Gastrodin promotes the secretion of brain-derived neurotrophic factor in the injured spinal cord

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Abstract
Gastrodin, an active component of tall gastrodia tuber, is widely used in the treatment of dizziness, paralysis, epilepsy, stroke and dementia, and exhibits a neuroprotective effect. A rat model of spinal cord injury was established using Allen’s method, and gastrodin was administered via the subarachnoid cavity and by intraperitoneal injection for 7 days. Results show that gastrodin promoted the secretion of brain-derived neurotrophic factor in rats with spinal cord injury. After gastrodin treatment, the maximum angle of the inclined plane test, and the Basso, Beattie and Bresnahan scores increased. Moreover, gastrodin improved neural tissue recovery in the injured spinal cord. These results demonstrate that gastrodin promotes the secretion of brain-derived neurotrophic factor, contributes to the recovery of neurological function, and protects neural cells against injury.

Key Words
neural regeneration; spinal cord injury; gastrodin; brain-derived neurotrophic factor; microenvironment; traditional Chinese medicine; spinal structure; animal behavior; central nervous system injury; grants-supported paper; neuroregeneration

Research Highlights
(1) Gastrodin significantly contributes to the recovery of neurological function in rats with spinal cord injury.
(2) Gastrodin promotes the secretion of brain-derived neurotrophic factor in the injured spinal cord.
(3) Gastrodin can maintain a uniform distribution of brain-derived neurotrophic factor in the spinal cord tissue, and stabilize the microenvironment following spinal cord injury.

INTRODUCTION
Recently, substantial progress has been made in the treatment of spinal cord injury. In particular, immunotherapy, tissue transplantation, and other advanced reconstruction methods have immensely improved the treatment of spinal cord injury. However, a number of obstacles remain, such as tissue matching, immunological rejection, low inductive activity, difficulty in sampling, and ethical considerations.

Because of the limited regenerative ability of the spinal cord, it is difficult to fully recover from spinal cord injury\(^1\)\(^2\). Spinal cord injury includes primary injury and secondary injury. Primary injury refers to the initial physical damage to neural tissue, mainly to neuronal cell bodies and neurites. Secondary injury refers to a series of pathological changes following primary injury, accompanied by metabolic and genetic changes, edema, inflammatory reaction, local ischemia, release of excitatory amino acids, lipid peroxidation and Ca\(^{2+}\) overload, resulting
in neural cell apoptosis\textsuperscript{[3-4]}. This complex pathogenetic process strongly impairs the recovery of spinal cord function\textsuperscript{[3-4]}. Spinal cord injury therapy is hindered by the numerous changes in the microenvironment of the injured spinal cord, which impair neuronal survival, axonal growth, nerve cell renewal and synapse formation, thereby limiting spinal cord repair. The strategy for treatment of spinal cord injury is to improve the microenvironment, to reduce the impact of disadvantageous factors, and to promote spinal cord repair and functional reconstruction\textsuperscript{[5-6]}. Scientists have used many methods, such as drug treatment, surgery, transplantation, gene therapy, hyperbaric oxygen and mild hypothermia\textsuperscript{[5-6]}. Nevertheless, there is no single method that can completely cure spinal cord injury. However, a combined treatment approach can provide satisfactory therapeutic efficacy.

Brain-derived neurotrophic factor is a member of the neurotrophin family of growth factors, helping to support the survival of existing neurons, and encourage the growth and differentiation of new neurons and synapses\textsuperscript{[7]}. Brain-derived neurotrophic factor can reduce neuronal death following spinal cord injury\textsuperscript{[8]}. The increased expression of brain-derived neurotrophic factor contributes to neuronal regeneration, differentiation and maturation, and decreases neuronal apoptosis\textsuperscript{[9]}. However, brain-derived neurotrophic factor secretion in vivo is insufficient to promote neuronal survival or axonal regeneration; thus, the application of exogenous brain-derived neurotrophic factor is necessary to obtain noticeable clinical improvement\textsuperscript{[10-11]}. However, host rejection is an obstacle, and it is difficult for the protein to traverse the blood-brain barrier\textsuperscript{[12]}. There is a lack of drugs that promote the secretion of endogenous brain-derived neurotrophic factor in the clinic; therefore, it is important to seek an effective drug for this purpose.

Gastrodin, an active component of tall gastrodia tuber, improves the elasticity of large- and medium-sized artery walls, expands cerebral vessels, increases blood supply, calms, hypnotizes, relieves pain, and imparts resistance to convulsions\textsuperscript{[13-14]}. Gastrodin exerts neuroprotective effects by suppressing excitotoxicity, inhibiting free radical injury, resisting impairments in energy metabolism and suppressing apoptosis\textsuperscript{[15]}. Investigators have conjectured that the therapeutic effect of gastrodin on spinal cord injury is possibly associated with the secretion of brain-derived neurotrophic factor. In the present study, we sought to examine the effects of gastrodin on recovery following spinal cord injury and determine whether it could promote neurotrophic factor secretion.

## RESULTS

### Quantitative analysis of experimental animals

A total of 45 rats were equally and randomly assigned to gastrodin, model and sham surgery groups. The spinal cord injury model was established using Allen’s method in the gastrodin and model groups. Gastrodin was injected into the subarachnoid cavity immediately after spinal cord injury in the gastrodin group. From then on, gastrodin was intraperitoneally given. Three rats in the model group and two rats in the gastrodin group died of bladder rupture following spinal cord injury. Dead rats were supplemented by new ones in both groups. A total of 45 rats were included in the final analysis.

### Gastrodin improved neurological function in rats with spinal cord injury

After spinal cord injury, the maximum angle in the inclined plane test decreased, and the Basso, Beattie and Bresnahan score diminished ($P < 0.01$ or $P < 0.05$). After gastrodin treatment, the maximum angle in the inclined plane test was significantly greater and the Basso, Beattie and Bresnahan score was significantly higher ($P < 0.05$). Moreover, with increasing time, the maximum angle in the inclined plane test gradually rose and the Basso, Beattie and Bresnahan score gradually increased ($P < 0.05$; Figure 1).

### Gastrodin promoted the recovery of spinal cord tissue

Hematoxylin-eosin staining demonstrated that neural cells were normal in the spinal cord of rats from the sham surgery group, showing a clear cell boundary and regular nucleus shape, without swelling, disruption or nuclear fragmentation. In the model group, at 1 week following spinal cord injury, cell swelling was visible in the spinal cord tissue. With increasing time, the amount of cell debris rose, but cell swelling diminished. In the gastrodin group, at 1 week following spinal cord injury, nerve cell swelling appeared in the spinal cord tissue. With increasing time, the amount of cell debris rose and irregular neural cells were observed. At 4 weeks following spinal cord injury, normal nerve cells appeared and the number of cell debris decreased (Figure 2).

### Gastrodin increased brain-derived neurotrophic factor expression in the injured spinal cord

Immunohistochemistry results showed that compared with the sham surgery group, brain-derived neurotrophic factor expression...
factor expression was higher in the spinal cord tissue at 1 week after spinal cord injury in the model group. Brain-derived neurotrophic factor expression decreased at 2 weeks. Brain-derived neurotrophic factor expression was uneven in spinal cord tissue and was not visible in some regions, but abnormally high expression was observed in some regions at 4 weeks. In the gastrodin group, brain-derived neurotrophic factor expression rose in the injured spinal cord, with levels increasing with time. Brain-derived neurotrophic factor expression slightly increased at 1 week, gradually increased over time, peaked at 2 weeks, and then gradually decreased. Brain-derived neurotrophic factor expression was uniformly distributed at 4 weeks (Figure 3).

Gastrodin plays a role in anti-convulsion, sedation and analgesia, and can be used in the treatment of dizziness, paralysis, epilepsy, stroke and dementia[20]. Gastrodin traverses the blood-brain barrier, enters the cerebrum, and is rapidly decomposed into p-hydroxybenzyl alcohol in the brain, liver and blood[21]. Gastrodin alleviates transient focal cerebral ischemic damage, reduces reactive oxygen species levels, hippocampal neuronal death and excitotoxicity[22], and protects cortical neurons against hypoxia[23]. Gastrodin can enhance learning and memory abilities[24-25]. Gastrodin injection in the treatment of nerve injury can improve the microenvironment, elevating growth-related gene expression, suppressing neuronal apoptosis, and promoting neuronal repair[26-29]. Gastrodin inhibits glial cell activation and hyperplasia, and reduces interleukin-1, interferon gamma, interleukin-6, and tumor necrosis factor alpha expression by suppressing the nuclear factor-κB signaling pathway and mitogen-activated protein kinase phosphorylation, resulting in a diminished inflammatory reaction following spinal cord injury[30-31]. Gastrodin protects the spinal cord against damage following injury by modulating various processes following nerve injury. It protects against apoptosis and amino acid excitotoxicity, inhibits glial cell reactivity, and is an antioxidant[32]. Furthermore, gastrodin reduces lactate dehydrogenase release, increases superoxide dismutase activity, reduces malondialdehyde content, decreases free radical levels, and inhibits lipid peroxidation[5-6, 33-34].

Results from this study show that gastrodin promotes the recovery of motor function following spinal cord injury. This effect was not noticeable in the short term, but became gradually more apparent over time. Gastrodin was found to promote brain-derived neurotrophic factor secretion, and this effect reached a peak at 2 weeks and then gradually decreased, but brain-derived neurotrophic factor expression was still uniform in the injured region.
Figure 2 Effects of gastrodin on morphology of the spinal cord in rats with spinal cord injury (SCI; hematoxylin-eosin staining, light microscope, × 400).

In the sham surgery group, normal neurons were visible in the spinal cord tissue. In the model group, obvious cell swelling was observed at 1 week after SCI. Cell debris increased, but cell swelling decreased over time. In the gastrodin group, cell swelling was visible in spinal cord tissue at 1 week. Cell debris increased at 2 weeks. Normal neural cells appeared and cell debris significantly decreased at 4 weeks.

Figure 3 Effects of gastrodin on brain-derived neurotrophic factor (BDNF) expression in the spinal cord tissue of rats with spinal cord injury (SCI) (immunohistochemistry, light microscope, × 400).

Arrows indicate BDNF positive expression. In the sham surgery group, BDNF expression was not abundant. In the model group, BDNF expression increased at 1 week, decreased at 2 weeks, and became uneven at 4 weeks. In the gastrodin group, BDNF expression slightly increased at 1 week, peaked at 2 weeks, and decreased at 4 weeks.
In comparison, brain-derived neurotrophic factor expression was not uniform in the model group, which was probably associated with differences in the local microenvironment following spinal cord injury. Taken together, our findings demonstrate that an increase in brain-derived neurotrophic factor expression contributes to neuronal repair, and that gastrodin can promote brain-derived neurotrophic factor secretion and maintain microenvironmental stability.

In summary, gastrodin significantly enhances motor functioning in rats with spinal cord injury, promotes brain-derived neurotrophic factor expression, maintains a uniform distribution of brain-derived neurotrophic factor in the spinal cord tissue, and contributes to microenvironmental stability, protecting the injured spinal cord.

MATERIALS AND METHODS

Design
A randomized, controlled animal experiment.

Time and setting
Experiments were performed at the Liaoning Provincial Key Laboratory of Tissue Engineering, First Affiliated Hospital of Liaoning Medical University, China from September 2011 to March 2012.

Materials
Animals
A total of 45 male Sprague-Dawley rats aged 2–3 months and weighing 225 ± 25 g were provided by the Experimental Animal Center, Liaoning Medical University, China (animal license No. SCXK (Liao) 2003-0019). The animals were housed in individual stainless steel cages in a room with a 12-hour light/dark cycle. The temperature was controlled at 21 ± 1°C with a relative humidity of 50%. The protocols were conducted in accordance with the Guidance Suggestions for the Care and Use of Laboratory Animals, formulated by the Ministry of Science and Technology of China[35].

Drug
Gastrodin [chemical name: 4-(hydroxymethyl)phenyl beta-D-glucopyranoside; molecular formula: C_{13}H_{18}O_{7}; molecular weight: 295.38; chemical structural formula shown in Figure 4], a colorless clear liquid, was purchased from Jinan Limin Pharmaceutical Co., Ltd., Jinan, Shandong Province, China (approval No. GYZZ H20059653; batch No. 11100602; form of drug: injection; specification: 2 mL, 200 mg).

Methods
Establishment of the spinal cord injury model using Allen’s method
The rats were intraperitoneally anesthetized with 10% chloral hydrate (3 mL/kg). After depilating and sterilizing, a longitudinal incision was made on the back along the posterior median line to expose the spinous process, vertebral plate and transverse process. The T_{10} vertebral plate was removed to form a square bone window to expose the spinal cord. Allen’s impactor[36] (New York University, NY, USA) (60 g·cm) was used in this study. Standards for success: edema, hemorrhage, entire purple spinal dura mater, distended, spastic tail, retraction of lower limbs and the body, and flaccid paralysis[36]. Sham surgery group only received laminectomy.

Drug interventions
In the gastrodin group, 5 mg (0.05 mL) gastrodin was injected into the subarachnoid cavity immediately after spinal cord injury. From then on, gastrodin 100 mg/kg was intraperitoneally given, once a day, for 7 consecutive days. Rats in the model group were injected with 0.05 mL saline. All rats were housed in their cages.

Behavioral observation
Inclined plane test: at 1, 2 and 4 weeks following spinal cord injury, the inclined plane test was performed. Using a modified Rivlin method[37], rats were vertically placed on the inclined plane. The angle of the inclined plane was gradually increased from 0°. Grading standard was the maximum angle of the inclined plane the rat could stay on for 5 seconds without falling off.

Basso, Beattie and Bresnahan score: at 1, 2 and 4 weeks following spinal cord injury, rat behavior was analyzed using the Basso, Beattie and Bresnahan locomotor rating scale[38]. Experimenters who were familiar with the scale performed the experiment using the blind method. The Basso, Beattie and Bresnahan scale ranges from 0 to 21. A score of 21 indicates normal movement, and a score of 0 represents no movement.
Observation time was 4 minutes.

**Hematoxylin-eosin staining for morphological examination of the rat spinal cord**

At 1, 2 and 4 weeks following spinal cord injury, the rats were intraperitoneally anesthetized with 10% chloral hydrate (3 mL/kg). The chest was opened. After left ventricle-aortic cannula, the right auricle was incised for perfusion of sterile saline (200 mL), followed by fixation with 4% paraformaldehyde (about 200 mL) for 30 minutes. The injured spinal cord was placed in 4% paraformaldehyde solution overnight, embedded in paraffin, sliced into sections, and stained with hematoxylin and eosin. Pathological changes in the spinal cord tissue were observed under the light microscope (Olympus, Tokyo, Japan).

**Immunohistochemical observation of brain-derived neurotrophic factor expression in the rat spinal cord**

The rats were intraperitoneally anesthetized with 10% chloral hydrate (0.5 mL/100 g) and perfused with 4% paraformaldehyde via the heart. The injured spinal cord was excised and processed into paraffin sections. After dewaxing and hydrating, antigen was retrieved using citrate buffer solution, followed by treatment with 3% H2O2 for 20–30 minutes. The specimens were treated with a blocking solution for 20 minutes, incubated with rabbit anti-rat brain-derived neurotrophic factor polyclonal antibody (1:500; Santa Cruz Biotechnology, Santa Cruz, CA, USA) at 4°C overnight, then in horseradish peroxidase–labeled goat anti-rabbit IgG (1:1 000; Beijing Zhongshan Co., Beijing, China) at room temperature for 2 hours, in streptavidin–biotin complex for 30 minutes, and then developed with diaminobenzidine (Boster, Wuhan, Hubei Province, China) for 30 minutes, followed by hematoxylin–eosin staining for 0.5 minutes. Sections were dehydrated through a graded alcohol series, permeabilized with xylene, mounted in buffered glycerol, and observed under the light microscope.

**Statistical analysis**

The data were analyzed using SPSS 16.0 software (SPSS, Chicago, IL, USA). Measurement data were analyzed using a test of normality. Data, which obey a normal distribution, were expressed as mean ± SD. Intergroup mean comparisons were done using analysis of variance (completely randomized) and independent samples t-test. A value of $P < 0.05$ was considered statistically significant.

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**Author contributions:** The experiment was designed, and evaluated by Xifan Mei. All authors performed the experiments and approved the final version of the paper.

**Conflicts of interest:** None declared.

**Ethical approval:** The project had full ethical approval from the Animal Ethics Committee of Liaoning Medical University in China.

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