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Early-stage Protective Effects of Tea Polyphenols on Hippocampal Neurogenesis and Cognitive Dysfunction in Alzheimer's Disease Model

Xin Lv[a,b], Jun Qiu[c], Haiping Jiang[a,c], Yang Tan[d]*

Abstract

Objective: The activation of glial cells may cause inflammatory responses to brain, leading to cognitive dysfunction. Green tea polyphenols have been reported to be neuroprotective. This study used the method of intracerebroventricular injection of $A\beta_{1-42}$ to establish an Alzheimer's disease (AD) model, and then treated with tea polyphenols. We aimed to investigate the effects and molecular mechanism of tea polyphenols on antagonizing the neurotoxicity induced by $A\beta_{1-42}$.

Methods: Three-month-old male C57BL/6J mice were injected with $A\beta_{1-42}$ into the lateral ventricle and tea polyphenols were administrated immediately after modeling. Morris water maze test was conducted to detect the cognitive function, Western blot assay was used to detect protein expressions of related signaling pathways in hippocampus tissue, and immunofluorescence assay was used to label microglia and astrocyte.

Results: Compared with AD model mice without tea polyphenols treatment, the latency to find the hidden platform of AD model mice with tea polyphenols treatment was significantly reduced, and the proportion of time spent in the quadrant was significantly increased. The expressions of BDNF and TrkB were significantly increased. In addition, microglia/astrocyte cell proliferation was significantly reduced and the activation of pro-inflammatory signaling pathway factors was down-regulated, while anti-inflammatory signaling pathway factors was up-regulated.

Conclusion: This study indicates that tea polyphenols attenuate $A\beta_{1-42}$-induced cognition dysfunction and the effects may be related to hippocampal neurogenesis and glial cell-related inflammatory response.

Keywords: Alzheimer's disease; cognitive dysfunction; neurogenesis; glial cells; tea polyphenols

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that ultimately develops to irreversible loss of neurons and defects to various intellectual abilities, including cognition and memory (Lane *et al.*, 2018). AD has become an important public health problem, because its symptoms specifically include physical, cognitive, and emotional dysfunction, as well as long-term apraxia of cognitive and sensory changes. These changes significantly affect the quality of life of patients (Elmaleh *et al.*, 2019). Although many research results and significant progress have been made in the occurrence and development of AD, there are still few effective diagnoses and treatment methods (Busche and Hyman, 2020). Therefore, the discussion of the pathological process of AD and the strong demand for therapeutic drugs has promoted the research interests in the neuroscience community and the medical industry in the development of AD treatment methods.

Recently, the effect of green tea and its main bioactive substances on neuronal cell death caused by spinal cord and brain injuries as attracted wide attention (Itoh *et al.*, 2011; Machova Urdzikova *et al.*, 2017). What's more, positive relationships have been revealed between higher green tea intake and the lower disease risk, such as AD and Parkinson's disease (PD) (Kuriyama *et al.*, 2006). Tea polyphenols are a group of bioactive chemicals extracted from green tea. Tea polyphenols, also known as catechin, is mainly composed of four components: epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC) and

[a.] Department of Clinical Nutrition, The First Affiliated Hospital of Jinan University, Guangzhou, Guangdong, 510630, China.
[b.] Guangzhou Key Laboratory of Molecular and Functional Imaging for Clinical Translation, The First Affiliated Hospital of Jinan University, Guangzhou, Guangdong, 510630, China.
[c.] Department of General Surgery, The First Affiliated Hospital of Jinan University, Guangzhou, Guangdong, 510630, China.
[d.] Department of Pathology, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, 518000, China
 # Corresponding author: Yang Tan, Email: tanyang80436@163.com.

epigallocatechin-3-gallate (EGCG). Among them, EGCG constitutes 50–80% of the total catechin content (Lin *et al.*, 2003). Previous studies have confirmed that tea polyphenols played a crucial role in antioxidant, lowering blood fat and neural protection (Park *et al.*, 2011; Masterjohn and Bruno, 2012; Delwing-Dal Magro *et al.*, 2016). Given the formidable anti-oxidative properties, tea polyphenols taken orally for 4 weeks significantly improved spatial cognitive disturbance in chronic cerebral hypoperfusion rats (Yan Xu *et al.*, 2010). In addition, tea polyphenols attenuated isoflurane-induced cognition impairment and the effects may be related to its antioxidant properties (Song *et al.*, 2019).

Our research is to establish an AD model by injecting $A\beta_{1-42}$ into the lateral ventricle, and then treat with tea polyphenols to evaluate the effect and molecular mechanism of tea polyphenols on antagonizing the neurotoxicity induced by $A\beta_{1-42}$.

Materials and methods

1. Animals

Three-month-old male C57BL/6J mice (23-28 g, 12 mice/group) used for this study were purchased from Peking Huafukang Laboratory Animal Center (Beijing, China). All mice were housed in a specific pathogen-free facility under a controlled temperature (23±1)°C and humidity (50±5)% environment with a 12-h light/dark cycle, allowed ad libitum access to food and water. The study was approved by the laboratory animal ethics committee of the Jinan University.

2. Experimental design

The purity of the green tea polyphenols (Shanghai yuanye Bio-Technology, China) was >95%, comprise four major epicatechin derivatives: EC, EGC, ECG, and EGCG, among which EGCG accounts for 70%. Mice were randomly divided into one of following four groups: control group, (control + 10mg/kg) group, $A\beta_{1-42}$ group, ($A\beta_{1-42}$ + 10mg/kg) group. Mice in ($A\beta_{1-42}$ + 10mg/kg) group were slowly injected with $A\beta_{1-42}$ ($A\beta_{1-42}$ peptide was dissolved in 1% $NH_3 \cdot H_2O$ at a concentration of 1μg/ml) into the lateral ventricle and then given a subcutaneous injection of tea polyphenols (3 mg/day) for 7 days. $A\beta_{1-42}$ group was injected with $A\beta_{1-42}$ and without tea polyphenols treatment. The (control + 10mg/kg) group was injected with the same amount of normal saline with tea polyphenols treatment. The control group was only injected with normal saline. After the completion of the behavioral testing, all animals were killed to collect the hippocampus tissue.

3. Morris water maze

To evaluate spatial learning and memory abilities, MWM test was performed with the DMS-2 Morris water maze test system (Institute of Materia Medica at Chinese Academy of Medical Sciences, China). The MWM test has two phases, namely, an acquisition test and a spatial probe trial. During the six consecutive days of the acquisition test, swimming time was recorded as the latency of seeking escape. After the final day of the acquisition test, the platform was removed and the spatial probe trial was carried out only once. Recorded during this trial was the time spent in the targeted quadrant. Decreased value of escape latency indicates better spatial learning ability, and increased values of time spent in the targeted quadrant indicate better memory ability.

4. Western blotting to detect the expression of signaling pathway proteins

The hippocampus was separated from the brain sample on ice. The hippocampus tissue extracts were prepared in tissue lysis buffer (Beyotime, China) with a motor-driven tissue homogenizer (PT1200E, Switzerland), and the protein concentration was determined with a BCA protein assay kit (Boster Biological Technology, China). Equivalent amounts of extracted protein were separated on 12% sodium dodecyl sulfate-polyacrylamide gel by electrophoresis, and then were transferred to PVDF membranes (Merck Millipore, USA). After blocking with 5% (w/v) bovine serum albumin for 1 h at RT, the membranes were incubated with rabbit anti-BDNF antibody (1:1000, Bioss, China), rabbit anti-TrkB (1:1000, Bioss, China), rabbit anti-phosphorylated TrkB (1:1000, Bioss, China), rabbit anti-STAT3 (1:1000, Bioss, China), rabbit anti-phosphorylated STAT3 (1:1000, Bioss, China), rabbit anti-CREB (1:1000, Bioss, China), rabbit anti-phosphorylated CREB (1:1000, Bioss, China), rabbit anti-ERK (1:1000, Bioss, China), rabbit anti-phosphorylated ERK (1:1000, Bioss, China), rabbit anti-cytochrome-c (1:1000, Bioss, China), rabbit anti-Bax (1:1000, Bioss, China), rabbit anti-caspase-3 (1:1000, Bioss, China), rabbit anti-activated-caspase-3 (1:1000, Bioss, China), rabbit anti-IL-1β (1:1000, Bioss, China), rabbit anti-TNF-α (1:1000, Bioss, China), rabbit anti-IL-6 (1:1000, Bioss, China), rabbit anti-TGF-β (1:1000, Bioss, China), rabbit anti-FIZZ1 (1:1000, Bioss, China) and rabbit anti-β-actin (1:2000, Bioss, China) overnight at 4 ℃. After washing with TBST, immunoblots were incubated with Horseradish Peroxidase-conjugated goat anti-rabbit IgG antibody (1:2000, Proteintech, China) for 1 h at RT. Finally, the immunoblots were visualized using chemiluminescence reagent

(Merck Millipore, USA) and a ChemiDoc XRS+ Imaging System (Bio-Rad, USA). The intensity of each protein band was quantified by ImageJ software and normalized to the respective β-actin band.

5. Immunofluorescence analysis

Immunofluorescence analysis of the paraffin embedded tissues was performed using standard protocols provided by the antibody manufacturers. Briefly, sections were fixed in 4% paraformaldehyde, blocked with 10% normal goat serum, and then incubated overnight at 4 °C with the primary antibodies: mouse anti-Iba1 antibody (1:100, Bioss, China) and rabbit anti-GFAP antibody (1:100, Bioss, China). Thereafter, sections were briefly washed with PBS and incubated for 1 h at room temperature with appropriate secondary antibodies (fluorescein isothiocyanate-labeled anti-mouse IgG; tetramethylrhodamine-conjugated anti-rabbit IgG; 1:100, Bioss, China). 4′, 6-diamidino-2-phenylinedole (DAPI; Solarbio, Beijing, China; 1 μg/ml) was used to dye the nuclei before 10 min of mounting. The sections were then analyzed with an Olympus IX81 microscope (Olympus, Tokyo, Japan) and Image-Pro Plus 6.0 software.

6. Statistical analysis

Results were expressed as mean ± standard deviation (SD). Comparisons among different groups were performed by one-way ANOVA and followed by Student–Newman–Keuls test for multiple comparisons. The statistical software package SPSS 24.0 (IBM Corp., USA) was used to evaluate differences among groups, which were considered statistically significant at *P*-value <0.05.

Results

1. Tea polyphenols treatment of the early stage of AD promoted the recovery of cognitive function

The MWM test was performed to evaluate spatial learning and memory ability. Compared （$A\beta_{1\text{-}42}$ + 10mg/kg） group with $A\beta_{1\text{-}42}$ group, escape latency was significantly reduced (*P*<0.05, Figure 1), and the proportion of time spent in the quadrant of the withdrawal platform was significantly higher (*P*<0.05, Figure 2). Taken together, the results showed that tea polyphenols treatment of the early stage of AD improved cognitive function.

2. Tea polyphenols treatment of the early stage of AD up-regulated the signaling pathways related to hippocampal neurogenesis in $A\beta_{1\text{-}42}$ mice

We investigated whether tea polyphenols could act through hippocampal neurogenesis related signaling pathways. Protein expressions of two neurogenesis-related genes, namely, brain derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB) were quantified by western blot assays. Additionally, phosphorylation level of three neurogenesis-related genes, namely, signal transducer and activator of transcription 3 (STAT3), cAMP-response element binding protein (CREB) and extracellular regulated protein kinases (ERK) were also quantified by western blot. As shown in Figure 3, the expressions of BDNF and TrkB proteins were significantly up-regulated. Following this, the downstream factors of the pathway were tested, and the activation of the STAT3/CREB/ERK signaling pathway was significantly increased.

3. Tea polyphenol treatment of the early stage of AD can down-regulate the viability of signaling pathways related to cell apoptosis

We investigated whether tea polyphenols could act through cell apoptosis-related signaling pathways. Three pro-apoptotic proteins, namely, cytochrome-c, bcl-2 associated X protein (bax) and activated-caspase-3 were quantified by western blot assays. As shown in Figure 4, in the early administration of $A\beta_{1\text{-}42}$ mice, the corresponding cell apoptosis-related signaling pathway factors were down-regulated.

4. Tea polyphenols treatment of the early stage of AD inhibited excessive proliferation of hippocampal microglia/astrocyte and regulated inflammatory response in $A\beta_{1\text{-}42}$ mice

As shown in Figure 5, microglia/astrocyte cell proliferation was significantly reduced in $A\beta_{1\text{-}42}$ mice treated with tea polyphenols. Then we investigated whether tea polyphenols could act through glial cell-related inflammatory response signaling pathways. Three pro-inflammatory proteins, namely, interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were quantified by western blot assays. Additionally, two anti-inflammatory proteins, namely, transforming growth factor-β (TGF-β) and foundininflammatoryzone1 (FIZZ1) were also quantified by western blot. As shown in Figure 6, the inflammatory response mediated by tea polyphenols down-regulated the activation of pro-inflammatory signaling pathways and up-regulated the activation of anti-inflammatory signaling pathways.

Discussions

$A\beta_{1\text{-}42}$ is β-secretase (enzyme) and γ-secretase produced by the cleavage of amyloid precursor protein (APP) (Wang *et al.*, 2017; Jørgensen *et al.*,

2020). Compared with various other starch derivatives, $A\beta_{1-42}$ plays a pivotal role in the pathogenesis of AD (Lee and Kim, 2017). Excessive Aβ protein leads to the formation of amyloid plaques and various neurological dysfunctions, including the activation of the inflammatory cascade (Minter *et al.*, 2016), such as the promotion of tau protein phosphorylation (Busche and Hyman, 2020), the increase of oxidative stress (Plascencia-Villa and Perry, 2020), the control of intracellular signal transduction pathways.

Previous studies have found that Aβ-mediated neurotoxicity, which in turn causes a decline in cognitive function and learning and memory, mainly includes oxidative stress, nerve apoptosis or inhibition of nerve regeneration, and synaptic remodeling. In vitro studies have confirmed that Aβ oligomers induce a rapid increase in intracellular calcium by activating N-methyl-D-aspartate (NMDA) channels, leading to a significant increase in ROS (Li and Selkoe, 2020; Wang *et al.*, 2020). Natural antioxidants such as ginkgo biloba extract (EGb 761) can inhibit ROS generation and neuronal apoptosis caused by Aβ, and have neuroprotective effects (Ge *et al.*, 2021; Tu *et al.*, 2020). The defects of the antioxidant system can lead to aggravation of oxidative stress, forming a vicious circle, and causing a significant increase of Aβ deposition. The extracellular Aβ oligomer binds to the receptor, leading to receptor dysfunction, and ultimately to nerve regeneration or neuronal apoptosis, including the receptor for advanced glycation end products (RAGE) and cellular prion protein (PrPC), NMDA receptor, and FccRHb and PirB immune receptors, etc.

The main cause of AD has long been believed to be neurotoxicity mediated by extracellular Aβ receptors. Recent studies have shown that intracellular Aβ accumulation also has a potential impact on the pathogenesis of AD. $A\beta_{1-42}$ accumulates in lysosomes and endosomes, and the increase in lysosomal membrane permeability leads to the release of lysosomal enzymes and triggers apoptosis of meridian cells. The intracellular deposition of Aβ can also occur in mitochondria. The reaction between Aβ and mitochondrial resident protein mediates the stress response of mitochondria and neurons, which in turn leads to neuronal apoptosis (Agrawal and Jha, 2020; Pradeepkiran and Reddy, 2020).

In this study, the viability of signal transduction pathways related to neurogenesis was detected. Tea polyphenols can activate the BDNF/TrkB pathway and up-ragulate STAT3/CREB/ERK signaling pathway, indicating that tea polyphenols treatment of the early stage of AD promotes hippocampal neurogenesis, thereby improving recognition function. BDNF plays a valuable role in neuron proliferation, differentiation, and survival. P-STAT3 and p-CREB are both key mediators regulating the hippocampus of long-term potentiation (LTP), which is considered as a physiological basis for memory.

The unique function of glial cells is maintaining the stability of the internal environment of the central nervous system (CNS), making quiescent cells quickly enter the activated form, and affecting soluble fibers $A\beta_{1-42}$. Regulation of glial activation and neuroinflammation are critical factors in the pathogenesis of AD (Lananna *et al.*, 2020). Microglia plays an important role in the development of the nervous system. In the hippocampus, microglia is involved in the modification and remodeling of nerve protrusions. Based on the secretion mode of cytokines, the activation of microglia can be classified as M1 (classical activation) or M2 (surrogate activation). The activation of different types of microglia plays very different roles. Microglia in the M2 state phagocytoses damaged nerve cell fragments through the release of anti-inflammatory factors, thereby promoting nerve cell repair, regeneration and nerve synapse remodeling (Malm *et al.*, 2015). However, the excessive activation of microglia will cause the transition from M2 state to M1 state. Microglia in the M1 state will release a large number of inflammatory factors. These inflammatory factors will produce neurotoxicity and cause neuronal apoptosis in hippocampus, which in turn leads to a decline in cognitive function. Therefore, maintaining the M2 state or preventing the transition of microglia from the M1 state to the M2 state through intervention, and reducing the release of neuroinflammatory factors, are essential for neuroprotection (Hansen *et al.*, 2018). Astrocytes are the most abundant cells in the central nervous system and are considered to play a major role in maintaining the normal function of the brain and spinal cord (Zhang *et al.*, 2019). They interact closely with neurons, provide structural support, metabolic energy and nutritional support, and actively participate in the regulation of neuronal excitability and neurotransmission by controlling the extracellular level of ions and neurotransmitters (Sofroniew, 2015). It has been discovered that Tau accumulation in astrocytes of the dentate gyrus induces neuronal dysfunction and memory deficits in AD (Richetin *et al.*, 2020).

In this study, the level of glial cell proliferation increased significantly in mice injected with $A\beta_{1-42}$, while the glial cell proliferation decreased in the early tea polyphenol group. In addition, the

expressions of pro-inflammatory cytokines (IL-1β, TNF-α and IL-6) were enhanced, while the expression levels of anti-inflammatory cytokines (TGF-β and FIZZ1) were weakened. In summary, tea polyphenol therapy not only promotes hippocampal neurogenesis in the early stages of AD, but also avoids changes in central nervous system homeostasis due to inflammation.

In conclusion, we found that tea polyphenol treatment increases hippocampal neurogenesis and promotes the recovery of cognitive function, and up-regulates the signaling pathways related to hippocampal neuron regeneration in the early stages of the pathological process of AD in $A\beta_{1-42}$ mice. Tea polyphenol can reduce inflammatory responses, down-regulate the activity of signal pathways related to cell aptosis, and inhibit the excessive proliferation of hippocampal glial cells. Our findings provided a preventive strategy for alleviating cognitive dysfunction in the clinic.

Funding

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Figures

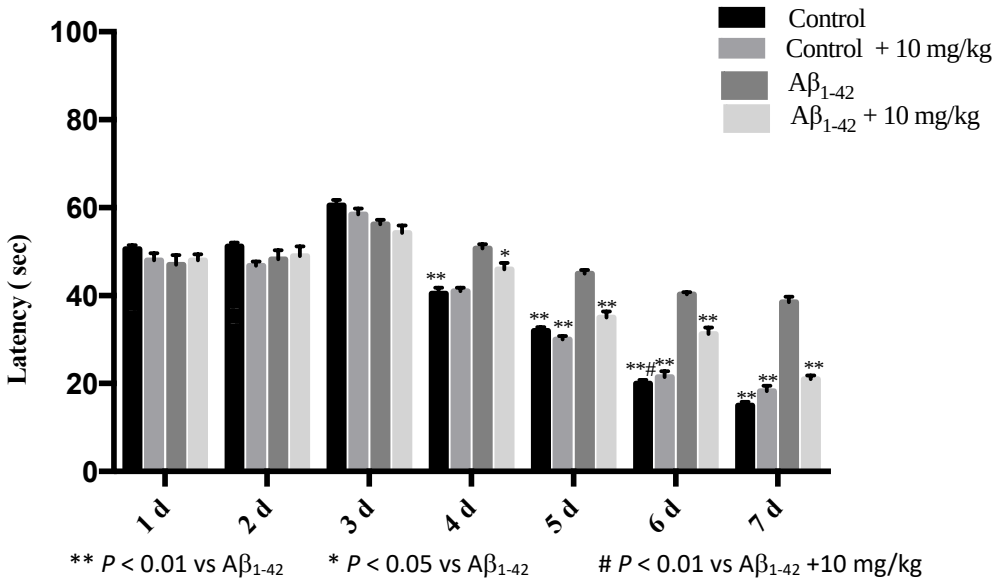


Figure 1. **The effect of tea polyphenols on escape latency in Morris water maze (MWM) test.**

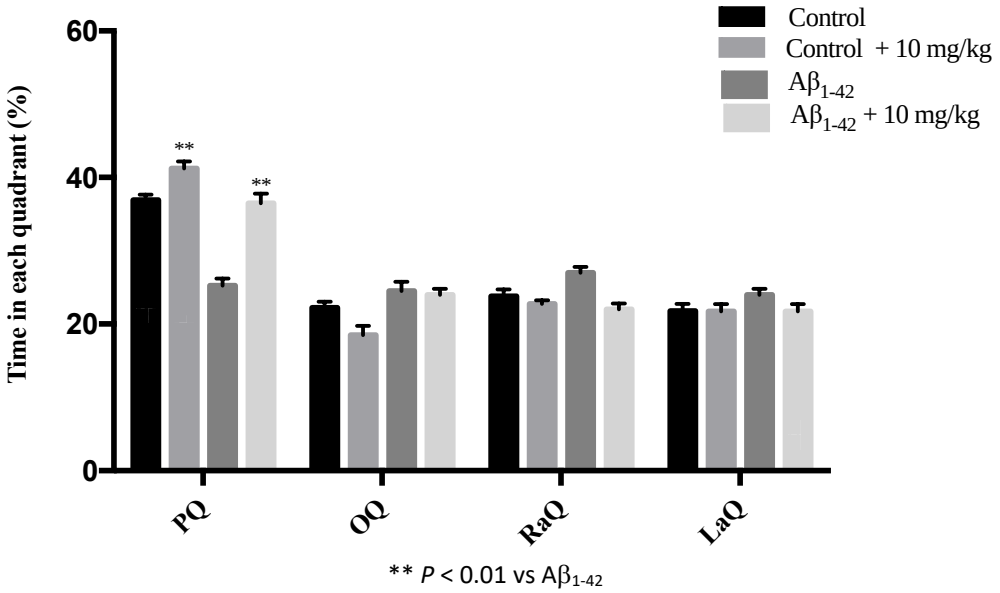
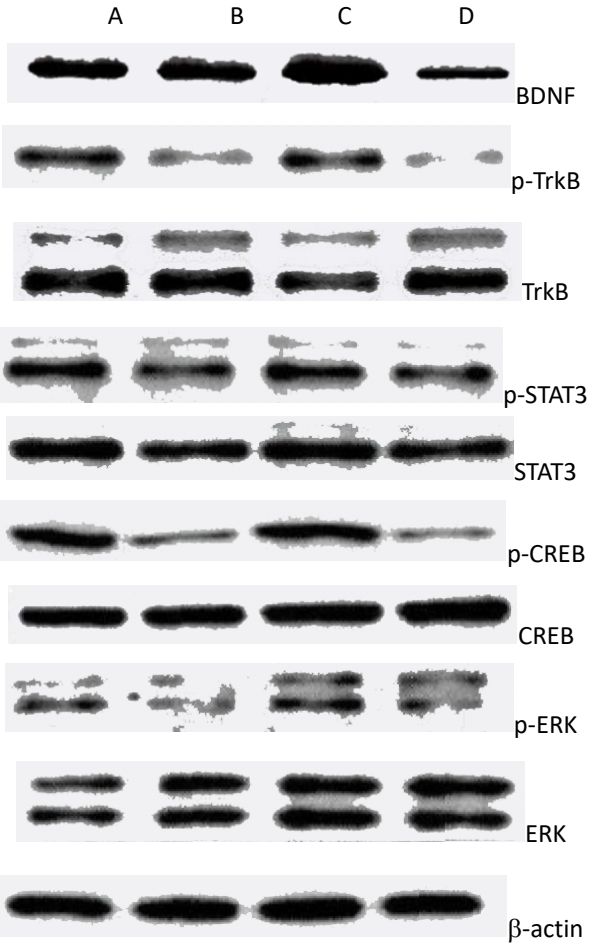
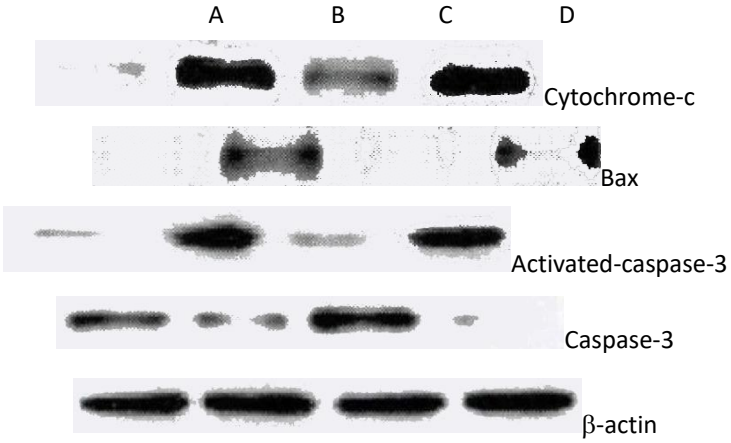


Figure 2. **The effect of tea polyphenols on proportion of time spent in the quadrant of the withdrawal platform in MWM test.**



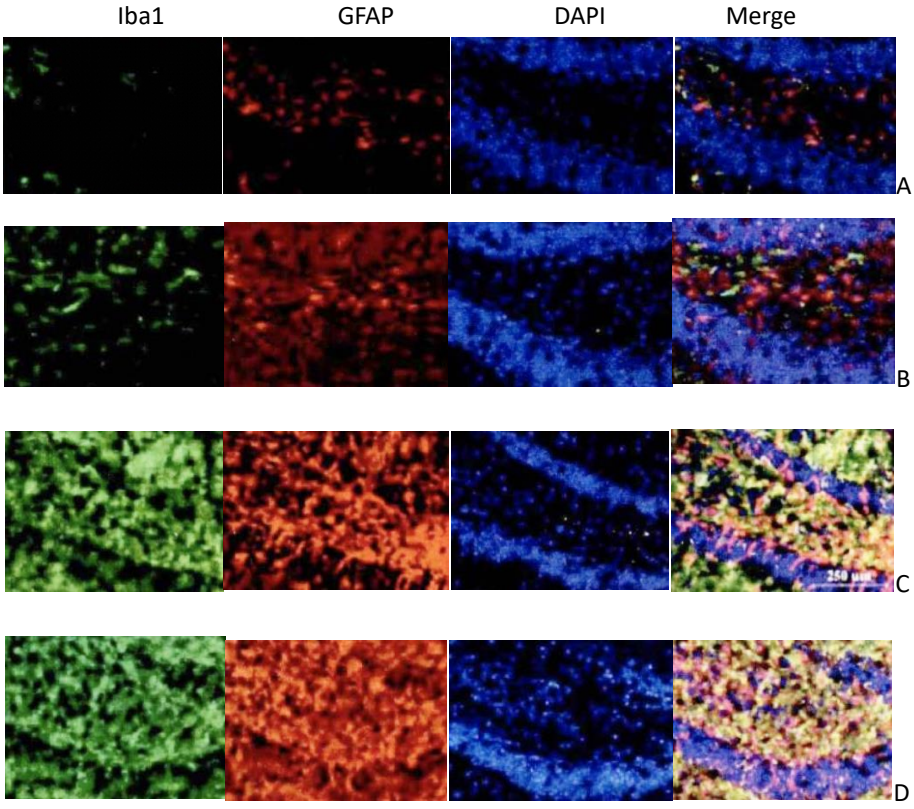
A: Control+10mg/kg B: Control C: $A\beta_{1-42}$+10mg/kg D: $A\beta_{1-42}$

Figure 3. **The effect of tea polyphenols on the expressions of important proteins related to hippocampal neurogenesis signaling pathways.**



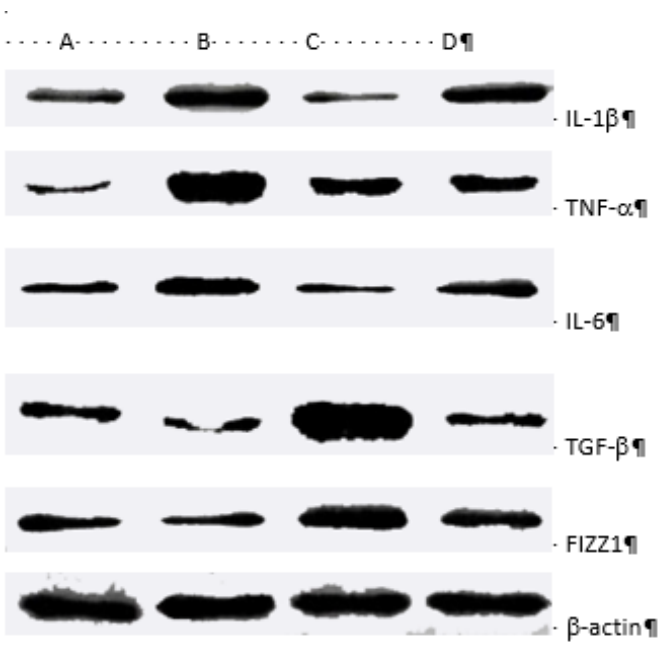
A: Control+10mg/kg B: Control C: $A\beta_{1-42}$+10mg/kg D: $A\beta_{1-42}$

Figure 4. **The effect of tea polyphenols on the expressions of important proteins related to pro- apoptotic signaling pathways.**



A: Control+10mg/kg B: Control C: $A\beta_{1-42}$+10mg/kg D: $A\beta_{1-42}$

Figure 5. **The effect of tea polyphenols on the activation of microglia and astrocyte in coronal brain slices. Iba1 is a specific marker of microglia, while GFAP is a specific marker of astrocyte.**



A:·Control+10mg/kg· B:·Control· C:·$A\beta_{1-42}$+10mg/kg D:·$A\beta_{1-42}$·

Figure 6. **The effect of tea polyphenols on the expressions of important proteins in glial cell-related inflammation pathways.**