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Research paper

Treatment with ginseng total saponins improves the neurorestoration of rat after traumatic brain injury

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ABSTRACT

Ethnopharmacological relevance: Ginseng, the root of *Panax ginseng C.A. Meyer*, is a traditional medicinal herb that has been widely used in Asia for the treatment of many diseases through its effects of reinforcing vitality, strengthening the bodily resistance to pathogenic factors, engendering body liquids and allaying thirst, relieving uneasiness of the body and mind and benefiting intelligence, reducing body weight and prolonging life. Ginsenosides are the most important biologically active substances in ginseng. Many reports have suggested that ginsenosides could exert prominent neuroprotective and neurotrophic effects, promote neural stem/progenitor cell (NSC) proliferation and promote neurite outgrowth and neuronal network formation. The present study aimed to investigate whether treatment with ginsenosides could facilitate NSC proliferation in the hippocampal formation after traumatic brain injury (TBI) and contribute to the recovery of neurological functions including learning and memory.

Materials and methods: The modified Feeney's method was used to induce a TBI in rats. Ginseng total saponins (GTS) were treated intraperitoneally twice a day for 1 week after the TBI. The neurological functions, morphology of the hippocampus, expression of nerve growth-related factors and number of NSCs in the hippocampal formation ipsilateral to the trauma were determined.

Results: We determined 1) GTS (5–80 mg/kg) treatment after a TBI improved the recovery of neurological functions, including learning and memory, and reduced cell loss in the hippocampal area. The effects of GTS at 20, 40, 60, and 80 mg/kg were better than the effects of GTS at 5 and 10 mg/kg. 2) GTS treatment (20 mg/kg) after a TBI increased the expression of NGF, GDNF and NCAM, inhibited the expression of Nogo-A, Nogo-B, TN-C, and increased the number of BrdU/nestin positive NSCs in the hippocampal formation.

Conclusions: GTS treatment in rats after a TBI alleviated the secondary brain injury and ameliorated the neurological functions with an effective dose limit of 5–80 mg/kg. GTS regulated the expression of nerve growth-related factors and improved the proliferation of neural stem/progenitor cells, which might facilitate neural regeneration and tissue repair, and might contribute to the recovery of neurological functions, including learning and memory. These effects of GTS might provide a foundation for the use of ginseng as a medicinal herb to enhance intelligence, reduce the aging process and prolong life in the traditional medicine.

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1. Introduction

Traumatic brain injury (TBI) refers to brain tissue injury caused by trauma, including falls, motor vehicle-traffic injury, being struck (by/against), assault, and unknown/other causes (Maas et al., 2008; Coronado et al., 2011). TBI is a major global problem and affects approximately 10 million peoples annually; therefore it has a substantial impact on the healthcare system throughout the world (Hyder et al., 2007; Corrigan et al., 2010; Gean and Fischbein, 2010). TBI not only produces high mortality and morbidity, but also significantly affects the socioeconomic lives

Abbreviations: BrdU, 5-Bromo-2′-deoxy-uridine; GDNF, glial cell line-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GTS, ginseng total saponins; NCAM, neural cell adhesion molecule; NGF, nerve growth factor; Nogo-A, neurite outgrowth inhibitor A; Nogo-B, neurite outgrowth inhibitor B; NSC, neural stem/progenitor cell; PBS, phosphate buffer saline; TBI, traumatic brain injury; TN-C, tenascin-C

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of survivors, some of which even have long-term disabilities (Hyder et al., 2007; Corrigan et al., 2010; Gean and Fischbein, 2010; Feigin et al., 2013). TBI can result in significant motor, sensory, cognitive and emotional impairments. Even mild TBI can be associated with headache, nausea/vomiting, dizziness, tinnitus, vision changes, impaired balance and coordination, mood and memory changes, difficulty with memory and attention, and fatigue and/or sleep disturbances (Winston, 1979).

TBI includes the primary injury produced by transient mechanical damage and the secondary brain injury caused by many molecular and cellular responses triggered by a series of subsequent cascades (Rovegno et al., 2012). Due to the irreversibility of the primary injury, many treatment strategies for TBI have been tested to prevent and reduce the secondary injury after TBI, but the results of clinical trials on neuroprotective agents have been disappointing (Xiong et al., 2010a). There is currently no specific treatment available for TBI other than supportive care (Maas et al., 2010; Rovegno et al., 2012). Recent preclinical data suggest that neurorestorative strategies that promote angiogenesis (formation of new blood vessels from pre-existing endothelial cells), axonal remodelling (axonal sprouting and pruning), neurogenesis (generation of new neurons) and synaptogenesis (formation of new synapses) provide promising opportunities for the treatment of TBI (Picard-Riera et al., 2004; Richardson et al., 2010; Xiong et al., 2010a, b). However, there are many factors that impact the neuroregeneration of brain tissue (Picard-Riera et al., 2004; Richardson et al., 2010). The involved mechanisms are very complicated, and there have been no substantial breakthroughs (Picard-Riera et al., 2004; Richardson et al., 2010).

The transplantation of cells or tissues tested to promote neural regeneration, the reconstruction of neurovascular units and brain tissue repair after injury includes peripheral nerve graft, Schwann cells, embryonic brain and spinal cord tissue, olfactory ensheathing cells, embryonic and neural stem cells, bone marrow stromal cells, activated macrophages, and others (Chiu et al., 2009; Richardson et al., 2010; Vaquero and Zurita, 2010; Shear et al., 2011), but the involved methodology is in its infancy, and the efficacy of transplantation is unreliable (Xiong et al., 2010b; Gögel et al., 2011; Jablonska and Lukomska, 2011). An alternative method is to promote the endogenous neural stem cell proliferation (Leker, 2009; Yoneyama et al., 2011) and to help these cells migrate to the injured area, repair the damaged brain tissue and restore the neurological functions. This method is still a long way from being used in clinical applications (Leker, 2009; Xiong et al., 2010b).

Ginseng, the root of *Panax ginseng C.A. Meyer* (Araliaceae), is a traditional medicinal herb. Through its effects of reinforcing vitality, strengthening the bodily resistance to pathogenic factors, engendering body liquids and allaying thirst, relieving uneasiness of the body and mind and benefiting intelligence, reducing body weight and prolonging life, ginseng have been widely used in Asia for the treatment of many diseases with symptoms such as consciousness uneasiness, insomnia, palpitations, fatigue and lack of strength, lack of appetite, thirst, and prostration (Attele et al., 1999; Ng, 2006; Chen et al., 2008). Ginsenosides are the most important biologically active substances extracted from *Panax ginseng C.A. Meyer*, and ginseng total saponins (GTS) are a mixture of ginsenosides with various ginsenoside ratios (Attele et al., 1999). Many reports have suggested a prominent neuroprotective effect of ginsenosides on the brain subjected to ischaemia or trauma (Lim et al., 1997; Ji et al., 2005) and on the neurons deprived of oxygen/glucose (Jiang et al., 2000, 2001; Jiang and Jiang, 2003) or damaged under other conditions (Rudakewich et al., 2001; Liao et al., 2002). It has been reported that ginsenosides might exert a neurotrophic effect (Liang et al., 2010) and promote neural stem cell transformation into neurons or glial cells (Shi et al., 2005; Liu et al., 2007). Shen and Zhang (2004) found that ginsenoside Rg1 promoted the proliferation of hippocampal progenitor cells. Ginsenosides could also increase the viability of hippocampal neurons (Gong et al., 2011; Liu et al., 2011) and promote neurite outgrowth and neuronal network formation (Tohda et al., 2005; Wang et al., 2006). Zheng et al. (2011) recently reported that GTS enhanced neurogenesis and might contribute to functional recovery after focal cerebral ischaemia.

No studies have been published regarding whether GTS could facilitate neurogenesis and neuronal regeneration after TBI and contribute to the recovery of neurological functions including learning and memory. The present study was performed primarily to investigate the neural stem/progenitor cell (NSC) proliferation-promoting effect in the hippocampal formation while documenting the neuroprotective effect and the effective dosage of ginseng total saponins used in rats after traumatic brain injury.

2. Materials and methods

2.1. Animals and materials

Male Sprague-Dawley rats (250–300 g body weight) were obtained from the Experimental Animal Center of Nantong University, Nantong, China. All the procedures were in strict accordance with the institutional guidelines of Nantong University, which complies with international rules and policies. Ethics in accordance with the ARRIVE (Animal Research: Reporting *In Vivo* Experiments) guidelines were followed in the animal experiments and approved by the Animal Care and Use Committee of Nantong University, Nantong, China (Permit number: 20120210-04). All the surgeries were performed under anaesthesia, and all efforts were made to minimise suffering. One hundred and sixty nine rats were randomly allocated to each experimental group (Table 1). Due to anaesthetic accidents and anaesthetic side effects such as adynamic ileus, some rats died during the experiments, and a portion of the sample was lost in each group (Table 1). The data obtained from these animals were excluded.

Ginseng total saponins, extracted from the stem and leaf of Jilin *Panax ginseng*, were purchased from the Department of Organic Chemistry, Medical School of Jilin University, Changchun, China.

Table 1
Number of rats used for each group with dead rats in parenthesis.

Group		Table 2	Fig. 2	Fig. 3	Fig. 4	Fig. 5	Fig. 6	Fig. 7	Fig. 8
Sham–operated		10(0)	6 rats from Table 2 for each group	6(0)	5(0)	6(1)	The same as Figure 4	6(1)	The same as Fig. 7
TBI		13(3)		8(2)	7(2)	7(2)		7(2)	
GTS (mg/kg)	5	12(2)							
	10	11(1)							
	20	11(1)		7(1)	6(1)	7(2)		6(1)	
	40	11(1)							
	60	11(1)							
	80	12(2)							

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