Research Status of *Astragali Radix* on Nerve Cells and Nerve System Diseases

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Abstract: *Astragali Radix* has a wide application in the nerve system diseases because of its obvious nerve cell protection and recovery effects. *Astragali Radix* has good clinical effects both in acute and chronic cerebrovascular diseases and neurological degenerative diseases. This paper reviews the experimental and clinical research status of *Astragali Radix* on nerve system and nerve system diseases, which may promote its experimental research and clinical application.

Key words: *Astragali Radix*; cerebrovascular disease; degenerative disease; nerve cell; nerve system diseases
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Introduction

Astragali Radix is the dry roots of *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao and *A. membranaceus* (Fisch.) Bge. The main constituents of *Astragali Radix* are *Astragali Radix* polysaccharide (APS), flavonoids, triterpenoids (astragallosides I—IV, AST I—IV), alkaloids, glycuronic acids, trace elements, etc. As one of the most widely used Qi-tonifying Chinese herbal medicines (CHM), *Astragali Radix* has sweet flavor and warm property. In the theory of traditional Chinese medicines (TCM), *Astragali Radix* has good effects, such as tonifying Qi and securing the exterior, inducing diuresis to alleviate edema, expelling toxin and pus, and promoting wound healing and tissue regeneration. The scientifical researches have confirmed that *Astragali Radix* has multi-pharmacological effects, e.g. dilating blood vessel, lowering blood pressure, antiplatelet aggregation, improving microcirculation, reducing blood viscosity and blood fat, removing oxygen free radicals, immune regulating, strengthening the heart, inducing diuresis, antibiosis, and anti-inflammation (Pan, Zhang, and Zhang, 2006; Chen and Huang, 2008; Chen *et al*, 2009). In this paper, the researches of *Astragali Radix* on nerve cells and nerve system diseases are summarized as follows.

Effects of *Astragali Radix* on normal nerve cells

On neurons

The major cells in nerve system are neurons. *Astragali Radix* could improve the vitality of new and adult neurons. It is confirmed that *Astragali Radix* could inhibit the apoptosis of primary cortical neurons in rats. *Astragali Radix* could enhance the nucleotides absorption stimulated by nerve growth factor (NGF), which may be related to promoting NGF binding with its receptor (Zhang, Yang, and Hu, 2010). *Astragali Radix* may also improve the low vitality of adult cortical neurons induced by myelin membrane protein (Xie *et al*, 2007).

On neural stem cells

Neural stem cells (NSCs) have multi-potent differentiation into neurons and glial cells and the ability to repair tissue damage. It is found that *Astragali Radix* could promote the differentiation of NSCs into neurons. Astragaloside significantly promotes the proliferation of NSCs *in vitro*, probably through increasing the expression of Hes l, Hes 5, and cyclin D1, or regulating other proliferation pathways (Xie *et al*, 2004; Liu *et al*, 2006; Ishida *et al*, 2009; Chai *et al*, 2010).

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On olfactory ensheathing cells

Olfactory ensheathing cell (OEC) is a special type of glial cells, which could not only facilitate continuously updated olfactory sensory neurons in adult mammalian, but also accelerate survival and axon formation of a variety of neurons in the central nerve system. *Astragali Radix* could promote the secretion of glial-derived neurotrophic factor (GDNF), reduce the apoptosis of OECs. So, *Astragali Radix* injection in combination with OECs could improve the recovery of spinal cord injury (Wang *et al*, 2010).

On myelin membrane protein

Myelin membrane protein is a membrane protein inhibiting nerve growth expressed in myelin and oligodendrocytes of white matter in the central nerve system. And its main components are myelin-associated inhibitory protein (Nogo), myelin associated glycolprotein (MAG), oligodendrocyte myelin glycoprotein (OMgp), and so on. *Astragali Radix* could enhance nerve growth, and the effect may be related to inhibition on phosphodiesterase neurons lipase and RhoA, increase of cAMP levels in nerve, promotion of Cdc42, and the fight against inhibition on nerve growth by myelin membrane protein (Zhou, Wei, and Liu, 2006; Xie *et al*, 2007; Wei, Yang, and Tan, 2008).

Effects of *Astragali Radix* on nerve cells under different conditions of diseases

For cerebral ischemia/reperfusion injury

Cerebral ischemia-reperfusion (I/R) injury is the common pathological mechanism in a variety of cerebral vascular diseases, such as transient ischemic attack, cerebral thrombosis, lacunar infarction, and cerebral embolism. Currently researches of *Astragali Radix* on I/R injury were focused on the influence on apoptosis of nerve cells. Experiments have shown that *Astragali Radix* could reduce neural apoptosis and neurons death through various means both *in vivo* and *in vitro*. For example, (1) Focal cerebral I/R model rats were established by occluding the external carotid artery with thread, and more apoptotic cells could be detected in the ischemic brain tissue and mainly located in the surrounding brain tissue of the infarct. *Astragali Radix* may inhibit apoptosis of neurons through increasing the expression of Bcl-2 protein, and decreasing the expression of Bax protein, i.e. increasing the Bc1-2/Bax ratio, so as to play a protective role in cerebral I/R injury in rats (Qu *et al*, 2007); (2) It was found that AST could increase the mRNA expression of brain-derived neurotrophic factor (BDNF) and tyrosine kinase B (TrkB), decrease the expression of neurotrophin receptor p75 (p75NTR) mRNA in the middle cerebral artery occlusion (MCAO) model. AST could promote the function recovery of nerve from focal cerebral I/R injury. It was also found that extract of *Astragali Radix* has protective effects on hypoxia/reoxygenation neurons, which may be related with that *Astragali Radix* could activate the PI3K/AKT cellular signaling pathway and promote phosphorylation of AKT protein (Yi *et al*, 2009; Zhu *et al*, 2009); (3) *Astragali Radix* plays a role in protecting hippocampal neurons through inhibiting the apoptosis while improving activity of hippocampal neurons after hypoxia/hypoglycemia and reoxygenation. The possible mechanisms might be inhibiting the mRNA expression of apoptosis-related genes c-Jun N-terminal kinase 3 (JNK3), blocking the mitogen-activated protein kinase (MAPK) signal transduction pathway, and reducing the expression of caspase 3 (Zhang *et al*, 2009; Yan *et al*, 2010; Ye *et al*, 2010)

For intracerebral hemorrhage

Intracerebral hemorrhage (ICH) is one of the severe clinical emergencies with high incidence and mortality. The main cause of the cells death in ischemic penumbra surrounding the hemorrhagic focus after ICH is the apoptosis, which is caused by extravasation of too much cytokine after mild cerebral hemorrhage and cerebral ischemia. *Astragali Radix* injection could be used to treat ICH, by reducing cerebral edema, decreasing neuron apoptosis, and improving ultrastructure of neurons in perihematoma. And *Astragali Radix* should be used as early as possible (Xu *et al*, 2008; Zhang *et al*, 2009). Apoptosis is a pattern of death after ICH, and the expression of NF-κB is an important step in apoptotic cell death after ICH. APS could effectively alleviate apoptosis after ICH by preventing the expression of NF-κB. APS could enhance the expression of heme oxygenase-1 (HO-1) protein, which may be related with its anti-edema and neuron protective effect following ICH (Liu *et al*, 2007; Liu, Xiao, and Ding, 2007). *Astragali Radix* could inhibit the excessive activation of astrocytes and over-

expression of glial fibrillary acidic protein (GFAP) in ICH and could maintain moderate proliferation and activation of astrocytes, which contributes to the recovery of neurological function after ICH (Zhang *et al*, 2005).

For craniocerebral and nerve injury

Because the nerve cell regeneration and repair capacity are relatively limited, the brain parenchyma and nerve repair after injury has been always a clinical problem. *Astragali Radix* has good capacity of brain cells protection and reconstruction, and has a positive effect in brain and nerve damage. *Astragali Radix* could reduce the concentration of serum neuron specific enolase (NSE), myelin basic protein (MBP), and S-100 protein B (S-100B) in the patients with acute severe craniocerebral injury. *Astragali Radix* showed significant clinical effect on craniocerebral injury and its main mechanism may be related to that *Astragali Radix* could improve the cerebral microcirculation after traumatic brain injury, scavenge oxygen free radicals, and block calcium overload in nerve cells (Li *et al*, 2008). *Astragali Radix* has a protective effect on nerve cells after craniocerebral injury by reducing Ca^{2+}, glutamate, and plasma endothelin (ET) levels, inhibiting the reduction of Mg^{2+}, and improving cerebral circulation emblem, but different doses of *Astragali Radix* (5, 10, and 20 mL/kg) did not show a dose-effect relationship (Liu *et al*, 2008). Transplantation of mesenchymal cells (MSCs) is an effective method in the treatment of spinal cord injury (SCI). It was found that *Astragali Radix* could reduce the secondary SCI by decreasing the production of endogenous monocyte chemoattractant protein-1 (MCP-1) after SCI. *Astragali Radix* injection could help MSCs differentiate into neurons, and could synergize with MSCs to promote the repairing of SCI in rats (Yu *et al*, 2010). APS could promote the sciatic nerve regeneration after peripheral nerve injury through increasing the recovery rate of sciatic motor nerve conduction velocity (MNCV) and numbers of myelinated nerve fibers (Sang *et al*, 2008).

For Alzheimer's disease

The basic pathological features of Alzheimer's disease (AD) are senile plaques deposited outside neurons, neurofibrillary tangles located in the neurons, and reduction of neurons mainly in the basal forebrain and hippocampus. Extracts from *Astragali Radix* (20, 40, and 80 mg/kg) enhanced the expression of Bcl-2 and Bcl-xl to restrain the apoptosis of the hippocampal neurons and improved the learning and memory of AD rats induced by $A\beta_{25-35}$ (Zhang *et al*, 2007). It was observed that GDNF and neuron survival rate increased, and the morphological changes in neurons improved in BV2 microglia cell conditioned medium treated with 80 mg/L extract from *Astragali Radix*. It could be indicated that extract from *Astragali Radix* could reduce the toxic effect of $A\beta_{25-35}$ on neurons by reducing oxidative damages and apoptosis (Liu, Liu, and Liu, 2010).

For neurotoxicity of some drugs

Many drugs have neurotoxicity. APS pretreatment could reduce the neurotoxicity of intrathecal injection of Bupivacaine in rats, which is related to reducing apoptosis by the down-regulation of caspase-9 protein and P38 kinase (Xu *et al*, 2010; Wang *et al*, 2009). *Astragali Radix* injection could restrain the hippocampus neuronal cell apoptosis induced by Oxaliplatin (L-OHP), probably via increasing NGF level in the hippocampus neurons primary culture in SD rats (Li *et al*, 2010).

Other effects of *Astragali Radix* on nerve-related cells

Astragali Radix has many other effects on nerve cells. AST IV could protect the dopaminergic neurons against 6-hydroxydopamine-induced degeneration, promote the neurite outgrowth, and increase the thyrosine and nitrite oxide synthase immunoreaction of dopaminergic neurons. So, AST IV has therapeutic potential in the treatment of Parkinson's disease (Chan *et al*, 2009). *Astragali Radix* has an effect of decreasing the excitement of nerve and muscle, and relaxing the fatigue of the center-nerve-muscle junction. The possible mechanism might be to decrease the activities of Na^{+}-K^{+}-ATPase and Ca^{2+}-Mg^{2+}-ATPase. *Astragali Radix* alleviates the growth and regulates the monoamine neurotransmitters level of brains in stressed rats. For example, *Astragali Radix* could increase the dopamine (DA) content in striatum and decrease the DA content in the prefrontal cortex of chronic stressed rats (Zhang, Cao, and Li, 2008). *Astragali Radix* injection could significantly protect the neurons from

the apoptosis induced by radiation injury (Tang *et al*, 2010). Bone marrow mesenchymal stem cells (BMSCs) were induced using *Astragali Radix* with the diluted concentration of 200 mg/mL, then cell's morphological changes were observed by inverted microscope on days 1, 3, and 6, respectively and the expression of nestin, NSE, GFAP, and microtubule associated protein-2 (MAP-2) was measured by immunohistochemistry. It was found that *Astragali Radix* could make BMSCs differentiate into neural stem cells, induce the non-specific differentiation into neurons or glial cells, and promote the differentiated cells further maturation (Wang *et al*, 2008).

Conclusion

Astragali Radix is widely used in clinic to treat cerebrovascular diseases and neurological degenerative diseases due to the obvious nerve cell protective and recovery effects. However, the optimum dosage of *Astragali Radix* under different pathological conditions should be clarified. And the constituents in *Astragali Radix*, which play a major role in pharmacology, and the molecular mechanisms should be further researched in order to develop effective nerve regeneration drugs.

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