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Current Perspective

Neural Regeneration: Role of Traditional Chinese Medicine in Neurological Diseases Treatment

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Abstract. The effects of a single compound and a mixture of traditional Chinese medicine (TCM) on promoting proliferation, differentiation, and migration of neural stem cells and regulating their microenvironment have been observed by Chinese scholars in recent years. These results showed good prospects in improving neural regeneration and repair of neurological disorders such as ischemic brain injury, Alzheimer's disease, Parkinson's disease, and depression. According to the TCM theory, the relationship between life of an individual and the disease was regarded as an entirety, and the theory emphasized the treatment based on syndrome differentiation since ancient times. In this paper, we attempted to introduce these medicines, which belong to natural products and have already been proved to possess clear therapeutic action on human bodies in the clinical setting. We summarized their effects promoting brain neurogenesis and repairing brain injuries in animal models and some mechanisms at the cellular and molecular levels.

Keywords: traditional Chinese medicine (TCM), neural stem cell, neural regeneration, neurological disease

1. Introduction

It has been 20 years since Reynolds and Weiss isolated neural stem cells (NSCs), which were characterized as having continuous proliferation, multiple differentiation potential in vitro from adult mouse striatum in 1992 (1). This discovery not only challenged the theory that the central nervous system (CNS) was not renewable after maturity, but also brought hope for CNS repair and functional reconstruction in life science, becoming one of the most influential research areas. With a profound understanding of stem cell research, traditional Chinese medicine (TCM) scholars considered that stem cells are closely related to "congenital essence" in the basic theories of TCM. Then a new viewpoint was proposed: stem cells have the same properties of congenital essence, and stem cells are the physical manifestation of congenital essence at the cellular level, which provides a new combining site for modernization of TCM research.

TCM has its own theory on CNS diseases, has accumulated rich experience of treatment, and has clear efficacy. Long history, ancient tradition, wide use, and a large number of medical records are the highlight of overall value of TCM. In recent years, the studies on the relationship between effective components (and/or prescription) of Chinese medicine and NSCs have been published in international journals. These reports enabled people to understand the mechanisms of TCM with a new perspective, providing a modern theoretical basis for clinical applications. In terms of TCM theory, we here introduce the effects of Chinese medicines on neural regeneration and internal environment and its effects on several major diseases of the CNS in animal models such as cerebral ischemia, Alzheimer's disease, Parkinson's disease, and depression, which probably provided the reference for clinical treatment or drug researches.

2. Regulation of NSCs

Neurogenesis is a complete process, including NSC proliferation and division into progenitor cells in a symmetric or asymmetric manner, followed by gradual

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migration of the NSC to the functional region, ongoing plasticity changes, establishing synaptic connection with other neurons, and subsequently resulting in neurological function. It is regulated by various kinds of factors, including physical and pathological factors in the adult mammalian brain. It is widely known that about 200 – 300 cells are generated in unilateral hippocampus of young rats every day, of which about 100 – 150 survive, accounting for 0.03% in all neurons of the dentate gyrus (DG), and the number reduces gradually with aging. The proliferation of NSCs is not only influenced by regulation of intrinsic genes, but also affected by the microenvironment. The factors including a rich environment, learning, exercise, energy restriction, and growth factors [such as basic fibroblast growth factor, brain-derived neurotrophic factor (BDNF), and insulin-like growth factor-1] can promote proliferation. Inhibition factors include opioid, aging, stress, and brain injury induced by oxidative stress or mechanical injury. Proliferation is regarded as the increase of $Nestin^+$ and bromodeoxyuridine ($BrdU^+$) cells in the brain of a pathological animal. In the stage of differentiation, specific differentiation is the key of neural regeneration, and the control mechanism is very complicated. For example, signal transducer and activator of transcription 3 (stat3), basic helix-loop-helix (bHLH) gene families, are important cellular signal molecules in the regulation of cell fate and neural stem/precursor cells differentiation. The expression of genes or not and the level of expression verify the situation of differentiation. Some Chinese medicines have an influence on this process; for example, baicalin, a flavonoid compound isolated from *Scutellaria baicalensis*. The effect of baicalin was first observed in E15 – 16 embryonic neural precursor cells (NPCs), in which it promoted neural differentiation but inhibited glial formation by regulating expression of stat3 and bHLH (2). Due to the ability of penetrating the blood–brain barrier (BBB), baicalin can be developed as a therapeutic agent to promote neurogenesis. The migration of NSCs is a key step for exerting neural function. Correct migration requires a special microenvironment; the molecules involved include temporospatial expressions of slit protein, migration inducing activity factor, inflammatory chemokine, and polysialylated neural cell adhesion molecule, which are required for attraction, repulsion, and guidance. Of course we cannot divide neurogenesis into three stages absolutely, but improvement of neural microenvironment and functional integration provide power for neural regeneration.

3. The effect of TCM on promoting neural regeneration and repair

3.1. Action of anti-ischemic brain injury

With the discovery of NSCs, research on stroke has been focused on endogenous neural functional reconstruction and restoration, instead of the neuroprotective mechanism. With the character of inducible endogenous NSCs, TCM shows desirable therapeutic potential for treatment of cerebral ischemia. For example, *Ginseng* is used to treat stroke and chronic wasting diseases. Ginseng saponin is the effective component of *Ginseng*, whose therapeutic mechanism is unclear. Zheng et al. (3) used intraperitoneal injections of Ginseng total saponins (GTS, 25 mg/kg per day) 3 days before the permanent middle cerebral artery occlusion model establishment. GTS-treated rats had better neurological scores compared with the model group at the 14-day time point. And the numbers of $BrdU^+$ cells and $BrdU^+/NeuN^+$ cells were significantly increased in the ipsilateral subventricular zone (SVZ) and in the ipsilateral infarct area, respectively, which indicated its effect on promoting neurogenesis. In addition, Rg1, one of the main components of GTS, was found to increase cell proliferation in many studies (4, 5). In the same pathological condition, tetramethylpyrazine (TMP) has a neuroprotective effect by reducing the volume of infarction, neuronal loss, and water content. TMP not only increased the number of BrdU-positive cells in SVZ, but also stimulated the cell differentiation after ischemia. The neural nitric oxide synthase (nNOS) expression in the cortex and DG was reduced by TMP. These results indicate that TMP could protect brain from ischemic damage and promote cell proliferation and differentiation, which might be related to the reduction of nNOS expression (6). Using the ischemic model induced by oxygen glucose deprivation in vitro, Si et al. (7) observed that Panax notoginseng saponins, with blood-activating and stasis-dissolving properties, could promote proliferation and differentiation of hippocampal NSCs by enhancing the expression of Nestin/BrdU and mRNA expressions of Tuj-1, vimentin, and nestin in hippocampal NSCs, which suggested its potential benefits on neural regeneration in cerebral ischemic injury. Xu et al. (8) investigated antioxidant activities of *Dracocephalum tanguticum* Maxim extract (DME), which contained 52% of total flavonoids, and up-regulation of the expression of neurotrophic factors in a rat model of permanent focal cerebral ischemia. DME (30 mg/kg per day for 7 days) was effective in enhancing BDNF, neurotrophin-3 mRNA expression, and protein synthesis in the ipsilateral frontal cortex and hippocampus of model rats. Meanwhile, DME also increased endogenous antioxidant (superoxide dismutase, glutathione

peroxidase, and catalase) activities and decreased malondialdehyde content. These findings suggested that DME has ability to treat ischemia-induced brain damage through increasing antioxidant activity and stimulation of neurotrophic factor synthesis. Baicalin, which was previously mentioned, was also found to exert protection against ischemic injury of the brain by regulating proteins in energy metabolism but had relatively weak ability to promote neurogenesis (9).

Among the Chinese herbal compounds, Taiwan scholars (10) reported the neuroprotective effect of Bu-yang Huan-wu decoction (BHD) by an integrative neural-functional and genomic approach in ischemic stroke mice. BHD is a famous TCM formula that has been used clinically in Asia to treat stroke-induced disability for centuries. Using a model of acute ischemic stroke induced by middle cerebral ischemic/reperfusion, BHD (0.5 and 1.0 g/kg) successfully restored brain function, ameliorated the cerebral infarction, and improved the neurological deficits. Genome-wide transcriptome analysis showed that BHD can up-regulate neuroprotective genes associated with neurogenesis and nervous system development and decrease the expression of destructive genes including induction of inflammation, apoptosis, angiogenesis, and blood coagulation. The changes in gene expressions exerted by BHD are beneficial for treating ischemic stroke. It is similar with study of Similar conclusions were obtained in the study by Cai et al.: they proved that BHD can stimulate the proliferation of neural progenitor cells and enhance the expression of vascular endothelial growth factor (VEGF) and its receptors, which were useful for the recovery from the neurological dysfunctions after ischemic stroke (11).

Ischemic stroke has shown high occurrence of death and disability. The literature contains many reports of stroke-induced neurogenesis in the adult brain (12). Newborn neurons can migrate to the ischemic area and differentiate into different functional neurons according to ischemic types, which reflect self-repair ability. However, drug treatment is necessary for promoting this process or providing a beneficial regeneration microenvironment (13) because the degree of self-repair and establishment of synaptic plasticity are imperfect. The combined application of the above medicines or compounds often has been used for stroke treatment. Through these studies, we learn that they could achieve the recovery of neural function by promoting neurogenesis or improving the neural regeneration microenvironment.

3.2. Action of anti-Alzheimer's disease

Since there is still lack of effective treatment for Alzheimer's disease (AD) at present, more and more research will be focusing on Chinese herbal medicine because it is obtained from a natural source. Due to uncertainty of the pathogenesis of AD, TCM with the characteristic of having multiple targets may have better curative effect.

Catalpol, purified from a TCM herb *Rehmannia glutinosa*, a non-cholinesterase inhibitor compound, could improve the symptoms and pathological changes in animal and cellular models of memory-related neurodegenerative diseases. Xia et al. (14) compared catalpol with donepezil with respect to their mechanism in an animal model induced by β-amyloid (Aβ) plus glutamate-receptor agonist. It was found that donepezil, at the selected doses, only partially raised the decreased brain muscarinic receptor density and choline acetyltransferase activity, which are still lower than normal level. However, catalpol fully retrieved these two parameters. Then catalpol, instead of donepezil, can elevate brain BDNF level, which was the same as the results of Wang et al. (15). It can also increase BDNF mRNA in A$\beta_{25\text{-}35}$-treated primary culture of forebrain neurons. Because BDNF is an important endogenous protective factor in neurodegenerative diseases, catalpol plays an important role in mediating cognitive improvement and neurogenesis. Unfortunately, neurogenesis was not observed in the study, but it is still hypothetical that catalpol has the ability to promote neuroregeneration.

Curcumin is a relatively small mass of phenolics, extracted from the ginger family plant. It has extensive pharmacological properties including anti-oxidation, anti-inflammation, immunomodulatory, anti-cancer, and so on, mostly by modulating the expressions of cytokines, growth factors, and transcription factors, which may be responsible for its beneficial effects during tissue injuries (16). In recent years, its neuroprotective effects have been studied widely and related mechanisms were involved in many aspects (17, 18). Here we only introduce studies involving neurogenesis. Dong et al. (19) explored its neuroprotection against aging. Curcumin (3 mg/day per rat) can improve spatial and non-spatial memory in the Morris water maze and the social recognition test, respectively. And it also increases cell proliferation of DG in aged rats after they were fed curcumin-fortified diets for 6 – 12 weeks. They also found a transcriptional network interaction of genes involved in neurotransmission, neuronal development, signal transduction, and metabolism. The results suggest that prolonged treatment with curcumin can promote neurogenesis and cognition, which may be due to its effects on genes related to growth and plasticity.

Ginkgo biloba extract EGb 761 exhibits beneficial effects in patients with AD. It was previously demonstrated that it protects neurons from toxicity of Aβ oligomerization in vitro and improves cognitive defects in vivo, respectively. Using a double transgenic (TgAPP/

PS1) AD mice expressing human mutant amyloid precursor protein (APP) and persinilin-1 (PS1) model, Tchantchou et al. (20) observed the neurogenic potential of EGb 761 and its effect on cAMP response element binding protein (CREB). EGb 761 significantly increases cell proliferation in the hippocampus of both young (6 months) and old (22 months) TgAPP/PS1 mice, which may be mediated by activation of CREB. EGb 761 has therapeutic potential for the prevention and improved treatment of AD. They further identified effective components of EGb 761, bilobalide and quercetin, which can dose-dependently promote cell proliferation in DG. The mechanisms of enhancing neurogenesis and synaptogenesis are mediated by phosphorylation of CREB (21). Quercetin, one of the most abundant polyphenolic flavonols occurring naturally in fruits, vegetables, and herbal medicines, has been proved to have neuroprotective effect resulting from its antioxidant property in many studies.

Cornel iridoid glycoside (CIG) is a main component extracted from the Chinese herb *Cornus officinalis*. Here we introduce the studies of Zhao et al. (22) on the neuroprotective effect of CIG, using model rats with fimbria–fornix transaction (FFT). They showed that memory was significantly improved by CIG (20, 60, and 180 mg/kg) treatment in the Morris water maze and step though task. CIG treatment attenuated the loss of neurons in the hippocampus. CIG significantly increases hippocampal protein levels of nerve growth factor, tyrosine-specific protein kinase A, BDNF, synaptophysin, and Bcl-2, while decreasing decreasing cytochrome c and Bax. It is indicated that CIG can protect neurons from FFT injury mainly depending on promoting neuronal survival and providing a beneficial environment for brain repair.

Gossypium herbaceam extract (GHE) is an active standardized extract obtained from *Gossypium herbaceam*; the latter has nootropic effect and was produced in Xinjiang (China). In our group, we found that GHE exerted an improved effect on the learning and memory impairment in rats induced by Aβ (23) or ibotenic acid (24) in the behavioral tests. Its mechanisms may be related to improvement of anti-oxidative activities and reduction of apoptosis via inhibition of NF-κB and decreasing the ratio of Bax / Bcl-2 and the expression of caspase-3. Moreover, GHE can enhance the activity of Ca^{2+}-ATP enzyme and the level of Calbindin-D28. In the aspect of anti-inflammation, increasing the ratio of IL-1RA / IL-1β is also one of the related mechanisms. Recently, we (25) have further investigated the effect of GHE on aging rats. We found that oral administration with GHE (35, 70, and 140 mg/kg) have a vital role in improving the ability of learning and memory of aged rats. The numbers of NeuN, proliferating cell nuclear antigen, and NPC-positive cells were significantly increased in the CA1 subregion of the hippocampus. Taken together, neurogenic niche improvement could be involved in the mechanism underlying neurogenesis of GHE, and it might be a potential agent as a cognitive-enhancing drug that delays or halts mild cognitive impairment progression to AD or treatment of aging-associated cognitive impairment.

Fuzhisan (FZS), a Chinese herbal prescription including *Ginseng*, *Scutellaria baicalensis*, rhizome of *Acorus calamus* L., and Radix *Glycyrrhizae*, has been used to treat AD for more than 16 years. Using aged SAMP-8 mice, Yang et al. (26) observed the effect of FZS and the related mechanism. The results showed that FZS (2.4, 4.8 g/kg per day) improved cognitive ability, increased hippocampal neurogenesis and the long-term survival of BrdU-positive cells without affecting the proportion of $BrdU^+$ neurons and glial cells. FZS also increased the number of BrdU-positive cells in the SVZ of the lateral ventricles. These studies suggest that FZS upregulates neurogenesis by increasing proliferation of NPCs and prolonging survival of the newborn cells in the hippocampal DG. FZS may be beneficial for the treatment of senile dementia, especially AD.

3.3. Action of anti-Parkinson's disease

Parkinson's disease (PD) is a chronic neurodegenerative motor disorder disease, with a character of dopaminergic neurons loss in the substantia nigra par compacta (SNpc). The new therapeutic methods on delaying or reversing the process of neurodegeneration have been getting more and more attention. Sun et al. (27) found that harpagoside, an iridoid purified from the Chinese medicinal herb *Scrophularia ningpoensis*, can protect dopaminergic neurons from neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) / 1-methyl-4-phenylpyridinium (MPP^+) and has definite curative effect. It clearly attenuated the loss of tyrosine hydroxylase (TH^+) neurons and shortening of axons induced by MPP^+ in vitro. Meanwhile harpagoside improved motor ability in rotarod test in a dose-dependent manner and increased TH^+ neurons in SNpc, density of dopamine transporter (DAT), the level of GDNF mRNA, and protein in the striatum in chronic MPTP-injured mice.

Chen et al. (28) observed the effect of (+)-cholesten-3-one, which was purified from *Plastrum Testudinis* in TCM. (+)-Cholesten-3-one can effectively promote the activity of TH promoter of P19 cells depending on bone morphogenetic protein (BMP) signaling. Phenotypic cellular analysis also indicated that it induces differentiation of NSCs to dopaminergic neurons with increased expression of TH, DAT, dopamine decarboxylase, and higher level of dopamine secretion. These findings raise

interesting questions about the role of (+)-cholesten-3-one in neurogenesis of PD treatment.

AD and PD are two major neurodegenerative diseases, and TCM plays a role in the regulation of neurogenesis in these pathological conditions, which provides an opportunity to promote the proliferation of endogenous and exogenous NSC. Some Chinese scholars studied Chinese medicine used for kidney tonifying in combination with NSC transplantation for the treatment of neurodegenerative diseases, which showed good prospects.

3.4. Action of anti-depression

In general, antidepressants play a role after a few weeks of administration. Aconite was used to treat mental disorders for centuries in China. Yan et al. (29) found that Fuzi polysaccharide-1 (FPS), a new water-soluble polysaccharide isolated from *Aconitum carmichaeli* Debx., increased the number of newborn cells in the DG of adult mice, most of which differentiated into new neurons. FPS improved depression-like performance. Moreover, a 14-day regimen with FPS reverses avoidance behavior and inhibition of hippocampal neurogenesis induced by chronic defeat stress. While imipramine, a well known antidepressant, reverses this avoidance behavior only after 4 weeks of continuous administration. Acute treatment with FPS had no effect on brain monoamine levels in the frontal cortex but significantly increases BDNF in the hippocampus. FPS can promote neurogenesis and anti-depression, which may be involved with the BDNF signal pathway, and it could be developed as a potential antidepressant with fast action.

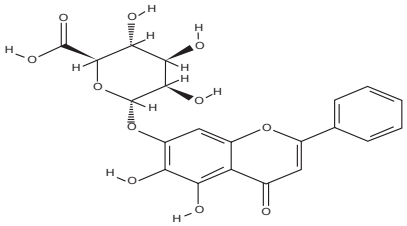
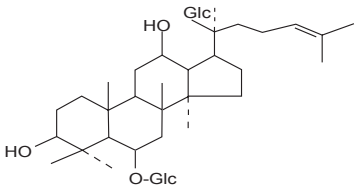
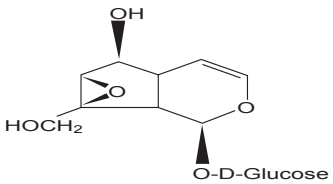
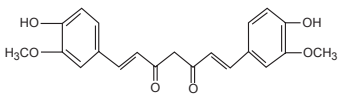
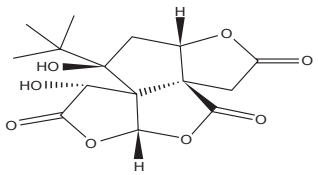
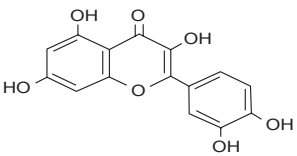
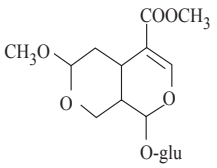
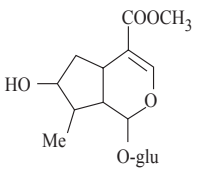
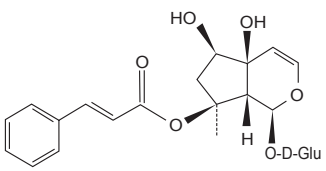
Ginsenoside Rg1 (Rg1), one of the major bioactive ingredients of *Ginseng* with little toxicity, has been shown to have neuroprotective effects. Jiang et al. (30) reported the effect of Rg1 in a mouse model of chronic mild stress (CMS). Rg1 has antidepressant-like effect in the forced swim test and tail suspension test, and it could up-regulate the BDNF signaling pathway of the hippocampus and down-regulate the level of plasma corticosterone. Moreover, Rg1 can reverse the decrease of dendritic spine density and hippocampal neurogenesis induced by CMS. Similarly it has no obvious effect on the monoaminergic system. It is the first evidence that Rg1 exerts antidepressant activity by activation of the BDNF signaling pathway and up-regulation of hippocampal neurogenesis.

The two components discussed above with anti-depression effect are completely different from the western medicines, which commonly have been used as positive control antidepressants. The latter are usually thought to act by blocking reuptake of norepinephrine and 5-hydroxytryptamine, increasing transmitter content in the synaptic gap subsequently. However, there are many adverse reactions, especially peripheral anticholinergic side effects. Chinese medicine components do not affect monoaminergic systems significantly, but can promote neurogenesis, mediated by the BDNF signal pathway.

4. Summary

Although the studies introduced in this paper are not thorough and systematic enough, there is still no doubt that the single ingredient, extracts, and compounds of TCM play effective roles in improving the internal environment, promoting neurogenesis, and repairing neural injury. Here we want to emphasize that TCM belongs to the dialectical and philosophical medical system, which is characterized as the holistic concept and syndrome differentiation. The application of Chinese medicine is inseparable from the guiding of TCM theory. Both in physiological and pathological conditions, it has the advantages of the overall adjustment, bidirectional regulation, and multiple prevention-treatment-repairing; that is to say, TCM has multi-target actions, rather than single effect, which is completely different from the western medical system. Due to limited space, only 30 literature reports related to this field were provided, each of which were published in international journals by mainly Chinese scholars in recent years. The studies on mechanisms of these components are fully based on long-term clinical effectiveness. We attach great importance to these effects of TCM on behaviors of animal pathologic models, and then mechanisms combined with modern medical indexes at the cell level. We think that all these roles are related with the effects of activating blood and resolving stasis of TCM (activating blood and resolving stasis are peculiar to TCM; “stasis” is similar to aggregated pathological and metabolic waste products in human body; using these Chinese medicines can eliminate them), then improving cerebral microcirculation, maintaining balance and harmony of the internal environment, and having the power of neural regeneration finally. Among them, 8 active components were chosen, which are natural products extracted from Chinese medicine, have definite chemical structure, and have been proved to be effective in the human body for thousands of years (Table 1). These ingredients are completely different from the synthetic compounds obtained by high-throughput screening. No matter if they could pass through BBB, they can play neuroprotective role. So it is thought that the effects of promoting neural regeneration at the cellular level have more important scientific significance and clinical therapy support.

Table 1. The effects of the components on brain neurogenesis and neurological diseases

Component	Structure	Ability of passing BBB	Neurogenesis or microenvironment	Neurological disease	References
Baicalin		+++	Promote neural differentiation	Ischemic brain injury	Li Y et al., 2012 (2); Zhang ZJ et al., 2009 (9)
Ginsenoside Rg1		+	Increase cell proliferation and up-regulate hippocampal neurogenesis	Ischemic brain injury, Depression	Cheng Y et al., 2005 (4); Shen LH et al., 2003 (5); Jiang B et al., 2012 (30)
Catalpol		++	Elevate brain BDNF level	Alzheimer's disease	Xia ZM et al., 2012 (14)
Curcumin		++	Increase cell proliferation of DG	Alzheimer's disease	Dong SZ et al., 2012 (19)
Bilobalide		++	Promote cell proliferation in DG	Alzheimer's disease	Tchantchou F et al., 2009 (21)
Quercetin		+++	Promote cell proliferation in DG	Alzheimer's disease	Tchantchou F et al., 2009 (21)
Cornel iridoid glycoside	Morroniside  Loganin 	+	Provide a beneficial environment	Alzheimer's disease	Zhao LH et al., 2010 (22)
Harpagoside		?	Increase GDNF level of striatum	Parkinson's disease	Sun XY et al., 2012 (27)

"+" is used to evaluate the degree of passing BBB: passes weakly (+), passes moderately (++), passes easily (+++).

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