Chapter 2

# Pharmacological and Nonpharmacological Therapeutic Strategies Based on the Pathophysiology of Acute and Chronic Spinal Cord Injury

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## Abstract

Spinal cord injury (SCI) induces a series of anatomic and physiological disorders which have severe repercussions on neural function. SCI is classified chronologically into an acute (primary and secondary phase) and a chronic phase. The primary phase results directly from the initial trauma and is comprised of disturbances in neural tissue (mainly axons), blood vessels, and spinal shock. Secondary injury results from a series of time-dependent pathophysiological changes, beginning in the first minutes after SCI and lasting days and weeks. This phase is characterized by biochemical and immunological alterations in the injury site and periphery, leading to neuronal over-excitation, apoptosis, and axonal demyelination. In chronic stages, the pathophysiology consists of disturbances in fiber organization, oligodendrocyte apoptosis, fibroglial scar formation, and cyst formation, leading to parenchymal alterations such as syringomyelia and hydromyelia hindering the possibility for functional basal axonal regeneration. This chapter will review a wide range of pharmacological and nonpharmacological therapeutic strategies in preclinical and clinical phases, each targeting different pathological mechanisms of SCI in acute and chronic stages of SCI; taking into account limitations, advances, scope, and new trends. The chapter focuses on the general aspects of SCI pathophysiology, pharmacological and nonpharmacological treatments acute and chronic stages of SCI.

**Keywords:** spinal cord injury, pharmacological strategies, nonpharmacological strategies, therapeutic, acute and chronic

## 1. Introduction

The spinal cord (SC) has three major functions in human beings: sensibility, autonomous control, and motor control. Destructive mechanisms following SCI can have grave consequences on these functions [1, 2].

Traumatic SCI can originate devastating consequences on patients and those close to them, requiring a great number of lifestyle adjustments. This injury results most commonly from vehicular accidents, falls, and sports injuries, among other traumatic accidents. According to the World Health Organization (WHO), there are approximately between 250,000 and 500,000 cases of SCI per year. Among these, 90% are traumatic in nature with an increased mortality risk within the first year [3].

The pathophysiology of SCI can be divided into primary and secondary damage based on the self-destructive mechanisms following initial injury. These mechanisms can be further divided into three phases according to their temporality: acute, subacute, and chronic phase. The acute phase is characterized by ionic changes, which interrupt nerve impulses and lead to edema; the subacute phase involves a series of events including ischemia, vasospasm, thrombosis, inflammatory response, free radicals (FR) production, lipid peroxidation (LP), and the activation of autoimmune responses resulting in apoptosis. In the chronic phase, all the auto destructive mechanisms generated during the acute and subacute phase increase and demyelination processes are triggered, alongside the formation of a glial scar, which hinders axonal regeneration [4–6].

The objective of this chapter is to review a wide range of pharmacological and nonpharmacological therapeutic options, each targeting different pathological mechanisms in the different time phases of SCI.

## 2. SCI pathophysiology

### 2.1. Acute and subacute phases

Primary damage occurs mechanically at the moment of injury, leading to irreversible sequelae. There are three main mechanisms of injury:

**a.** Contusion in the SC without visible loss of its morphology producing a necrotic zone at the impact site, which mainly affects the dorsal region of the SC.

**b.** Laceration or transection, which results from the penetration of the SC or extreme trauma, and affects SC conduction depending on whether the tissue is partly or completely transacted.

**c.** Compression caused by fractures in the vertebral column, which limit irrigation and can occur without injuring the surrounding ligaments, resulting in ischemic damage in the area where the blood flow was interrupted [3, 5, 6].

Mechanical trauma initially tends to damage primarily gray central matter with a relative preservation of peripheral white matter. Irreversible damage to the gray matter occurs during the first hour after injury, with the same happening to white matter within the first 72 hours [5]. As a result of the mechanical injury, superficial vessels undergo vasospasm, originating an intraparenchymal hemorrhage, which damages the microvasculature of the gray matter [7]. This in turn leads to the decreased perfusion and local infarcts due to hypoxia and ischemia, depending on the severity of the lesion. Furthermore, these can be aggravated by neurogenic or hemorrhagic shock, arterial hypotension, bradycardia, arrhythmias, and intraparenchymal hemorrhage. Therefore, the damage initiated by mechanical trauma has a maximum extension from the third to fifth day after injury, extending from the rostral and caudal segments to the epicenter of the lesion, and affecting both gray and white matter. The main consequence of hemorrhage is neuronal death by necrosis, which is observed primarily in the gray matter [7–9].

The primary lesion causes the rupture of the blood brain barrier (BBB) at the injury site, leading to a focal destruction of neural tissue, which destabilizes neural and endothelial membranes [10]. This phenomenon results in the death of neurons in the hours following SCI, and is associated with edema, negatively impacting blood flow to the SC, thus extending the inflammatory response [11]. Therefore, primary injury gives rise to the cellular and molecular processes characteristic of the secondary injury stage, which promotes neuronal death and alter genetic expression patterns [12].

Autodestructive mechanisms triggered after SCI can persist with time, and thus be found in acute, subacute, or chronic phases. The acute and subacute phases are characterized by the following mechanisms:

#### *2.1.1. Ionic deregulation*

The first secondary mechanism appearing after SCI, ionic deregulation results from an increase intracellular $Na^+$ and $Ca^{2+}$ concentration and a decrease of $K^+$ and $Mg^{2+}$ ions. This results in the depolarization of neuronal membranes, decreased number of ionic channels, and increased transportation of water molecules associated with $Na^+$ and $Ca^{2+}$ ions, leading to edema [13].

#### *2.1.2. Edema*

Vasogenic edema initially appears as a consequence of the BBB rupture, and is further propagated by the loss of ionic regulation, giving way to water accumulation in extracellular spaces. Water accumulation is strongly related to the intensity of the initial trauma [14]. The presence of edema in any part of the CNS results in the compression of adjacent tissue, which leads to ischemia and promotes the development of other self-destructive mechanisms, such as the release of FR, LP, and inflammation [1, 14].

#### *2.1.3. Excessive release of intracellular calcium*

Once the lesion occurs, partial or total loss of the cellular membrane in neurons and axons is triggered, resulting in the depolarization due to the entrance of high concentrations of $Ca^{2+}$ [13].

The resulting ionic unbalance and edema contribute to the massive entry of $Ca^{2+}$, which is intrinsically related to neurotoxicity by the exaggerated release of glutamate and the activation of proteases and phospholipases. This activation triggers the destruction of neurofilaments and the destabilization of key proteins for cellular support, favoring axonal collapse, and fragmentation in the first hours or days post-trauma [15]. In addition to phospholipase activation, the increase in $Ca^{2+}$ contributes to the production of pro-inflammatory molecules, such as arachidonic acid, leukotriene, and thromboxane due to the release of fatty acids from membrane phospholipids [4]. Likewise, intracellular mobilization of cytosolic $Ca^{2+}$ generates reactive oxygen species (ROS), energetic failure, cytoskeletal damage, and errors in protein folding [16].

The sudden entry of intracellular $Ca^{2+}$ likewise leads to the aforementioned glutamate excitotoxicity. These mechanisms conjointly contribute to immediate cell death or the activation of calcium-dependent signaling pathways, which result in cellular death [15, 17].

### *2.1.4. Glutamate excitotoxicity*

SCI affects the regular equilibrium of glutamate and aspartate in the CNS, leading to significant alterations. Fifteen minutes after SCI, glutamate concentration increases to concentrations six times higher than physiological levels [18]. This increase is due to the overstimulation of ionotropic glutamate receptors (GluRs), provoked by the massive entry of $Ca^{2+}$ and $Na^{+}$. This ion flow can induce a secondary increase of intracellular $Ca^{2+}$, leading to an overstimulation of viable neurons and neuronal death. This toxic effect, known as excitotoxicity [19], leads to neuronal and oligodendrocytic death [18, 20].

This phenomenon is mainly evidenced in glial cells, with axonal-myelinating oligodendrocytes showing greater susceptibility. Excitotoxicity signals are regulated by 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate type GluRs; their overactivation facilitates oligodendrocyte death and consequent demyelination after SCI [21].

### *2.1.5. FR production*

Microvascular disruption, ionic deregulation, glutamate increase, mitochondrial dysfunction, and the activation of inflammatory mechanisms stimulate the formation of FR [4, 6, 22]. The cascade of FR production begins with intracellular $Ca^{2+}$ elevation and the production of uncoupled electrons, which bind to $O_2$ molecules, transforming them into superoxide radicals ($O_2^{-}$) capable of increasing oxidative damage by promoting further FR formation [23].

Damage induced by FR, denominated oxidative stress or nitrosative stress, occurs when excessive amounts of ROS and reactive nitrogen species (RNS) are produced, along with low levels of antioxidant defenses. FR production following SCI can damage cellular lipids, proteins, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA), causing mutations or irreversible damage, which leads to cellular death [24]. Moreover, peroxidase (Prx) 1/6 and manganese superoxide dismutase (MnSOD) are modified by phosphorylation, oxidation, or nitration during oxidative stress after injury, inhibiting their antioxidant functions [25].

*2.1.6. Lipid peroxidation*

One of the most important pathophysiological mechanisms derived from FR production is LP. ROS such as hydroxyl radicals (OH) and $O_2^-$, combine with nitric oxide (NO) to form the superoxidant agent peroxynitrite (ONOO). These reactants, in turn, can protonate at a physiological pH level, forming peroxynitrous acid (ONOOH) [23, 26].

At a physiological pH, ONOO reacts with polyunsaturated fatty acids (PUFAs), taking one electron to form a lipid radical (L•) that interacts with molecular oxygen to form peroxyl lipid radicals (LOO•). Without regulatory mechanisms, LP will result in membrane depolarization and ensuing demyelination in the SC [26, 27]. Substantial damage induced by FR involves an oxidative attack to the cellular membrane, which is made of PUFAs (arachidonic acid, linoleic acid, eicosapentaenoic acid, or docosahexaenoic acid) [28, 29]. Two aldehydic products arise from LP: 4-hidroxynonenal (4-HNE) y 2-propenal (acrolein). These molecules have been characterized in SCI models, forming covalent bonds with basic amino acids found in cellular proteins, and thus altering their structure and functional properties [28].

Likewise, the inflammatory response is partially responsible for FR production after SCI due to its stimulation of NO production. This molecule is produced by different cellular types after SCI and is capable of damaging medullar parenchyma when produced by inducible nitric oxide synthase (iNOS) [29]. High concentrations of NO, which are mainly produced by iNOS, require an immunological/inflammatory stimulus, such as inflammatory cytokines (IL-6, IL-1, and IFN-$\gamma$), resulting in nanomolar quantities produced for prolonged time periods [30, 31].

After SCI, high concentrations of NO (produced by iNOS) and peroxynitrite increase up to three or five times, reaching their peak 12 hours after injury [32]. Some studies have detected iNOS activity 3, 4, 24, and 72 hours following SCI, vinculating its presence to LP, and neural destruction [31–33]. High concentrations of NO simultaneously participate in cellular damage and increase vascular permeability. Consequently, NO contributes to the formation of edema, as well as excitotoxicity through the release of high concentrations of $Ca^{2+}$ and glutamate. Furthermore, NO alters the electron transport chain in the mitochondria, generating further FR by affecting enzymes with a sulfuric catalytic center, such as ubiquinone succinate [34]. In addition, iNOS expression and production of NO have a retroactive effect on the development of the inflammatory response, due to their role in the production of cyclooxygenase 2 (COX)-2, which increases the levels of inflammatory products such as prostaglandins and thromboxane [34, 35].

*2.1.7. Inflammatory response*

Immediately after the traumatic rupture of the BBB, an inflammatory reaction takes place. This reaction involves the actions of chemical mediators and the participation of inflammatory cells, derived from the activation of resident immunological cells (astrocytes and microglia) and recruitment of peripheral cells (macrophages, lymphocytes, etc.) [8, 36].

The production and release of pro-inflammatory cytokines and chemokines are some of the first inflammatory events triggered after SCI. Cytokines such as IL1, IL6, and tumor necrosis factor-alpha (TNF$\alpha$) are known as mediators of the peripheral inflammatory response, and are

synthesized and released by various cells in the CNS. TNF$\alpha$ promotes the immediate recruitment of neutrophils to the damaged site by inducing the expression of molecules, such as endothelial cell intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1). It also stimulates the release of IL8, an important neutrophil chemotactic factor, which modifies endothelial cells permeability and consequently affects the BBB. Furthermore, TNF$\alpha$ also stimulates astrocyte proliferation and hypertrophy, promoting the formation of a glial scar that acts as a barrier against possible regeneration [37, 38].

During the inflammatory response, the infiltration of immunological cells is the principal contributor to neuronal degeneration. These cells are guided from the periphery to the injury site by chemokines and cytokines released by microglia cells and astrocytes, which conjointly with peripheral macrophages constitute the main components of the injury [10, 39]. These events begin with the acute inflammatory response and persist in the chronic phase, characterized by a constant migration of cells (neutrophils, macrophages, lymphocytes, basophils, and eosinophils) from the periphery. This leads to the increased levels of inflammatory cytokines and extended damage, as well as the increase in neural destruction, which hinder the possibility of reparation and tissue regeneration [40, 41].

After injury, two infiltration waves have been described. The first wave, constituted by polymorphonuclear cells (PMN), predominates during the first few hours following injury. Neutrophils appear in the vein and venule walls surrounding the injury within the first 4 hours and have been observed from 8 to 24 hours post-trauma. The inflammatory response is reflected by increased number of leukocytes in the cerebrospinal fluid (CSF), infiltration by PMN, an increase in leukotriene levels (mainly $LTB_4$), and myeloperoxidase activity [41]. The second infiltration is characterized by the presence of macrophages, which are observed in the first 2 days, reaching peak levels at day 5–7. After 2 days, proliferation and recruitment of macrophages and microglia occurs, alongside leukocyte infiltration from the third to seventh day. All of these alterations and phenomena that occur in a molecular environment promote gradual tissue degeneration, destroying the necessary anatomic substrate for neurological recovery [40].

Macrophage and monocyte infiltration after SCI aims to remove cellular debris and stimulate the infiltration of new blood vessels and parenchymal cells. The infiltration of these cells helps T-cell interaction, regulating their activation and proliferation through their role as antigen-presenting cells (APC) [42]. The microglia are pluripotent resident cells capable of expressing different phenotypes. The intensity of inflammatory response varies according to lesion severity, affecting cell recruitment and the magnitude of the immune response at the site of injury. Regulation of the inflammatory response occurs due to the interaction of the microglia with T cells, leading to their activation against specific antigens, and thus regulating the immunological response and subsequent phases [43].

Microglia cells are distributed across the CNS, serving as pathological sensors, which react to harmful stimuli [44]. The activated microglia migrate to the pathogen-invaded injury site and transform from the resting phenotype (ramified cells) into amoeboid cells (phagocytic) [45]. Activated microglia can release a series of cytokines, chemokines, and enzymes, depending on the activation stimulus, including: IL1-$\beta$, IL-6, TNF$\alpha$, transformation growth factor-$\beta$1 (TGF-$\beta$1), macrophage-colony stimulating factors (M-CSF) [46]; iNOS, neural growth factor (NGF), neurotrophin-3 (NT-3) and brain neuronal derived factor (BNDF) [43, 47].

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Lymphocytes are cells that modulate the intensity of the inflammatory response. Their participation following SCI has also been related to neural tissue damage due to their production of pro-inflammatory cytokines, such as IFNγ and IL1β [43, 48]. IFNγ is directly related to neuronal destruction, inducing the expression of further pro-inflammatory cytokines (TNFα, IL6, IL12, and IL1β) and pro-inflammatory molecules (ROS and iNOs) through induction of nuclear factor kappa B (NFkB) and activator protein-1 (AP-1) signaling pathways [11, 43, 49].

After SCI, a self-reactive/autoreactive response, defined as an immune response against autologous constituents, is triggered within the CNS [50–52]. This response targets neural constituents, such as myelin basic protein (MBP), promoting an increase in the expansion of neurological damage at the injury site. This response is capable of increasing the damage to the nerve tissue, but is also able to promote protection and even restoration of damaged tissue [48, 52–55].

### 2.2. Chronic phase

In chronic stages of SCI, the formation of a barrier occurs, precluding axonal regeneration in the area surrounding the lesion. This barrier consists of two main components: glial (astrocytes) and fibrotic elements that synthesize inhibitory molecules, hindering interconnection and axonal regeneration [56]. It has been observed that the cicatrization process restores the vital function of the blood–brain-barrier and limits the resulting damage at the injury site. However, in addition to having beneficial effects, this process also prevents restoration [57].

During this phase, some disturbances regarding the organization of fibers are observed, such as demyelination, Wallerian degeneration, oligodendrocyte apoptosis, and the formation of a scar of collagen fibers [56, 58, 59]. In this phase, a strong, nonregulated interaction between the CNS and the immune system takes place, which includes the vegetative innervations to the lymphatic and endocrine tissue that aggravate the degeneration process of major functions [57].

The glial scar around the injury is formed by a wide net of fibrous astrocytes and collagen fibers, which release proteoglycans and neurofilaments, such as vimentin and nestin, which act as inhibitory molecules of neural growth [59, 60]. Therefore, the fibrous scar developed after an injury in the CNS is considered a hindrance for axonal regeneration [59]. Although traditionally astrocytes have been considered to be detrimental to regeneration, they possess beneficial effects when presented in their reactive form at the glial scar, including BBB repair and modulation of the immune response [61].

Astrocytes present a gradual response to the lesion, including changes in gene expression, hypertrophy, extension of the process, and in some cases cellular division [62, 63]. The currently known factors responsible for increasing the formation of glial scars in SCI are transforming growth factor β (TGF-β) [64] and INF-γ, among others [62].

Reactive astrogliosis, defined as an atypical increase of astrocytes, is characteristic of astrocytes surrounding the lesion. This phenomenon presents with a rapid synthesis of intermediate filaments, such as glial fibrillary acidic protein (GFAP), vimentin and nestin. Moreover, there is an excessive secretion of extracellular matrix (ECM) components, such as tenascins, type IV collagen, and chondroitin sulphate proteoglycans (CSPGs), which form a glial scar at the injury site. This scar develops into a fibrous barrier, preventing regeneration of nervous

connections adjacent to the lesion. Furthermore, the reactive astrocytes contribute to the release of pro-inflammatory cytokines, such as TNF-$\alpha$, INF-$\gamma$, IL-1$\beta$, and IL-6, which inhibit differentiation processes of neural stem cells (NSC) [65], and contribute to the chronic inflammatory response [62].

In addition, the formation of a glial scar favors cavitation, a process detrimental to regeneration at the injury site. This phenomenon can lead to the extension of the injury size days or even weeks after the lesion, resulting in the formation of an encapsulated scar, which prevents neuronal connection [66, 67].

At the chronic stage, the central canal is frequently involved in fluid-filled cyst development, which gives rise to malformations in the SC parenchyma; this condition is known as syringomyelia [68]. This term, first introduced by Ollivier D'Angers in 1827, derives from the Greek word for tube (syrinx) and is used to describe dilation of the central canal extending over many segments. Before trauma, CSF normally flows into the inner parts of the brain and SC. However, SCI evokes morphological changes, which disrupt correct circulation enhancing the volumetric growth of cavities. Syringomyelia appears to be related to irregular pressure conditions and hydrodynamic mechanisms related to the CSF [68, 69].

Hydromyelia, a closely related term that is often used interchangeably, also refers to a dilatation of the central canal by CSF. Some have defined hydromyelia as a congenital dilatation [70] of the central canal, which is partially lined with ependymal cells, strongly associated with hydrocephalus, an obstruction of the foramina of Luschka and Magendie [71]. The term syringomyelia has been affixed to every kind of intramedullary cyst, with some authors defining it as a cavity distinct from the central canal and lined by ependymal cells or primarily glial cells [71, 72]. However, others restrict its use to certain subtypes of cystic lesions and distinguish syringomyelia, hydromyelia, or myelomalacia as separate entities. In spite of this, some authors combine these terms into syringohydromyelia or hydrosyringomyelia [71]. Lee et al. stated that a clear communication between intramedullary cavities and the ventricular system is rarely demonstrated, making it difficult to differentiate syringomyelia from hydromyelia, although a truly eccentric location within the spinal cord may be more characteristic of syringomyelia than of hydromyelia [73]. Batzdorf states that the distinction between syringomyelia and hydromyelia is no longer considered absolute or critical [72].

## 3. Therapy after acute SCI

In recent years, neuroprotective or neuroregenerative strategies regarding the injury site have been chosen to mitigate autodestructive events following a SCI. These strategies include: preservation or regeneration of damaged neural tissue, neutralization of toxic mediators, and increasing tissue resistance to toxicity [74].

Although there is a substantial evidence showing new preclinical strategies that aim to promote neuroprotection, achieved with certain efficiency in murine SCI models [75], there are few clinically approved treatments available to patients with SCI. Currently, clinical treatments

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are limited to surgical decompression, blood pressure control, and the possible use of methylprednisolone (MP), which is not recommended due to its secondary effects [76].

However, for each treatment strategy, it is important to consider the time elapsed between the injury and the initial treatments, in order to promote a beneficial effect by inhibiting or diminishing secondary damage as rapidly as possible. Despite the promising results shown by several treatments, there is currently no therapy that satisfies all the requirements necessary for an optimal recovery [77].

### 3.1. Pharmacological therapies

During the last 25 years, different preclinical and clinical studies evaluating neuroprotection in SCI have been conducted. As previously mentioned, careful consideration of the time frame for treatment after SCI is essential when selecting a therapeutic option. At the clinical level, conventional norms have recommended initiating treatment within the first 3 hours following injury. However, some preclinical studies have begun treatment administration within the first hour after lesion, which complicates the clinical application of these therapies [75]. Diverse drugs have been used in preclinical and clinical studies, with each having different effects depending of the therapeutic objective. However, the majority of drugs studied as possible neuroprotective agents focus solely on one type of damage, with some being tailored to specific mechanisms of the primary injury. The vast majority of these have consisted of pharmacological treatments, although many preclinical studies have included additional therapeutic strategies for acute and chronic SCI. Current pharmacological agents used in the treatment of acute SCI can be grouped into: ionic channel blockers, inhibitors of N-Methyl-D-asparate acid (NMDA), and AMPA-kainate receptors, inhibitors of FR and LP, antiapoptotics, and immunosupressors or immunomodulators [77]. All the therapies and their therapeutic objectives are mentioned in **Table 1**.

| Therapy | Mechanism of neuroprotection<br>↑ Increase<br>↓ Decrease<br>(−) Blocked<br>(+) Activated | Treatment outcome | References |
|---|---|---|---|
| Preclinical therapies | | | |
| Ionic channel blockers | | | |
| **Sodium** | | | |
| a) Tetrodotoxin | (−) Sodium entry channels after SCI | Binds to voltage-dependent sodium channels in nervous system cell membranes, facilitating motor function recovery by reducing long-term white matter loss, thus improving neural tissue preservation. | [78, 79] |
| b) Riluzole | | Increases the survival and reinnervating capacity of injured motor neurons; conferred significant neuroprotection and behavioral recovery, sparing both gray and white matter. | [80, 81] |

| Therapy | Mechanism of neuroprotection<br>↑ Increase<br>↓ Decrease<br>(−) Blocked<br>(+) Activated | Treatment outcome | References |
|---|---|---|---|
| **Calcium** | | | |
| a) Nimodipine | ↓Oxidative damage caused by FR | Decreases LP end products, such as MDA and 4-Hydroxy Acrolein, resulting in a better motor recovery. However, it should be noted that nimodipine does not allow membrane repair. | [82, 83] |
| **Inhibitors of NMDA and AMPA-kainate receptors** | | | |
| a) Memantine | ↓ Neurological damage by glutamate and NMDA. | Noncompetitive NMDA antagonist that prevents neurotoxicity. In combination with antiapoptotic agents, provides better histological and clinical results, diminished necrosis and apoptosis. | [84, 85] |
| b) Gacyclidine | (−)noncompetitive NMDA receptor | Improved motor recovery, neural tissue preservation in a dose–dependent manner. In rats, gacyclidine exerts dose- and time-dependent neuroprotection. | [86, 87] |
| c) NBQX | AMPA-kainate receptor antagonist. | Improves mitochondrial function and reduces levels of ROS and lipid peroxidation products. | [88] |
| **Inhibitors of FR and LP** | | | |
| a) PUFAs | ↓FR formation, scavenging of ROS and RNS. | Prevents white matter damage, increases synaptic connections, neuronal survival, and improves motor recovery. Possesses antioxidant and anti-inflammatory effects. | [89–96] |
| b) Glutathione (GSH) | (−) FR by the free thiol group. | Anti-excitotoxic peptide through the inhibition of the union between specific ligands and inotropic GluRs by the modulation of redox reactions. Improves motor recovery, rubrospinal tract neuronal survival, blood flow stabilization. | [97–100] |
| **Antiapoptotics** | | | |
| a) zDEVD-fmk | (−) Caspase 3 and 9 respectively | The application of z-DEVD-fmk reduces secondary tissue injury and helps preserve motor function. | [101, 102] |
| b) LEHD-fmk | | Electron microscopy showed that z-LEHD-fmk treatment protects neurons, glia, myelin, axons, and intracellular organelles. | |
| **Immunosuppressive or immunomodulatory drugs** | | | |
| **1. Inhibitors of cyclooxygenase** | | | |
| a) Indomethacin | (−) COX 1 and COX 2 | Mixed results: some report improved neurological function and blood flow to injury site, as well as decreased neuronal damage, while others report delayed recovery. | [103, 104] |
| b) Celecoxib | (−) COX 2 | Reduction of prostanoids and FR synthesis, inhibition of arachidonic acid pathways. Increased motor recovery and diminished damaged spinal tissue. | [103] |
| c) Meloxicam | (−) COX 2 | Improved neurological function, amelioration of LP. | [105] |

| Therapy | Mechanism of neuroprotection<br>↑ Increase<br>↓ Decrease<br>(−) Blocked<br>(+) Activated | Treatment outcome | References |
|---|---|---|---|
| **2. Immunophilin ligands** | | | |
| a) Cyclosporine A | (−) Calcineurin activity | Inhibits the proliferation of T-helper lymphocytes and interferes with cytokine production (IL-1, IL-2 e IL-6), cytoskeleton motility of neutrophils, and activation of iNOS or ROS production.<br>Reduces LP levels, glutamate excitotoxicity, and demyelination processes, increasing neuronal survival and motor recovery. | [104, 106–109] |
| b) Tacrolimus | | NF-kB and caspase 3 inhibition, leading to improved recovery and reduced neuronal loss.<br>In mesenchymal stem cells (MSCs) transplantation, improves MSCs survival and neurological recovery after SCI.<br>Tacrolimus may induce neuroregeneration by binding to heat shock protein 90. | [110–114] |
| **3. Immunomodulatory peptides** | | | |
| a) Monocyte locomotion inhibitory factor (MLIF) | ↓ VCAM-1, pro-inflammatory cytokines (IL-1$\beta$, IL-6, IL-12, and IFN-$\gamma$) | Motor recovery and survival of ventral and corticospinal tract neurons associated with a reduction in iNOS gene expression and up regulation of IL-10 and TGF-β expression. MLIF also reduces the concentration of nitric oxide and the levels of lipid peroxidation in systemic circulation. | [115, 116] |
| b) Nogo-A | (+) T-cell-mediated protective autoimmunity | Nogo-A-derived peptide p472 and the transfer of anti-Nogo-A T-cells showed a significant reduction in neuronal loss.<br>Promotes motor recovery and the long-term production of BDNF and NT-3. | [117, 118] |
| c) A91 | (+)T-cell-mediated protective autoimmunity | Reduces LP levels, iNOS expression, NO levels, caspase 3 activity, and TNF-$\alpha$ concentration.<br>A91 combined with GME induced a better motor recovery, a higher number of myelinated axons, and better rubrospinal neuron survival than A91 alone. | [100, 119–125] |
| **Clinical therapies** | | | |
| Methylprednisolone | (−) Immune response | Contradicting data, with some showing improved motor recovery and others showing no recovery and increased side effects. | [126–128] |
| Minocycline | Multiple anti-inflammatory pathways | Improved motor recovery and decreased cell death through inhibition of caspase 3, matrix metalloproteinases, NO levels, and TNF-$\alpha$. | [129–131] |
| GM-1 Ganglioside | ↓ Excitatory neurotoxicity | Improved motor recovery evaluated by American Spinal Injury Association (ASIA) motor, light touch, and pinprick scores. | [132–134] |

**Table 1.** Pharmacological treatments used in acute SCI.

### 3.2. Nonpharmacological therapies

Nonpharmacological interventions are frequently advocated, although the benefit and harm profiles of these treatments are not well established. This may be due in part because of methodological weaknesses in available studies. However, preclinical studies have demonstrated neuroprotective effect, although results from clinical studies remain controversial and require further studies. These treatments are summarized in **Table 2**.

| Therapy | Mechanism of neuroprotection<br>↑ Increase<br>↓ Decrease<br>(−) Blocked<br>(+) Activated | Treatment outcome | References |
|---|---|---|---|
| **Preclinical therapies** | | | |
| **Vitamins** | | | |
| a) Vitamin B3 (niacin) | Phenotypic shift in macrophages from M1 to M2 | Reduced p65 NF-κB phosphorylation, reducing M1 markers such as iCD86, IL-12, and IL-6 and increasing anti-inflammatory M2 markers, such as CD206, IL-10, and IL-13. | [135] |
| b) Vitamin C (ascorbic acid) | (−) FR formation | Reduces tissue damage and improves functional recovery in rats. | [136, 137] |
| c) Vitamin E (alpha-tocopherol) | (−) FR formation | Improves cell survival and motor function significantly following SCI. | [137, 138] |
| **Resveratrol** | ↑ Transcription factor Nrf-2 and sirtuin (SIRT) 1 | Reduces neutrophil infiltration, production of inflammatory cytokines (IL-1β, IL-10, TNF-$\alpha$), and myeloperoxidase (MPO) by inhibition of NF-κB; diminishes iNOS expression, apoptosis, and caspase-3, as well as inducing important locomotor recovery. | [139–142] |
| **Gene therapy Chondroitinase gene therapy via lentiviral vector (LV-ChABC)** | (−) Chondroitin sulfate proteoglycans (CSPGs) | Reduced cavitation and enhanced preservation of spinal neurons and axons. Improved sensorimotor function and increased neuronal survival correlated with reduced apoptosis. | [143] |
| **Hypothermia** | Vasoconstriction,<br>(−) Inflammatory response | Decreases the degree of the hemorrhage at the injured site and neurotoxicity by reducing the levels of glutamate and glutamanergic receptors.<br>Prevents changes in the BBB, thus hindering extravasation of leukocytes into the CNS.<br>Inactivation of production of pro-inflammatory cytokines, such as IL-1β, IL-18, and TNF-$\alpha$. Also reduces $O_2^-$, NO, and OH FR. Reduces cell death and apoptotic mechanisms through caspase-3 and cytochrome C inhibition. | [144, 145] |
| **Cell therapy** | | | |
| a) Schwann cells | (+) Myelination | Treatment with these cells improves sensitive and motor functions due to the | [146, 147] |

| Therapy | Mechanism of neuroprotection<br>↑ Increase<br>↓ Decrease<br>(−) Blocked<br>(+) Activated | Treatment outcome | References |
|---|---|---|---|
| | | remyelinating potential of Schwann cells, permitting the transmission of action potentials through regenerated axons wrapped in Schwann cells. | |
| b) Embryonic stem cells. | Pluripotent cells capable of differentiating into every type of cell | Induce motor recovery through the ability to transform into astrocytes, oligodendrocytes, and/or neurons *in vitro* prior to transplantation, in order to avoid their tumorigenicity. | [148] |
| c) Olfactory ensheathing cells (OECs) | Found in the center and periphery of the olfactory nerve; capable of differentiating into neuronal or glial lineage cells | Enhanced locomotor recovery, axon myelination, and neuroprotection. | [149] |
| d) MSCs | Obtained from bone marrow; capable of differentiating into every type of cell | MSCs may facilitate recovery from SCI by remyelinating spared white matter tracts and/or enhancing axonal growth with low immunogenicity. Modulate the inflammatory microenvironment to reduce pro-inflammatory cytokine levels. | [150, 151] |
| **Low-energy extracorporeal shockwave therapy (ESWT)** | ↑ Electric stimulus | Improved motor and sensory recovery, decreased neural cell death. Stimulates angiogenesis and neurogenesis. | [152] |
| **Physical therapy** | ↓ Spasticity<br>↑Neurological outcome | Upregulates the expression of NT3, NT4, BDNF, and GDNF, while reducing levels of apoptosis-related proteins such as caspase 3 and 9.<br>Induces axonal regeneration, broadening the scope of physical therapy from neuroprotection to neuroregeneration. | [152–156] |
| **Clinical therapies** | | | |
| **Cell therapy** | | | |
| Autologous transplant of MSC | Obtained from bone marrow; capable of differentiating into every type of cell | Improved motor, sensory recovery, and neurological outcome.<br>Improved sexual function and bladder and bowel control<br>Increased levels of BDNF, NGF, NT3, and NT4. | [157–161] |
| Physical therapy | ↓ Spasticity<br>↑Neurological outcome | Further translational studies are required in order to provide favorable results in patients similar to those seen in animal models of SCI. However, patients with incomplete SCI saw an improvement on their ASIA score after receiving physical therapy. | [162–164] |

**Table 2.** Nonpharmacological therapies used in acute SCI.

## 4. Therapies for chronic SCI

Many patients with chronic SCI experience little partial recovery with the use of acute phase treatments. When compared to acute SCI treatments, the efficacy of therapies that promote axonal regeneration in chronic models is reduced due to the generalized stability, induced by protective means or restoration promoters not present during the acute phase [165]. Studies indicate that this period of stability is reached in up to 3 months [166], followed by a progressive decline of neurologic functions in rodents that underwent SCI [167, 168].

Treatments for chronic SCI focus on avoiding or improving characteristic pathophysiological mechanisms, such as glial scar formation, demyelination, and astrogliosis. Moreover, it must be emphasized that while strategies for acute SCI are limited to preventing further damage, therapeutic strategies for chronic SCI instead focus on promoting neuronal regeneration and treating accompanying symptoms of chronic complications. Pharmacological and nonpharmacological therapies utilized in the treatment of chronic SCI are summarized in **Tables 3** and **4**.

| Therapy | Mechanism of neuroprotection<br>↑ Increase<br>↓ Decrease<br>(−) Blocked<br>(+) Activated | Treatment outcome | References |
|---|---|---|---|
| **Preclinical therapies** | | | |
| **Antagonists of Rho signaling pathway** | | | |
| a) C3 transferase | (−)Rho protein | Stimulates axonal growth and improves motor function. | [165] |
| b) Y27632 | (−)Rho protein, nonselective inhibitor | Promotes axonal regeneration and motor function recovery. | [166] |
| c) Fasudil | (−)Rho protein | Conjoint administration with MP promotes recovery of motor activity and reflex movements, as well as tissue preservation. | [167] |
| d) P21 | (−)Rho protein | Capable of stimulating axonal regeneration and improving motor function of extremities. | [168] |
| e) Ibuprofen | | Enhances recovery by limiting tissue loss and stimulating axonal growth. | [169] |
| **Glial scar inhibitors** | | | |
| a) 2,2′-bipiridine (BPY). | (−) prolyl 4-hydroxylase | Growth of corticospinal tract neurons through the injury site and improved motor function recovery. | [170] |
| b) Decorine | (−) TGF-β | Suppresses glial scar formation, favors axonal growth. | [171] |
| c) Olomoucine | (−) CDK1/Cycline B and related kinases | Limits astroglial proliferation and increases GAP-43 expression, improving motor function. | [172] |
| d) α,α′-dipyridyl | (−) prolyl-4 hydroxylase | Decreases collagen synthesis. | [173] |

| Therapy | Mechanism of neuroprotection<br>↑ Increase<br>↓ Decrease<br>(−) Blocked<br>(+) Activated | Treatment outcome | References |
|---|---|---|---|
| e) ChABC | (−) ECM molecules | Promotes spinal cord plasticity along injured corticospinal tract and uninjured serotonergic projections, facilitates growth of new fibers, and stimulates rubrospinal projection neuron growth. | [174, 175] |
| **Anti-Nogo therapies** | | | |
| a) Nogo receptor (NgR) | Myelin-associated inhibitors | NgR immunization markedly reduced the total lesion volume, improved locomotor recovery and grid walking performance. | [176] |
| **Clinical therapies** | | | |
| **Rho-ROCK inhibitor** Cethrin/VX-210 | (−)Rho protein | Significant improvement in long-term motor scores (18.5 ASIA points) for cervical patients. Currently under study in a phase III trial in patients with acute cervical SCI which commenced in 2016. | [177, 178] |
| **Anti-Nogo antibodies** | Myelin-associated inhibitors | Promotes axonal sprouting and functional recovery. | [117, 179] |

**Table 3.** Pharmacological therapies in chronic SCI.

| **Preclinical therapies** | | | |
|---|---|---|---|
| **Glial scar removal** | ↓ or (−) glial scar (Surgical) | Promotes axonal development, although surgical removal may lead to a second injury. | [180] |
| **Biocompatible matrices** | | | |
| a) Fibrin glue (Tissucol) | Fibrinogen and thrombin compound, potentially adequate biological vehicle for cell transplant. | Promotes growth and incorporation of primary myelinated and unmyelinated afferent axons, and intervenes in the support and directionality of axons with Schwann cells.<br>Fibrin-stabilizing factor (Factor XII), also contained in Tissucol, favors migration of MSCs on the highly reticulated structure of the glue and increases their proliferation. | [181, 182] |
| b) Alginate | Vehicle for drug release, cellular encapsulation and cellular transplant | Facilitates axonal guidance and cell adherence by delivering ECM components, such as fibronectin, laminin, collagen, and polyornithine, alongside progenitor neuronal cells. | [183] |
| c) Hyaluronic acid | Porous structures that gradually release growth factors, cellular encapsulation, or drugs | Minimizes the formation of glial scar and promotes astrocyte and microglia migration. | [184] |

| Preclinical therapies | | | |
|---|---|---|---|
| d) Polyethylene glycol | Seals injured membranes and allows them to reassemble | Repairs cell membranes in the CNS, although it does not provide three-dimensional support. | [185] |
| e) Matrigel | Matrix conformed by multiple growth factors and extracellular proteins | Compounds facilitate cellular adherence, differentiation, Schwann cell growth, and axonal regeneration. | [186] |
| **Cell therapies** | | | |
| a)Neural stem cells | Integrates with host circuits to enhance behavioral recovery | Improves phrenic motor output after high cervical SCI, improving spontaneous respiratory motor recovery. | [187, 188] |
| b) Mesenchymal stem cells | Modulate inflammatory response, promote angiogenesis | Promotes repair by anti-inflammatory molecule secretion and stimulation of macrophage polarization, secretion of trophic and neurotrophic factors. | [189–195] |
| c) Schwann cells | Stimulation of remyelination | Promotes angiogenesis, prevents apoptosis, and stabilizes the BSB through astrocyte regulation, forming axonal guidance filaments through the injury site. Increased preservation of white matter and host Schwann cells and astrocyte ingress, as well as axon ingrowth and myelination. | [196, 197, 201] |
| d) OECs | Phagocytosis of debris and microbes, growth factor signaling | Improves neurite outgrowth and endogenous remyelination, as well as white matter preservation, sensory, and motor recovery. | [198–200, 202–204] |
| **Combination therapy** | | | |
| a) Cocktail with 10 growth factors. | ↑ NT-3, BDNF, EGF, βfgf, GDNF, PDGF, αfgf, HGF, IGF-1, and calpain inhibitor in a fibrin gel conjointly with NSC transplantation | Induces significant motor recovery. | [205] |
| b) Anti-Nogo-A antibody followed by ChABC and physical rehabilitation. | Myelin-associated inhibitors<br>(−) ECM molecules<br>↓ spasticity | Spontaneous recovery of forelimb functions reflected the extent of the lesion on the ipsilateral side and improved motor recovery when compared to the groups receiving individual treatments. Histological results showed increased neuronal regeneration. | [206, 207] |
| c) ChABC and NSCs | (−) ECM molecules<br>Integrate with host circuits to enhance behavioral recovery | Allows the transplanted cells to differentiate into neuroglial cells and permits proper axonal regeneration and growth across the injury site, leading to significant motor recovery. | [208] |
| d) A91 and surgical glial scar removal. | ↑ Growth factor<br>(−) glial scar | Increases motor function.<br>Facilitates the axonal regeneration in the region caudal to the injury site. | [122] |

| | | | |
|---|---|---|---|
| **Preclinical therapies** | | | |
| e) Degenerated peripheral nerves with MSCs and fibrin glue | ↑ Growth factor<br>(+) neural regeneration | Induces axonal regeneration and myelination with molecules associated to GAP-43 and neuritin, which are present in axonal growth cones and axonal remyelinization. | [209] |
| **Clinical therapies** | | | |
| Physical therapy | ↓ Spasticity | Upregulation of BDNF, IGF-1, other growth factors.<br>Improves axonal plasticity and regeneration, motor function. | [210–215] |
| Muscle electrical stimulation | ↑ Muscle electric stimulus | Improvement in their motor and sensory function, as well as an increase in muscle size and strength | [216] |
| Spinal cord stimulation | ↑ Spinal cord electric stimulus | Treated patients were able to initiating limb movement and improve posture control, bladder emptying (urinary retention), and sexual function. This therapy also provoked escalated extension-flexion movements. Additional trials (NCT02592668, NCT02313194) are now ongoing to assess safety/feasibility and validate this exciting finding, with results expected by 2018. | [217] |
| Glial scar removal with NeuroRegen scaffold. | ↑ Spinal cord regeneration | Better recovery of autonomous nervous functions, as well as the recovery of somatosensory-evoked potentials of lower limbs. | [218] |
| **Cell therapies** | | | |
| a) NSC transplant | | Cervical transplant (n = 31; NCT02163876) and thoracic transplant (n = 12; NCT01321333). Preliminary results from these trials do not show increased complication rates, although results on motor and sensitive recovery remain pending. | [219, 220] |
| b) Oligodendrocyte precursor cells | | Asterias Biotherapeutics Inc. phase I/II dose-escalation trial (n = 35; NCT02302157).<br>This study is expected to be completed in 2018. | [220] |
| c) MSCs transplant | | Phase II/III clinical trial in South Korea (NCT01676441) by Pharmicell Co. with intraparenchymal and intrathecal administration of MSC. Results are still pending, with an estimated completion date of 2020. | [220–222] |
| d) Schwann cells transplant | | An open-label phase I trial (n = 10) by the Miami Project to Cure Paralysis is now | [220] |

| Preclinical therapies | | |
|---|---|---|
| | investigating Schwann cells in the treatment of patients with chronic ASIA A, B, and C cervical or thoracic injuries, with results expected by 2018. | |
| e) OECs transplant | Phase I clinical trial, with results showing an improvement in sensory and motor function, along with improved preservation of white matter at the site of injury. | [223, 224] |

**Table 4.** Nonpharmacological therapies in chronic SCI.

## 5. Conclusion

In conclusion, despite promising innovative advances in preclinical treatments, there is currently no consolidated therapeutic strategy at clinical settings. Further research is needed to establish novel therapeutic strategies, including immunomodulatory strategies and combinatorial therapy, in order to improve recovery and therefore the quality of life for patients.

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