-regulation of protein kinase C (PKC) blocked the EGCG-induced sAPPα secretion through induction of the phosphorylated PKC. EGCG also rescued PC12 cell against the Aβ toxicity. Similarly, Rezai-Zadeh et al. [23] demonstrated that EGCG promoted cleavage of the α-*C*-terminal fragment of APP to produce sAPPα along with elevated α-secretase activity and enhanced hydrolysis by tumor necrosis factor (TNF-α)-converting enzyme, a primary candidate α-secretase. These findings were confirmed in an experiment of transgenic mice over-expressing Aβ.

3. Effects of Coffee/CGA on AD

3.1. Human Studies of Coffee/CGA on AD

There is accumulating evidence that coffee consumption may provide beneficial effects on various NDDs [24][25]. A meta-analysis of studies carried out between 1990 and 2002 allowed Quintana et al. [26] to find an approximately 28% lower risk for AD among coffee consumers compared with non-consumers. The subgroup analysis of another meta-analysis of 11 prospective studies on 29,155 participants showed a significant inverse association with a summary relative risk (RR): 0.73 (CI: 0.55, 0.97) between highest coffee consumption and the risk for AD [27]. A 5-year follow-up study with Canadian participants aged ≥65 years showed that coffee consumption, wine

consumption, use of nonsteroidal anti-inflammatory drugs, and regular physical activity were associated with a reduced risk of AD [28].

A meta-analysis of prospective cohort and retrospective case-control studies on risk factors such as diet, medications, biochemical exposures, psychological condition, pre-existing disease and lifestyle in 323 papers found 4 dietary exposures (coffee, folate, vitamins C and E) as protective factors of AD [29]. A dose–response meta-analysis of 9 prospective cohort studies involving 34,282 participants found that compared with <1 cup/day, drinking of 1–2 cups/day of coffee was inversely associated with the risk of cognitive disorders (AD, dementia, cognitive decline, and cognitive impairment) with a pooled RR of 0.82 (CI: 0.71, 0.94) [30]. A clinical study with multimodal neuroimaging to examine cerebral Aβ deposition in 411 non-demented older adults found that lifetime coffee intake of ≥2 cups/day was significantly associated with a lower Aβ positivity compared to coffee intake of <2 cups/day, suggesting that higher coffee consumption may contribute to reduction of the risk of AD or related cognitive decline by decreasing pathological cerebral amyloid deposition [31].

Oppositely, several human studies did not show beneficial effects of coffee on AD. An examination for dementia in 1991-1993 showed no significant associations between coffee or caffeine intake and risk of AD, cognitive impairment, overall dementia, vascular dementia, or moderate/high levels of the individual neuropathologic lesion types, although higher caffeine intake was associated with lower odds of having any of the lesion types at autopsy [32]. A meta-analysis of 5 studies revealed no association between coffee consumption and AD. The RR of AD per 1 cup/day increment of coffee consumption was 1.01 (CI: 0.95, 1.07) [33]. Two-sample Mendelian randomization applied to large case-control and cross-sectional studies suggested that coffee may not have beneficial effects on AD, depression or type 2 diabetes [34].

3.2. Basic Studies of Coffee/CGA on AD

Ishida et al. [35] investigated the effect of CGAs on the prevention of cognitive dysfunction in APP/PS2 transgenic mouse model of AD in which animals received either a control or a CGA diet. The results indicated that chronic ingestion of CGA ameliorated cognitive deficits and prevented Aβ deposition and neuronal loss in these mice. CGA enhanced the gene expression of hippocampal low-density lipoprotein (LDL) receptor-related protein 1, which has a key role for Aβ clearance and cognitive function maintenance, and restored the perivascular localization of aquaporin 4, which facilitates Aβ clearance [36]. In a Aβ-induced cell model experiments, Shi et al. [37] found that CGA increased the viability and decreased apoptosis of hippocampal neurons from newborn Sprague–Dawley rats treated with $A\beta_{25-35}$. CGA decreased activities of lactate dehydrogenase and the malondialdehyde (MDA) levels, and raised contents of superoxide dismutase (SOD) and glutathione peroxidase (GSH)-Px in $A\beta_{25-35}$-treated cells, suggesting that CGA restrained the apoptosis of $A\beta_{25-35}$-induced hippocampal neurons by improving the anti-oxidant capacity, mitochondrial injury, and the state of ER stress in cells.

A study using an experimental protocol that combines NMR spectroscopy and atomic force microscopy showed that green and roasted coffee extracts, CGA, and melanoidins can inhibit Aβ aggregation and toxicity in human neuroblastoma SH-SY5Y cells [38]. Han et al. [39] found that when SH-SY5Y cells were incubated with 10 μM Aβ

along with 20 μM CGA, the cells became more viable compared to SH-SY5Y cells incubated without CGA. The results of an animal experiment showed that the administration of CGA improved spatial learning and memory in SAMP8 mice, which are senescence-accelerated-prone mice that exhibit age-related deterioration in learning and memory having plaques resembling AD like depositions of Aβ.

Another study conducted by Oboh et al. [40] demonstrated that CGA inhibited AChE activity in rat brain homogenates in a dose-dependent manner, suggesting its beneficial effect on AD, since inhibition of AChE represents the primary treatment modality against the cognitive impairment observed in AD [41]. Molecular docking studies revealed that CGA has the most significant binding affinity towards AChE [42]. As an additional model of learning and memory impairment like AD, scopolamine has been used to induce cognitive impairment in rodents [43]. Scopolamine is a muscarinic receptor antagonist that elevates oxidative stress in the brain by inhibiting ATPase and significantly increasing AChE and MDA levels in the hippocampus and cortex [44]. Kwon et al. [45] demonstrated that CGA improved the impairment of short-term or working memory and cognitive impairments induced by scopolamine. CGA inhibited AChE and decreased MDA levels in the hippocampus and frontal cortex.

In an experiment using SH-SY5Y cells, Fukuyama et al. [46] found that roasted coffee reduced Aβ accumulation in culture medium and β-secretase expression to 70% of control levels at 12 h-incubation. Coffee activated cAMP-dependent protein kinase and pyrocatechol, a product from CGA during roasting, also reduced α-secretase expression with activation of proteasomal activity and Aβ production in these cells. These results suggest that the roasted coffee may be useful for the protection of AD. Peroxisome proliferation-activated receptor (PPAR)-α activates gene coding of α-secretase, which is responsible for non-amyloidogenic pathway of APP degradation and downregulates β-secretase, the main enzyme responsible for Aβ peptide release in AD. A recent study showed that gene expression of PPAR-α and PGC-1α was decreased in AD [47]. Since CGA significantly elevated the expression level of mRNA and protein expression in hepatic PPAR-α [48], one can suggest CRC's upregulation of α-secretase and downregulation of β-secretase, leading to AD prevention.

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