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Research Progress on the Therapeutic Mechanism of Tea Polyphenols in Neurodegenerative Diseases

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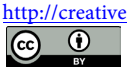

Abstract

In recent years, the incidence of neurodegenerative diseases, mainly Alzheimer's disease, Parkinson's disease, vascular dementia, and cerebral ischemia, has been rising gradually, which has a serious impact on the physiological state and quality of life of human beings in old age, and the current clinical drugs are unsatisfactory in terms of therapeutic efficacy and healing, which has made this kind of diseases become a social medical problem. Tea polyphenols are the main functional components of tea and have great potential in neuroprotection. In this paper, we review the research on tea polyphenols in neurodegenerative diseases, with the aim of providing a new entry point for the treatment of neurodegenerative diseases.

Keywords

Neurodegenerative Diseases, Tea Polyphenols, Neuroprotection

1. Introduction

Neurodegenerative diseases are a group of chronic, progressive disorders characterized by the loss of nerve cells in specific areas of the brain. Alzheimer's disease, Parkinson's disease, vascular dementia, cerebral ischemia, etc. all belong to the category of neurodegenerative diseases. In recent years, the incidence of neurodegenerative diseases has been increasing with the aging of the population, but there is a lack of effective clinical treatments, so research teams around the world are trying their best to explore new interventions.

Free radical oxidative damage and abnormal neuronal metabolism are important factors in the development of neurodegenerative diseases [1]. Tea polyphe-

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nols, the main monomer component of tea, have been attracting attention from the medical community for their powerful antioxidant properties, and are widely recognized as having great potential in neuroprotection. As a result, studies on the role of tea polyphenols in abnormal proteins, cellular transduction pathways and other neurological fields are emerging, and the rich biological activities and potential neurological mechanisms of tea polyphenols have been gradually explored one by one. In this paper, we provide an overview of the preventive effects of tea polyphenols on neurodegenerative diseases and related mechanisms, and analyze the process of medicinal research and development prospects of tea polyphenols, with a view to providing references for their application in neurodegenerative diseases.

2. Circulation and Metabolism of Tea Polyphenols

Tea polyphenol is the general name of polyphenolic compounds in tea, and is also the main component that determines the efficacy of tea, accounting for about 20% - 30% of the dry weight of tea leaves. The most abundant chemical substance in each component of tea polyphenols is epigallocatechin gallate (EGCG), whose mass fraction is about 70% of the total amount of tea polyphenols [2]. If administered orally, tea polyphenols are ingested and reach the intestines, where they are biotransformed and then enter the body circulation, where they reach various target organs in the body along with the bloodstream. A radiolabeling method was used to trace the pathway that 200 μl of EGCG traveled through the body of mice, and the results showed that 24 hours after administration, the radioactivity accumulated in tissues throughout the body, including the concentration of EGCG in the brain, which reached 0.22 μmol/L [3]. After administration of 100 mg/kg of tea polyphenols to rats, metabolites of tea polyphenols could be detected in rat brain tissues by high performance liquid chromatography [4]. These results demonstrate that tea polyphenols and their degradation components can enter the brain tissue through the blood-brain barrier, providing a basis for their neuroprotective effects.

Tea polyphenols are metabolized at a rapid rate, and the concentration of EGCG in human plasma can reach its peak within 2 hours of tea consumption, followed by a slow decline, with a drug elimination half-life of approximately 3.4 hours, and the concentration of tea polyphenols within human plasma can be reduced to baseline levels within 24 hours of tea consumption [5]. During this period, tea polyphenols are utilized by the tissues of the body, and the final metabolites are excreted from the body via urine or feces.

3. The Protective Effect of Tea Polyphenols on Neurodegenerative Diseases

3.1. Tea Polyphenols and Alzheimer's Disease

Alzheimer's disease (AD) is a kind of consciousness disorder mainly manifested by memory loss, slow thinking, and behavioral abnormalities, and is ranked as

the world's No. 1 neurodegenerative disease due to its unknown etiology, poor prognosis, and large patient base. Scholars are still exploring the etiology of AD, and through histological studies of experimental animals with AD, it is found that the formation of extracellular amyloid plaques in the brain can damage neuronal cells, and such damage can seriously affect cognition, memory and other functions, and then progressively form consciousness disorders.

β-amyloid (Aβ) is the core component of amyloid plaques. During the aging process, Amyloid precursor protein (APP), which is widely present in brain tissue, has two splitting modes: during normal processing, APP is hydrolyzed by α-secretase to sAPPα, which is not neurotoxic; during abnormal processing, APP is hydrolyzed by β-secretase, a portion of which releases sAPPβ, and the remainder is then broken down by γ-secretase into insoluble amyloid peptides containing amino acids, known as Aβ [6].

Studies have shown that EGCG promotes APP degradation in a normal manner [7]. Continuous oral administration of EGCG (2 mg/kg) for 2 weeks resulted in a significant increase in the amount of sAPPα in the hippocampal region tissues of AD mice; treatment of AD rat neuronal cell lines with EGCG, followed by a comparison of intracellular sAPPα content before and after the treatment, showed that the production of sAPPα was increased nearly 6-fold by EGCG [8].

At the same time, EGCG also inhibits Aβ production. In 2005, Rezai-Zadeh K [9] incubated primary neuronal cells from mice transfected with the APP gene with EGCG in vitro, and found that EGCG decreased Aβ production by 38%; after intraperitoneal injections of EGCG (20 mg/kg) into this species of mice for two consecutive months, neurons were assayed for the Aβ isoforms 1 - 40 and 1 - 42 levels in neurons, the data showed a 47% reduction in Aβ 1 - 40 and a 38% reduction in Aβ 1 - 42. In 2008, his team again explored the role of EGCG, this time they changed the intervention method to mixing EGCG into the drinking water of the trans-APP gene mice, and the results showed that drinking EGCG solution for 6 months also reduced the levels of Aβ 1 - 40 and Aβ 1 - 42 in the trans-APP gene mice [10].

The mechanism by which EGCG inhibits Aβ production may be closely related to its regulatory effect on the activities of α, β, and γ secretases. Rezai-Zadeh K *et al.* [9] observed the effect of EGCG on α secretase in the brain of mice overexpressing the APP gene, and the results showed that the activity of α secretase was significantly increased in the neuronal cells of the mice after the intravenous injection of EGCG, whereas the expression level of Aβ was significantly decreased. After in vitro EGCG incubation of neurons from AD mice with mutations in the APP gene, the transcription and translation of the β-secretase were inhibited, its enzymatic activity toward APP was reduced, and eventually the deposition of Aβ plaques was reduced accordingly [11]. Lipopolysaccharide-induced AD model mice that were orally administered EGCG for 3 weeks were detected to have diminished activities of both β-secretase and γ-secretase, whereas the activity of α-secretase was relatively increased [12], suggesting that EGCG can reduce the chances of erroneous splitting of amyloid precursor pro-

tein into β-amyloid by intervening in the enzyme activity.

3.2. Tea Polyphenols and Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease in the world. It is characterized by resting tremor, often accompanied by kinematic symptoms such as delayed reaction time, skeletal muscle tonus, and unsteady gait, therefore, it is often referred to as "paralysis agitans" in the research field. The incidence of PD is positively correlated with increasing age, and its pathology is characterized by progressive degeneration and loss of dopaminergic neurons in the substantia nigra and striatal regions of the midbrain, and abnormal accumulation of Lewy bodies in the remaining dopaminergic neurons. The degenerative loss of dopaminergic neurons leads to a significant reduction in dopamine levels in the brain, which in turn leads to a significant reduction in the inhibition of skeletal muscle excitation, and ultimately to a range of motor function abnormalities.

The cause of PD is still unknown, but it is widely recognized that genetic factors are extremely important. To date, nine genes have been shown to be associated with the development of PD, and the α-synuclein gene is one of them. Under physiological conditions, α-synuclein is an unfolded soluble protein without a fixed form, which participates in the normal biological functions of the organism; however, under the guidance of mutants of the α-synuclein gene, the spatial conformation of the α-synuclein protein is misfolded, and then a series of structural changes are generated—oligomers first appear in the misfolded proteins and gradually aggregate into soluble protofibrils; with the gradual increase of fibrillar proteins, solubility changes and insoluble fibrillar filaments begin to appear and further aggregate, and finally participate in the formation of Lewy bodies [13]. Intermediates such as oligomers and fibrillar substances induced to form during this process are neurotoxic and can directly cause damage to dopaminergic neurons; excessive aggregation of non-neurotoxic end-products, Lewy bodies, in residual dopaminergic neurons can also indirectly cause apoptosis of dopaminergic neurons.

Tea polyphenols were found to be effective in counteracting the increase in α-synuclein toxic oligomers and the decrease in dopaminergic neurons in the brain tissue of animal models of PD. However, the exact mechanism by which tea polyphenols exert their therapeutic effects on PD is not clear. It has been suggested that molecular structures carrying more than three hydroxyl groups on the aromatic ring can bind to amyloid and thus inhibit the fibrotic process [14], and therefore, many experts have proposed that tea polyphenols with this type of structure may achieve neuroprotection through their anti-aggregation properties. A large number of cellular studies have shown that tea polyphenols not only bind directly to α-synuclein, which has not yet undergone misconfiguration, to avoid its transformation into toxic oligomers [15], but also bind to intermediates produced during amyloid fibrillation and inhibit further aggregation

of intermediates [16]. In addition, EGCG can also depolymerize fibrillar filaments of larger size and toxicity into amorphous aggregates of smaller size and toxicity [17]. Beyond the cellular level, animal experiments have also shown that tea polyphenols can cause a significant decrease in the content of *α*-synuclein oligomers in the brain tissues of primate PD model animals [18], the mechanism of which may be related to the predominant motifs in the molecular structure of tea polyphenols.

With the in-depth research of contemporary scholars, the mechanism of action of tea polyphenols on PD has been further explored, for example, Pan T *et al.* [19] analyzed the research direction of dopamine reuptake, and found that tea polyphenols may intervene in the catabolism of dopamine transporter. In the pathological process of PD, dopamine located in the synaptic gap is often reuptaken by transporters and sent to the presynaptic membrane for catabolism, so that the concentration of dopamine in the brain tissue is significantly reduced, and tea polyphenols may intervene in the catabolism of dopamine in the brain tissue through their effects on dopamine reuptake. Tea polyphenols may inhibit dopamine reuptake and increase dopamine concentration, thereby improving motor control disorders in PD.

The results of animal experiments by other researchers seem to support Pan T. Zhou ZD *et al.* [20] observed the effect of tea polyphenols on dopamine in the striatum of the brain of mice with PD, and the results showed that 7 days after intraperitoneal injection of tea polyphenols, the dopamine content in the brain tissue of the mice was significantly increased, and its metabolite concentration was also increased simultaneously. Weinreb *et al.* [21] found that tea polyphenols could effectively inhibit the apoptosis of dopaminergic neurons and increase the dopamine content in the mouse brain by treating PD mouse models with tea polyphenols. In addition to rodents, tea polyphenols have the same effect on primates, which are very similar to humans. Administration of tea polyphenols to the PD monkey model significantly improved its motor dysfunction, and immunohistochemical results also confirmed that tea polyphenols could increase the dopamine content in the nigral-striatal pathway of the PD monkeys, and at the same time the number of their nigral dopaminergic neurons and the metabolic level of their striatal dopaminergic neurons were correspondingly elevated [22].

Tea polyphenols, as one of the drugs that may have neuroprotective effects, have been selected by our Parkinson's Disease Research Group for clinical trials. A researcher grouped 5668 testers, of which 1418 PD patients and 4250 non-PD people were controlled, and after Meta-analysis, it was found that long-term tea consumption was effective in reducing the risk of PD (OR = 0.85), however, the correlation between dose and efficacy is still unknown. In addition, 410 patients with early-stage PD who did not receive any treatment underwent a 1-year randomized double-blind controlled trial. During the trial, patients were randomized to take 0.4 g, 0.8 g, and 1.2 g of tea polyphenols per day, and at the end of the trial, researchers found that tea polyphenols were effective in improving

motor function in patients with PD, although they slightly increased the probability of insomnia [23].

3.3. Tea Polyphenols and Cerebral Ischemia

3.3.1. Chronic Phase of Cerebral Ischemia—Vascular Dementia

Vascular dementia (VD) is a neurodegenerative disease in which the cerebral blood vessels are in a state of prolonged hypoperfusion, resulting in pathological changes such as apoptosis of hippocampal neurons and demyelination of cerebral white matter, leading to memory impairment, cognitive deficits, personality disorders and other manifestations. The current therapeutic means for the treatment of VD in the middle and late stages of the disease is not very satisfactory, the patient's symptoms are poorly reversible, and the survival rate is low. Modern research has found that early intervention in VD can effectively improve the patient's condition, which has a more prominent effect on hyperlipidemia, cerebral atherosclerosis, and so on.

Recent studies suggest that tea polyphenols may positively affect cognitive function in VD patients. Animal experiments revealed that VD model rats treated with long-term tea polyphenols by gavage had a longer jumping latency and a significantly lower number of errors in the jumping test than VD model rats without any treatment, suggesting that tea polyphenols have a clear therapeutic effect on memory dysfunction in VD [24]. Taking the dosage of tea polyphenol as the research direction, the treatment groups were divided into three groups of high, medium and low doses, and each group of VD model rats was given 10, 5 and 2 mg/kg tea polyphenol solution for gavage treatment, after 28 days, the Morris water maze test was performed to detect the improvement of memory function, and the results showed that the avoidance latency of the rats in the three treatment groups was significantly shortened, and the shortening was positively correlated with the dose of tea polyphenol [25], which suggests that there exists a certain dosage relationship between tea polyphenol on the improvement of the memory ability of the rats with VD.

As for how tea polyphenols affect VD, some scholars have suggested that it may be related to its function of regulating blood lipids and anti-atherosclerosis. Tea polyphenols can be involved in multiple aspects of lipid synthesis, the most important of which is the total cholesterol (TC), low density lipoproteins (LDL) and high density lipoproteins (HDL) in the serum content of the effect. Studies have shown that the serum TC and LDL levels of rats were significantly reduced after prophylactic administration of tea polyphenols to high-fat-fed rats ($P < 0.01$) [26]; Comparison of blood TC, LDL, HDL levels and aortic pathological morphology between rabbits of high-fat-fed model group and high-fat-fed tea polyphenol group showed that tea polyphenols not only reduce the levels of TC and LDL in the rabbit's blood, and increase the content of HDL, but also effectively reduce the area of atherosclerotic plaques induced by high-fat diet [27]; obese patients were instructed to continuously ingest tea polyphenols for three

months, and after three months, the patients' serum levels of TC and LDL were significantly reduced, while HDL levels were relatively elevated [28]. Tea polyphenols can also down-regulate the expression of adipogenic genes, inhibit the activity of endogenous triglyceride key synthase, thereby effectively reducing the body's triglyceride content, while increasing serum HDL levels and reducing the atherogenic index [29].

In addition, tea polyphenols may improve lipid levels by inhibiting intestinal absorption of endogenous and exogenous cholesterol [30] and accelerating lipid excretion. Numerous data have shown that tea polyphenol-rich beverages increase fecal cholesterol excretion in people on high-fat diets [31], and Friedrich [32] has suggested that tea polyphenols increase fecal lipid excretion without affecting food and energy intake.

3.3.2. Acute Phase of Cerebral Ischemia—Reperfusion Injury

Brain tissue undergoing acute ischemia regains blood supply after a period of time, and the extent of its damage does not decrease, but rather increases rapidly and dramatically, is known as cerebral ischemia-reperfusion injury. This phenomenon occurs because after the onset of cerebral ischemia, the existing ATP in the tissues is rapidly depleted, and the activity of the Na^+-K^+-ATPase is reduced to fail maintaining the normal low intracellular sodium level; at the same time, the activity of the Ca^{2+}-ATPase is also impaired, and Ca^{2+} begins to accumulate intracellularly. After blood flow is restored, the tissue immediately obtains ATP supply, due to the high intracellular Na^+ concentration, in addition to Na^+-K^+-ATPase, the sodium-calcium exchanger is also activated to accelerate the outward transport of Na^+, and at this time a large amount of Ca^{2+} is displaced into the cell, which further aggravates the burden of intracellular Ca^{2+}, resulting in Ca^{2+} overload. Ca^{2+} overload can directly damage the cell membrane, organelle plasma membrane, and can cause structural decomposition of cytoskeleton and nucleic acids, exacerbating brain tissue cell damage and neuronal apoptosis [33]. In addition to the direct destruction of cellular structures, Ca^{2+} overload can also indirectly cause damage to the brain by promoting the generation of free radicals.

Tea polyphenols can improve energy metabolism and reduce reperfusion damage to the brain by regulating the activities of Na^+-K^+-ATPase and Ca^{2+}-ATPase in ischemic brain tissue. Pre-administration of tea polyphenols to rats in a cerebral ischemia-reperfusion model significantly increased the activity of Na^+-K^+-ATPase and Ca^{2+}-ATPase in rat brain tissue, reducing Na^+ and Ca^{2+} accumulation in brain cells during ischemia, thereby inhibiting Ca^{2+} overload during reperfusion and protecting ischemic brain tissue [34]. Some scholars have pointed out that tea polyphenols can not only increase the activity of Na^+-K^+-ATPase and Ca^{2+}-ATPase, but also maintain the stability of the cell membrane where the two enzymes are located, and maintain the structure and function of brain tissue cells and neurons [35].

In addition, tea polyphenols also have powerful antioxidant properties, so for

free radical damage during cerebral ischemia-reperfusion, many scholars believe that tea polyphenols may have a certain mitigating effect on it. Lv J *et al.* [36] prepared a rat model of ischemia-reperfusion using common carotid artery ligation to explore the effects of tea polyphenols on malondialdehyde and superoxide dismutase in rat brain. Among them, malondialdehyde is one of the products generated by the reaction of membrane unsaturated fatty acids with oxygen radicals, and its content reflects the degree of lipid peroxidation. Superoxide dismutase is an antioxidant enzyme that can scavenge free radicals, and is often used as an indicator to evaluate the antioxidant capacity of the body. Experimental results showed that intraperitoneal injection of tea polyphenols (200 mg/kg) decreased malondialdehyde content by 21.80% and increased superoxide dismutase activity by 54.02% in the brain of reperfused model rat. Similar studies have been done by many subsequent research groups, all of which verified that tea polyphenols can increase the activity of superoxide dismutase, thereby accelerating the rate of free radical scavenging, resulting in a reduction of malondialdehyde, a decrease in lipid peroxidation, and ultimately attenuating the neuronal damage caused by ischemia-reperfusion [37].

4. Conclusion

In summary, in vitro cell models and animal experiments have confirmed that tea polyphenols have an ameliorative effect on a variety of neurodegenerative diseases, and their neuroprotective function can be realized by inhibiting toxic amyloid generation and aggregation, regulating cell signaling pathways, participating in lipid metabolism, reducing lipid peroxidation, and counteracting calcium overload. However, there is a lack of evidence that tea polyphenols can exert the same pharmacological effects in the human body. It is recommended that in-depth clinical trials on the neuroprotective effects of tea polyphenols should be conducted, and that complementary medicines with preventive healthcare activities should be further developed to provide more effective interventions for patients with neurodegenerative diseases, with a view to enhancing the quality of life of the aging human population in the future.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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