Neural plasticity after spinal cord injury

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Abstract
Plasticity changes of uninjured nerves can result in a novel neural circuit after spinal cord injury, which can restore sensory and motor functions to different degrees. Although processes of neural plasticity have been studied, the mechanism and treatment to effectively improve neural plasticity changes remain controversial. The present study reviewed studies regarding plasticity of the central nervous system and methods for promoting plasticity to improve repair of injured central nerves. The results showed that synaptic reorganization, axonal sprouting, and neurogenesis are critical factors for neural circuit reconstruction. Directed functional exercise, neurotrophic factor and transplantation of nerve-derived and non-nerve-derived tissues and cells can effectively ameliorate functional disturbances caused by spinal cord injury and improve quality of life for patients.

Key Words: spinal cord injury; plasticity; synapse; functional exercise; neurotrophic factor; cell transplantation; tissue transplantation; reviews

INTRODUCTION
Over the past 30 years, the concepts of the central nervous system (CNS) have changed. The CNS is an organ with plasticity and has the ability to regulate and adapt after environmental transition or injury. Specifically, the uninjured neurons and axon lateral branches can grow in denervated regions to reconstruct neural circuits to compensate for impaired sensory and motor function[1]. Because the axonal lateral branch connection forms distal to the injury site, it avoids limitations to axonal growth and elongation due to an inhibitive environment in the injury site. However, the ability of axonal regeneration and elongation is limited in adult humans and other animals. Thus, improving neural plasticity is critical for repair of CNS injury. Increasing numbers of studies have confirmed that functional exercise targeting the denervated region, neurotrophic factor and transplantation of tissues and cells can effectively improve neural plasticity. Retrieval strategy regarding articles included in this review is shown as follows.

Inclusion criteria: studies discussing advances in neural plasticity after spinal cord injury (SCI).
Exclusion criteria: outdated and repetitive studies were excluded.
Article inclusion: 231 articles were first collected, which were all published in English. The titles and abstracts were read, and 146 were excluded, including 35 repetitive studies. The remaining 52 English articles comprising 41 basic studies and animal experiments, and nine review articles were used for further analysis. These articles analyzed conditions for modulation of neural plasticity and reconstruction of the neural circuit and summarized methods for improving neural plasticity changes.

CONDITIONS FOR MODULATION OF NEURAL PLASTICITY AND RECONSTRUCTION OF NEURAL CIRCUITS

Due to the limitation of axonal regeneration in the adult injured CNS, spontaneous sensory and motor functional recovery after SCI has been regarded as reconstruction of neural circuits by axonal or dendritic elongation connections[2]. The reconstruction of neural circuits is generated in the spinal cord, brain stem, thalamus, and sensorimotor cortex[3], and is mainly comprised of synaptic reorganization, axonal sprouting, and neurogenesis.

Synaptic reorganization
Dendritic spines have been commonly regarded as target connections for synapses, so the number and structural changes of dendritic spines directly influence synaptic reorganization. It has been demonstrated that CNS dendritic plasticity changes contribute to the abnormal surrounding environment, sensorimotor learning, cortical or peripheral nerve injury and SCI[4]. Enhancement of existing nerve connections benefits neural plasticity in a short period of time[5], but...
axon sprouting is the main regeneration after SCI, but a large number of studies indicate spontaneous axonal growth. For example, electrostimulation induces changes in neck length and head appearance and the size of the dendritic spine. Laser confocal microscopy has revealed that dendritic spine density in rat motor cortex with overhemisection injury at the C4 level was reduced in 7 days and partly recovered in 28 days, and the spine head diameter significantly increased in a layer-specific manner, and SCI led to a roughly 10% increase in mean spine length. In addition, filopodium-like long dendritic protrusions were more frequently observed after SCI, suggesting morphological changes in the synapse after SCI. Morphological changes of dendritic spines can be modulated by combinatorial treatment with embryonic transplants and neurotrophin-3.

**Axonal sprouting**

Little evidence indicates spontaneous axonal regeneration after SCI, but a large number of studies have demonstrated that axonal sprouting is the main pattern for axonal accommodation and compensation. Sprouting is different from regeneration. Axonal regeneration is a process whereby injured axons re-grow at the broken ends, but axonal sprouting is a process of lateral branch sprouting and elongation of uninjured axons. SCI can cause a glial scar, which has a strong physical and chemical barrier function that inhibits axonal regeneration. Fortunately, axonal sprouting occurs at a site distal to the glial scar, which lays a foundation for reconstruction of the neural circuit based on injured neural compensatory connections. After incomplete SCI in rats, transected hind limb corticospinal tract axons were reported to sprout into the cervical gray matter to contact short and long propriospinal neurons, which arborized onto lumbar motor neurons, creating a new intraspinal circuit that relays cortical inputs to its original spinal targets at 12 weeks. Axonal sprouting of the injured reticulospinal tract was found after lateral thoracic hemisection of the spinal cord, which accompanied partly recovered motor function in the hindlimbs. Moreover, this recovery occurred in parallel with an increased number of collaterals of spared reticulospinal tract fibers entering the intermediate lamina below the injury at L2. Most evidence of injury-induced axonal sprouting is obtained from rats, but it remains poorly understood whether this sprouting is associated with the injury.

**Neurogenesis**

Normally, neurogenesis occurs mainly in the subventricular zone, hippocampus, and olfactory bulb of adult mammals, and also appears in the marginal zone of the CNS after specific injury or disease. Although the mechanism of neurogenesis remains uncertain, the CNS has been shown to induce neurogenesis in response to specific pathological changes. Neurogenesis was found in an animal model of corpus striatum ischemia, and the newly generated nerve exhibited good physiology, neuronal appearance, and synapse phenotype. Normally, neurogenesis is impossible in the adult animal spinal cord, but recent evidence indicates that special SCI or a related disease can induce neurogenesis in the spinal cord. Direct trauma to the spinal cord can induce a large number of glial cells, thus facilitating the formation of glial scars. Astrocytes in the scars can release insulin-like growth factor binding protein 6 and core proteoglycan, which can inhibit axonal sprouting and other regeneration-related processes. Therefore, neurogenesis was not detected in an animal model of hemisection of the spinal cord or posterior horn injury. However, neurogenesis can occur after a peri-lesion in the spinal cord with little, or even no glial scar formation, and dorsal horn-induced sensory disturbance in the thumb, index and middle fingers has been well discovered. Moreover, dorsal root injury can induce neurogenesis within the spinal cord and the sensorimotor cortex, demonstrating that dorsal root injury can induce neurogenesis at multiple sites in the projection pathway.

**METHODS FOR PROMOTING NEURAL PLASTICITY**

Axonal regeneration and sprouting in the adult CNS are limited by inhibitory factors released or upregulated after injury. Although the underlying mechanisms remain poorly understood, a variety of methods have been developed to stimulate neural plasticity, promote axonal sprouting and neural circuit reconstruction.

**Functional exercise**

Functional exercise can improve neural plasticity to promote functional recovery after CNS injury. The rodents were raised in a special container, with a voluntary running wheel, which can enhance animal motor activity or promote sensory and cognitive function, which manifests as an increase in the cerebral cortex size, dendritic branch quantity and neurogenesis in the hippocampus. These changes can promote motor functional recovery after SCI and stroke. In addition, stimulation on sensory function and special exercises, such as multimodal early onset stimulation, can effectively restore motor function after brain injury. However, these interventions focus on organism motion or autonomic mechanical motion, and functional recovery in some delicate activities after SCI remains controversial. Some studies reported that functional recovery of the CNS can be achieved by some special functional exercises, and recovery of function to get something after SCI requires enhancement of reaching training, but
not the ladder climbing test\textsuperscript{[31]}. Endurance exercise in combination with skill training (run + reaching) greatly recovered reaching ability but did not transfer to postural support or gait in Sprague-Dawley rats with middle cerebral artery occlusion\textsuperscript{[32]}. In addition, microtubule-associated protein 2 expression was slightly enhanced in the contralateral motor cortex compared with the contralateral sensory and ipsilateral cingulate cortices, suggesting that running preceding reaching training may have resulted in more dendritic branching within the motor cortex. However, running exercise alone has minimal effects on motor function of forelimbs of rats\textsuperscript{[33]}.

The potential mechanisms of this functional training may be associated with increased nerve growth factor expression and a reconstructed neural network related to motor function in the spinal cord\textsuperscript{[34]}. Although running significantly promoted functional recovery after SCI, rehabilitation treatment for functional recovery of the hands and upper limbs after cervical SCI is still lacking\textsuperscript{[31]}. Constraint-induced movement therapy has been shown to effectively promote projection pathway functional reorganization of the corticospinal tract (CST)\textsuperscript{[35]}, including functional exercise in the presence of upper limb suspension, plaster cast fixation, gloves or splint fixation of the upper limbs\textsuperscript{[36]}. Some hand functional recovery can improve the quality of life for patients after cervical SCI. Girgis et al\textsuperscript{[31]} observed that after 6 weeks of training in a single pellet reaching task, collateral sprouting of the lesioned CST fibres rostral to the injury was increased, along with cortical levels of growth associated protein-43 (GAP43), which improved motor function of rats. In addition, after a unilateral CST injury at the brainstem level, the contralateral impaired forelimb of rats was either restricted by a cast, or forced, by casting the unimpaired forelimb. After 3 weeks of constraint-induced movement therapy, the function of the impaired forelimb was significantly improved, which was accompanied with significant changes in the cell adhesion molecule nectin-3y, matrix metallopeptidase 3, heat shock protein 70-related protein, collapsin response mediator protein-2A, and calyxtenin 2, neuregulin 1, and membrane-bound C2 domain containing protein, suggesting that functional exercise plays an important role in axonal growth and elongation after SCI (Figure 1).

**Neurotrophic factors**

Nerve growth factor, brain-derived neurotrophic factor (BDNF), and neurotrophic factors 3, 4, and 5 can enhance neuronal survival by binding neuron surface receptors (trk tyrosine kinase, p75\textsubscript{NGF-R})\textsuperscript{[38]}. Recent evidence indicates that neurotrophic factor expression in motor neurons was increased after CNS\textsuperscript{[39]} and peripheral nerve\textsuperscript{[40]} injuries. Growth factors of motor neurons can mediate spinal nerve development and survival\textsuperscript{[38]}. Axonal collateral branch formation is the base of the neural circuit, and the filopodium is critical for the formation of a collateral branch and presynaptic structure\textsuperscript{[41]}. One study of sensory nerve axons showed that filopodia formed during F-actin accumulation in a short period of time (24 seconds when F-actin accumulation reached its peak), i.e. actin pathway, and nerve growth factor promoted the initiation of actin patch precursors to the formation of axonal filopodia\textsuperscript{[42]}.  

![Figure 1](image)  

**Figure 1** Effects of functional exercise on neural plasticity in rats with unilateral corticospinal tract injury (CST)\textsuperscript{[37]}.  

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The limited axonal sprouting ability after SCI may be associated with insufficient growth factors, inhibitory molecules, and physical barriers that inhibit axonal growth and extension\textsuperscript{[43]}. Therefore, various studies have utilized growth factors or anti-inhibitory molecules in animal models of SCI to promote compensatory axonal sprouting. After treatment with monoclonal antibody IN-1, axonal sprouting in the injured CST was significantly enhanced and motor function of rats was improved\textsuperscript{[44]}. In another animal model of CST injury, inosine was injected into the sensorimotor cortex, resulting in extensive axon collateral growth in the rat CST after injury\textsuperscript{[45]}. A replication-defective adenoviral vector carrying the neurotrophin-3 gene was delivered to the spinal motorneurons of rats with an injured unilateral CST\textsuperscript{[46]}. After 3 weeks, growth of axons from the intact CST crossed the midline to the denervated side. In this study, we have investigated whether terminals of the intact corticospinal tract in the rat would sprout following ablation of a parallel descending pathway, the rubrospinal tract. CNS axons can sprout in response to local environmental changes, such as injury. Neurotrophin-3 administration in an animal model of rubrospinal tract ablation resulted in marked increased density of corticospinal innervation in the superficial dorsal horn\textsuperscript{[47]}. Studies have demonstrated that BDNF plays an important role in synaptic plasticity\textsuperscript{[48]}. BDNF administration to the red nucleus resulted in increased expression of GAP43, which promoted the regeneration and sprouting of these chronically injured rubrospinal axons\textsuperscript{[49]}. Recombinant BDNF or syngeneic fibroblasts genetically modified to secrete high amounts of BDNF were grafted into the rats with subcortical lesions which increased the survival of corticospinal neurons\textsuperscript{[50]}. Moreover, recombinant BDNF protein injection into the lesioned rubrospinal tract increased GAP43 and Tα1-tubulin mRNA expression and inhibited axonal injury-induced neurotrophy. Formation of a neural circuit primarily depends on axonal growth and extension, dendritic formation and connection with their targets. A series of molecules are involved in this process, including glial cell-derived neurotrophic factor (GDNF) and nerve cell adhesion molecule, the interaction of which can induce axonal outgrowth\textsuperscript{[51]}. Similar to BDNF, GDNF can prevent corticospinal neuronal death induced by axonal injury and promote axonal growth of injured motor neurons\textsuperscript{[52]}. Intraspinal injection of a non-replicating herpes simplex virus-based vector coding for GDNF at 2 hours after blunt trauma to the thoraco-lumbar spinal cord produced sustained improvement in motor function up to 5 weeks following injury\textsuperscript{[53]}. Cationic liposome-mediated GDNF gene was transferred in the injured site and induced axonal regeneration and extended the range from 5 mm to 9 mm from the lesion\textsuperscript{[54]}. **OTHER FACTORS INFLUENCING NEURAL PLASTICITY AFTER SCI**

Animal experiments and clinical studies have demonstrated that nerve- and non-nerve-derived tissues and cell transplantation can effectively ameliorate limb dysfunction induced by SCI and improve patient quality of life\textsuperscript{[55-56]}. This method has resulted in positive effects in pathophysiology, plasticity, axonal sprouting, and regeneration and functional recovery after SCI. Commonly used grafts of tissues include peripheral nerve, spinal cord or embryonic brain tissues, and grafts of cells include Schwann cells, olfactory nerve cells, neural stem cells, embryonic stem cells and bone marrow stromal cells. Recent brain imaging studies of stroke patients revealed that improving the activity of a specific region in the brain can benefit motor functional recovery dominated by the corresponding cortex\textsuperscript{[57]} using electrostimulation and transcranial magnetic stimulation\textsuperscript{[58]}. **CONCLUSION**

Neural plasticity after SCI has become a focus of research to enable repair of neurological function. Current treatments mainly highlight improving axonal sprouting and reconstruction of neural circuits. However, this process is multifactorial and complicated. Problems can influence plastic events of the central nerve, such as effective regulation of axonal growth to connect with target neurons to reconstruct neural circuits, effective maintenance and increasing of target neuron survival in denervation regions after SCI to ensure neural circuit integrity. Further studies are required to investigate the mechanism of neural plasticity changes and effective treatments for functional recovery after SCI.

**Author contributions:** Jian Liu drafted the manuscript. Xiaoyu Yang provided data, revised the manuscript and was in charge of funds. Lianying Jiang, Chunxin Wang, and Maoguang Yang provided and integrated data.

**Conflicts of interest:** None declared.

**Funding:** This study was supported by the National Natural Science Foundation of China (Goat model of ischemic injury in corticospinal tract projection path and axonal guidance of MPA-1B migration in the spinal cord), No. 30972153; the National Natural Science Foundation of China (Spinal cord ischemia/reperfusion injury and proteomics), No. 30872609.

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(Edited by Sun JJ, Liu SW/Su LL/Song LP)