

Neuroprotective effect of panax notoginseng saponins and its main components

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ABSTRACT

Stroke is the third leading cause of death and the first cause of adult disability in industrial countries [1]. It is characterized by hemiplegia, hemianopsia, aphasia, mouth askew and sever sequelae. It is considered that an ischemic disease without any specific treatment method and few effective drugs such as tPA (human tissue-type plasminogen activator) and Edaravone with specific therapeutic window will cause a lot of disadvantages if being used inaccurate. Root of Panax notoginseng (PN) which is one of traditional Chinese medicines (TCMs), was first found in “Shennong’s Classic of Materia Medica” around 200 AD. Panax notoginseng saponins (PNS) is a multi-components mixture containing ginseng and saponins as the most important bioactive components which are commonly used in clinical treatment. Also, ginseng and saponins form the main components of many herbal medicines in the market, e.g., Xueshuantong injection [2], Xuesaitong injection [3], Xuesaitong soft capsule [4] and so on. The main monomers of Panax notoginseng saponins (PNS) are Ginsenoside-Rb1, Gensenoside-Rg1, Gensenoside-Re, Gensenoside-Rd and Panax notoginseng saponins-R1 [5]. In this review, we found some important points as well as shortcomings that require special consideration. We therefore highlighted the advances in neuro-protection of PNS and its main monomers in the area of experimental research.

KEYWORDS

Panax Notoginseng Saponins; Cerebral Ischemia; Neuro-Protection; Neuron Regeneration

1. INTRODUCTION

Stroke is an acute cerebrovascular disease, and is one of

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the most Chronic diseases affecting vulnerable human and it is the country’s third-leading cause of death according to a Survey. More than 25% of stroke survivors older than 65-year-old are disabled sooner before intervention. Stroke can be divided into two different syndromes according to different etiology: hemorrhagic stroke, cerebral hemorrhage, cerebral infarction and ischemic stroke. Clinically, PNS and its products are used regularly to treat stroke in China, and many experiments have been done to understand its mechanism. Through literature search using similar word or combination of words, we reviewed the recent advances in experimental research and use of PNS and its monomers as neuro-protective bioactive substance.

2. PANAX NOTOGINSENG SAPONINS AND ITS MONOMERS

2.1. Panax Notoginseng Saponins (PNS)

Experimentally, PNS can significantly improve symptoms after stroke and behavioral scores after animal nerve damages [6,7], improve animal’s learning and Memor, reduce infarct size and edema [8] after cerebral ischemia. PN also has the ability to dilate Cerebral blood vessels, and increase cerebral blood flow. An experiment shows that PNS can make mean blood pressure (MBP) of femoral artery and cerebral vascular resistance decline in anesthetic rabbit and rat [9]. In addition, Determining the micro-vascular diameter and blood flow velocity of the meninges of anesthetized mice using JI-200 laser micro-circulation dynamic analyzer, it was found that PNS can significantly speed up the velocity of blood flow, reduce brain ischemic hypoxia phenomena, and antagonism glutamate mediated excitatory poisoning [10]. This mechanism may be related to calcium channel blocking effect of PNS, reducing inflammation and slowing nerve apoptosis. PNS could block calcium in case of overload

in nerve cells after brain injury [8,11], block Ca^{2+} and cell adhesion molecule (CaM) compounds forming, to reduce the release of free fatty acids and the generation of oxygen free radicals, reduce Malondialdehyde (MDA) content in blood and brain after brain ischemia, and may have protective effect on traumatic brain injury [12]. PNS can inhibit gene expression of caspase-3 and production and release of related inflammatory factors [13,14], and can affect the content of heat shock protein and the conversion protein [8]. PNS can significantly reduce neural cell apoptosis and the outflow of LDH [15], reduce NO content, TNF and IL-1 activity, to protect neuronal integrity after cerebral ischemia [16]. Thus PNS can alleviate inflammatory reaction of ischemia brain to protect the ischemia tissue.

2.2. Ginsenoside-Rb1

Ginsenoside-Rb1 is a main monomer of PNS. Rb1 can decrease the degree of cerebral edema, improve neuro-behavioral score, protect vascular system from thickening and spasm [17], inhibit lipid peroxidation in the brain [18], improve the symptoms of stroke in early and late stage [19], and improve the learning ability after stroke [20]. Furthermore, Rb1 is able to expand average size of blood vessels, reduce the thickness of blood vessels in basilar part, Attenuate blood brain barrier (BBB) destruction, promote the expression of terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling assay (TUNEL) after MCAO through resistant to apoptosis. After ischemia, Rb1 can weaken the activity of micro glia, decrease the up regulation of brain tissue mRNA tumor necrosis factor- α and interleukin-1 (IL-1), IL- β and IL-6. Decreases expression of cox-2 mRNA and protein content in brain tissue [21]. Rb1 can reduce infarct size, inflammation and nerve damage. Also, increase the expression of Glial-derived neurotrophic factor (GDNF), the number of BCL-2 positive cells, and inhibit apoptosis of nerve cells [22]. Thus, it is able to prolong response time after ischemia, prevent and delay neuronal cells apoptosis, and reduce vertebral nerve injury in Hippocampal CA1 area in the brain [23].

The inhibitory effect of Rb1 on local inflammation, may be related to cholinergic system and nerve nutrition system. After cerebral ischemia, Rb1 may increase the expression of choline acetyltransferase, kinase A mRNA of basal forebrain tyrosine and hippocampus nerve growth factor mRNA [24], increase hippocampus choline absorption to reduce the amount in cortex [25]. At the same time, Rb1 can promote stem cell proliferation and differentiation of hippocampus, increase its neural function and structural plasticity [26], increase the rate of hippocampus cell survival [27], protect neuron structure, and recover the amount of microtubule-associated protein LC3 and autophagy gene Beclin1.

The effect of neural protection and neuronal apoptosis inhibition after re-perfusion is linked to Increase expression of Bcl-2, and decrease expression of Bax [28]. Rb1 can selectively inhibit the activity of type-1 Ca^{2+} voltage-gated calcium channel of hippocampus [29], increase activity of Na^{+} and K^{+} ATPase and Ca^{2+} , Mg^{2+} ATPase to reduce the flow of Ca^{2+} [30] on the synaptosome in rat cortical. Rb1 can increase the neurotransmitter release [31], can obviously decrease the height of phosphorylation level of the Tau protein [32].

2.3. Ginsenoside-Rg1

Ginsenoside Rg1 can inhibit lipid peroxidation in the brain [33], improve the learning ability and memory function of rats [34], improve the spatial learning ability, reduce the size of infarction area, promote Functional recovery of brain tissue [35]. By activating Na^{+} and K^{+} ATP enzyme within synaptic corpuscle of mouse [36], Rg1 can increase the concentration of cyclic adenosine monophosphate in the hippocampus [37]. Thus, it can have an effect on the central nervous system [38]. Rg1 can strengthen and stabilize the signaling pathways of HIF-1 α , inhibit the activity of caspase-3 [39], facilitate the release of glutamate [40], to promote the recovery of brain, regulating cell survival, angiogenesis and neurogenesis [41,42]. Rg1 can accelerate the proliferation rate of neuronal cells [43] and neural stem cells [44,45] in cerebral cortex, and increased hippocampal dentate gyrus cell number [46,47], protect the integrity of the nerve cells in the Structural arrangement [48], promote growth and differentiation of synapse [49], and change the hippocampus synaptic density without changing the synaptic plasticity. thus, improve spatial learning ability [50]. Rg1 can promote brain functional recovery [51], inhibit calcium accumulation, reduce potassium loss [52], reduce neuronal and cell apoptotic death by increasing the expression of Insulin-like growth factor One (IGF-1) in the brain [53]. Rg-1 can increase neuronal survival, reduce the release of LDH, reduce the morphological changes of cells and the division of nuclear DNA.

2.4. Ginsenoside-Rd

Ginsenoside-Rd can attenuate the basal hypertrophic remodeling of the renal hypertensive rats, without affecting the overall blood pressure. While its mechanism may be related to Ginsenoside-Rd that can selectively compete with Ca^{2+} receptor [54], block Ca^{2+} influx, abate the expression of TRPM7 and ASIC1 α after ischemia [55,56]. After stroke, Rd can pass through the BBB to protect neurons [57], and inhibit the formation of hydroxyl, reduce production and accumulation of DNA, protein and lipid in the early stage, reduce oxidative and inflammatory damage [58,59], decrease lactate accumu-

lation from anaerobic glycolysis, increase the amount of pyruvate-production of aerobic glycolysis. Rd can protect nerve cells, relieve nerve injury, reduce inflammatory response within cortex and striatum [59], by protecting mitochondria, restoring energy, and reducing cell apoptosis [59,60]. Furthermore, it can reduce accumulation of ADP nucleotide caused by stroke, inhibit activity of PARP-1, attenuate nerve cell apoptosis and damage caused by inflammatory reaction [61].

Rd can increase L-Glutathione (GSH) content; improve antioxidant activity of catalase, superoxide dismutase (SOD), glutathione peroxidase to provide neural protection by reducing content of intracellular reactive oxygen species and the MDA [62]. Besides, Rd can promote the proliferation of neural stem cells without affecting the differentiation [63]. This provides us a reliable basis for the future treatment of nerve injury.

2.5. Ginsenoside-Re

Ginsenoside-Re can reduce lipid peroxide. It's mechanism is that Re can improve mitochondrial membrane fluidity by cutting a small viscosity, and increase activity of superoxide dismutase and GSH-Px [64]. The increase of MDA content in brain after reperfusion, prompt that oxidative stress reaction caused by brain injury is serious. While Re can reduce the MDA content, mitochondria swelling, and the apoptosis of H^+ -ATP in the brain [65].

2.6. Panax Notoginseng Saponins-R1

Notoginseng saponin R1 can protect viability of rat neural stem cells and neuronal cells from Glutamate (Glu) interference. Also it is found that R1 can inhibit over proliferation of cells and prevent intracellular free Ca^{2+} increases, reduce production of intracellular reactive oxygen species, inhibit potential depolarization process of mitochondrial membrane in the Glu, to block the pathway and inhibit the expression of Bcl-2 and up-regulate the expression of Bax. Reason for this is that the neural protective targets of R1 may be a complex receptor composed of N-methyl-D-aspartate (NMDA) and NR1/NR2B [66].

3. SUMMARY AND PROSPECT

In clinical treatment, improving the cerebral blood supply can help reducing brain damage caused by chemia, and reducing the neuronal injury after cerebral ischemia/reperfusion, thereby promoting recovery of neural function. Panax notoginseng saponins have long been studied for its activities and its product. Xueshuantong injection has been used clinically, but the previous Studies have not met the international standard for drug discovery. Occlusion of the rat middle cerebral artery (MCAO) has approximately become the model of choice for mi-

micking and studying the pathology and symptoms of human stroke [67,68]. But the mechanism and effect of ginseng on complex diseases are still unknown and need further study. With the rise in global demand for cerebrovascular drugs, the clinical application of notoginseng and its total saponins will have broader prospects in the field of medicine especially in the area of ischemic stroke.

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