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Chapter

Trends in Neuroprotective Strategies after Spinal Cord Injury: State of the Art

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Abstract

Spinal cord injury (SCI) is an important pathology leading to possibly fatal consequences. The most common repercussions are those affecting motor and sensitivity skills. SCI-damage occurs in its first phase—as a result of the lesion mechanism (contusion, compression, transection, and primary lesion). After this primary damage, there is a second phase with further deleterious effects on neural degeneration and tissue restoration. At the moment, several investigation groups are working on developing therapeutic strategies to induce neuroprotection. This chapter pretends to introduce the reader to a wide range of these therapies, particularly those with promising results and tested in preclinical and clinical studies. In the first section, physiopathology of SCI will be addressed. Afterwards, the chapter will review neuroprotective strategies such as cyclooxygenase, calpain, and apoptosis inhibitors. Finally, the effect of immunophilin ligands, neural-derived peptides, antioxidants, hypoglycemic agent, gonadal hormones, Na channel blockers, and transplant of cultured cells will also be reviewed.

Keywords: neuroprotection, SCI, therapies, acute phase

1. Introduction

Spinal cord injury (SCI) can be defined as damage to the spinal cord (SC). It causes anatomical and physiological changes that result in permanent or temporary alterations in its function [1]. The injury causes ionic deregulation, edema, ischemia, bleeding, free radicals production, and a generalized inflammatory response that will cause partial or total loss of sensitive and motor function below the site of injury [2, 3].

In the United States, there are around 17,500 new cases of SCI per year, with an approximate prevalence of 280,000 people [4]. SCI is found most frequently in men (79.8%) than women (20.2%) and the age distribution reflects a bimodal performance with a peak between 15 and 29 years of age and another one on ages above 50 years [4–6]. Traffic accidents are the main cause of traumatic SCI (38%), and they are most prevalent in young people. The low impact accidents like falls are the second cause of SCI (31%), and they are more common among people older than 60 years old [5]. In Mexico, the estimated annual incidence of SCI is about 18.1 per million inhabitants. Statistically, the number of people involved rises each year [7].

2. Pathophysiology

The Spinal Cord Injury could be divided by its etiology in traumatic and nontraumatic. The traumatic type is caused by physical damage (traffic accident, sportive, and fall), whereas nontraumatic is occasioned by an illness/sickness, such as tumors, infections or degenerative diseases which directly affect the SC [8]. In addition, SCI can be divided into primary and secondary injury [1, 9].

Primary injury is caused at the moment of physical damage and leads to irreversible affection on gray matter during the first hour post-lesion. There are three main mechanisms of injury: contusion, when there is not a visible alteration in its morphology, producing a necrotic region at the injury area; laceration or transection, when there is an extreme trauma or penetration, affecting SC conduction of nervous impulses depending on whether the tissue is partial or totally transected; compression from vertebral fractures leading ischemic damage in the area where blood flow was disrupted [10, 11].

After injury, superficial blood vessels undergo to vasospasm which provokes damage in the microvasculature of gray matter [12]. Reduction in the perfusion has two important implications: hypoxia and ischemia; which may involve to neurogenic shock characterized by arterial hypotension, bradycardia, arrhythmia, and intraparenchymal hemorrhage that causes neuronal death by necrosis. Afterwards, primary injury provokes the rupture of blood brain barrier and a cascade of destructive secondary phenomena leading to a further damage in SC and neurological dysfunction [1, 13]. Therefore, the primary lesion results in the development of a succession of cellular and molecular changes that alter gene expression patterns, which are processes that are already part of the secondary injury [11, 12]. During the acute phase, injury to the blood vessels and severe hemorrhages cause massive influx of inflammatory cells, cytokines, and vasoactive peptides. This phase is almost characterized by ionic deregulation that leads to edema, thus interrupting the conduction of nerve impulses. Following, subacute phase involves a sequence of events like ischemia, vasospasm, thrombosis, inflammatory response, free radicals (FR) production, lipid peroxidation (LPO), and activation of autoimmune responses causing apoptosis. The huge inflammatory responses after the acute and subacute phase, together with the disruption of the blood-brain barrier (BBB), contribute to the progressively swelling of the SC. This generalized edema may increase the mechanical pressure of the SC, aggravating the injury [1, 11, 14].

To counteract all these acute effects after SCI, neuroprotective strategies have been investigated to rapidly intervene decreasing the neuronal death occurring after damage mechanisms. Many pharmacological and nonpharmacological therapies have been developed, and others are still under investigation, this in order to improve the quality of life of patients.

3. Neuroprotective therapy after acute SCI

As we review previously, SCI leads to motor and sensory dysfunction, first with the primary mechanical injury and then with the complex cascade of secondary damaging events [15]. For several years, basic science, preclinical, and clinical studies are focused in overcoming elements involved in accurate recovery from SCI [1]. An ideal neuroprotective therapy must reduce neurological symptoms including degenerative changes; starting from there, we can discriminate between potential clinical therapies, which could have a better effect [16]. While these therapies are being searched, there are many preclinical and clinical investigations exploring pharmacological and nonpharmacological treatments.

3.1 Preclinical pharmacological therapies

This range of therapeutic approaches includes: ionic channel blockers, inhibitors of NMDA and AMPA-kainate receptors, inhibitors of FR and LPO, anti-apoptotic drugs, calpain inhibitors, immunosuppressive or immunomodulatory drugs, immunophilin ligands, immunomodulatory peptides, hypoglycemic agents, and gonadal hormones.

3.1.1 Ionic channel blockers

3.1.1.1 Sodium

3.1.1.1.1 Tetrodotoxin

Tetrodotoxin (TTX) is a low-molecular-weight guanidine neurotoxin that acts as a specific blocker of voltage-gated sodium (NaV) channel [17]. TTX has neuroprotective properties by blocking NaV channels, preventing neuronal death by diminishing depolarization, cellular Na⁺/Ca⁺² exchange, and neuronal glutamate release [18].

The beneficial effects of TTX in preclinical studies include a reduction of white matter loss after SCI [17–19], promoting a motor function restoration. The effect of TTX is time-dependent [20]. The administration of TTX 15 minutes after a SCI helps to restore the function of hindlimbs [21]. Despite these promissory effects, there are some limitations for the use of TTX in patients, one of them is its toxicity. This may appear as a consequence of its systemic distribution and it can involve the blocking of diaphragmatic nerves ending in respiratory tract paralysis [17]. Even with previous findings, current studies are needed to improve its use in SCI.

3.1.1.1.2 Riluzole

Riluzole is a benzothiazole anticonvulsant drug with neuroprotective effects in the SCI [22]. One of the mechanisms by which riluzole operates is the inhibition in the presynaptic terminals of glutamate, and this helps to limit the glutamateinduced toxicity [23]. In addition, riluzole blocks the NaV-gated channels, avoiding swelling and neuronal acidosis. Riluzole blocks the entry of H+ to the neurons through the Na⁺/H⁺ exchanger; this prevents the Ca⁺² from inducing the release of glutamate and excitotoxicity [22]. Investigations have shown that the interruption of events associated with glutamate release on the presynaptic space by reducing Ca⁺² influxes provokes a glutamate-mediated LPO reduction [23, 24]. Administration of riluzole within 12 hours of SCI was well tolerated and suggests that it may have a beneficial effect on motor outcome [25].

3.1.1.2 Calcium

3.1.1.2.1 Nimodipine

Nimodipine is a dihydropyridinic Ca⁺² channel antagonist that boosts the brain's blood flow, without compromising metabolism [26, 27]. It reduces malondialdehyde (MDA) levels, ED-1 markers for activated macrophages and myeloperoxidase (MPo). Studies have shown that nimodipine helps reducing FR, oxidative damage, resulting in the reduction of the damaged area and the infiltration of the inflammatory cells to the region, allowing SCI restoration [26]. Furthermore, the effect of inhibiting Ca⁺² flux by nimodipine reduces apoptosis and tissue damage after SCI, increasing cell viability [27].

3.1.2 Inhibitors of NMDA and AMPA-kainate receptors

3.1.2.1 Memantine

Memantine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, which through the inhibition of hypoxic or ischemic damage/necrosis helps to prevent the secondary damage in SCI [28, 29]. The use of an NMDA antagonist limits neuronal glutamate exposure caused by excitatory amino acid neurotransmitters [29]. The use of memantine with anti-apoptotic agents like Q-VD-OPh boosts the neuroprotective effect through the reduction in apoptosis and necrosis mechanisms. Moreover, it provides better clinical and histological outcomes by limiting neuronal necrosis [28, 29].

3.1.2.2 Gacyclidine

Gacyclidine is a noncompetitive NMDA antagonist that is able to reduce the extension of ischemic lesions in SCI. It has been proven that gacyclidine is efficient in enhancing the functional and histological condition of the injury, but their neuroprotective effects are time and dose-dependent [30, 31].

3.1.2.3 NBQX (2,3-dihydroxy-6-nitro-7-sulfamoylbenzoquinoxaline)

NBQX is an AMPA/kainate antagonist that during acute SCI improves mitochondrial function and diminishes reactive oxygen species (ROS) formation as well as LPO production [32, 33]. The treatment with NBQX reduces white matter loss following SCI. Further studies are needed to know more about its efficacious effects in acute SCI.

3.1.3 Inhibitors of free radicals and lipid peroxidation

3.1.3.1 Polyunsaturated fatty acids (PUFAs)

Omega-3 polyunsaturated fatty acids (ω -3 PUFAs) are structural compounds of the phospholipid membrane. They produce beneficial effects in neurodegenerative diseases by its anti-inflammatory, antioxidant, and membrane stabilizing properties [34]. ω -3 PUFAs, particularly docosahexaenoic acid (DHA), exert profound anti-inflammatory effects on the central nervous system (CNS), confer significant protection to the white matter, and help to increase neurite growth and synapse formation. DHA acts on cyclooxygenases (COX), cytosolic phospholipase A2 (cPLA2), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) [35, 36]. Deficiencies of lipids affect neural responses in CNS injuries, and this must predispose nerve cells to dysfunction [37]. According to previous findings, there are some investigations (**Table 1**) that have previously shown the effects of PUFAs in preclinical models.

3.1.3.2 Glutathione

Glutathione (GSH) is a tripeptide compound constituted by glutamine, glycine, and cysteine. The reduced form of GSH is glutathione-monoethyl-ester (GSHE), which is an endogenous, rechargeable antioxidant. Besides its anti-oxidant functions, GSHE plays a role in regulation of apoptosis, and it is important for

Treatment outcome	Ref.
α -linolenic acid (ALA) and DHA reduce lesion size and increase motor recovery and neuronal survival.	[34]
DHA reduces microglia activation in both ventral and dorsal horns and increases motor recovery, promoting beneficial functional effect in SCI.	[38]
ALA, combined with DHA, protects against neuronal necrosis and apoptosis.	[39]
DHA induces a reduction in neutrophil number in SC epicenter. The administration confers histological protection and improves motor recovery.	[40]
Prophylactic therapy with ω -3 has shown a reduction in cellular vulnerability. Supporting functional recovery, there is also an increase in levels of protein kinase B/Akt and CREB.	[37, 41]
DHA plus rehabilitation enhance a functional, anatomical, and synaptic plasticity in cervical SCI.	[42]

Table 1.

Polyunsaturated fatty acids in spinal cord injury.

cellular defense against ROS [43, 44]. Some studies have reported that GSHE diminishes SC LPO after SCI, while also acting as a vasodilator under conditions of oxidative stress [44, 45]. In addition, GSHE plays an anti-excitotoxic role by inhibiting the binding ligands to ionotropic glutamate receptors under redox modulation, which have been involved in excitotoxicity after SCI. As a consequence of the reduction of GSH after an injury, there is neuronal loss in the SC, probably due to oxidative stress and mitochondrial dysfunction. Combined therapy of GSHE with A91 resulted in a better motor recovery and axonal sparing associated with a higher axonal myelination [46]. The use of GSHE could be an interesting alternative for SCI therapy; however, it should be strongly evaluated before its use in clinical trials.

3.1.4 Anti-apoptosis therapy

3.1.4.1 Zdevd-fmk

Caspase inhibitor Z-DEVD-fmk is a selective caspase-3 inhibitor that also has antiinflammatory properties. Anti-apoptosis compounds are used to block apoptotic cell death but also to inhibit cytokine production. Treatment of SCI with z-DEVD reduces secondary tissue damage, ischemic injury, preserves motor function, and provides neuroprotection via the inhibition of cell death in all of cell types in the SC [47, 48]. Low doses of z-DEVD-fmk combined with basic fibroblast growth factor (bFGF) reduce neurological deficit in ischemia, therefore providing neuroprotection [49].

3.1.4.2 z-LEHD-fmk

Caspase inhibitor z-LEHD-fmk acts as a selective caspase-9 inhibitor with antiapoptotic properties. This drug helps decreasing levels of apoptosis biochemical markers, reducing lesion size and remaining active during treatment to maintain its therapeutic effect. Treatment with z-LEHD-fmk helps to prevent apoptosis in a variety of cell types like neurons, astrocytes, oligodendrocytes, and microglia populations [50]. Further studies are needed to understand more about its effects and benefits in acute SCI.

3.1.5 Calpain inhibitors

Calpains belong to the family of calcium-dependent nonlysosomal cysteine proteases, which can be found expressed through the CNS. They are involved in

neurodegeneration, degradation of cytoskeleton, and apoptosis via caspase-3 due to its proteolytic activities, in SCI. The influx of Ca^{+2} stimulates Ca^{+2} -dependent enzymes, within them are calpains, which seem to play a role in proteolysis by contributing to apoptosis in CNS cells. The cell death decreases mRNA expression and transcription of myelin basic protein (MBP) and proteolipid protein (PLP), which are axonal neurofilament proteins [49, 51, 52]. The administration of a calpain inhibitor such as E-64-d (1 mg/kg) to injured rats blocks apoptosis and helps to re-establish MBP and PLP genes [51]. The administration of other calpain inhibitors such as SJA 6017 and calpeptin has demonstrated their ability to induce neuroprotection after SCI [53, 54]. Despite the study efforts and the promising therapeutic effects for functional neuroprotection, there are no clinical trials testing these drugs, so further studies are needed for the use of calpain inhibitors in patients.

3.1.6 Immunosuppressive or immunomodulatory drugs.

3.1.6.1 Inhibitors of cyclooxygenase

3.1.6.1.1 Indomethacin

Indomethacin, a nonsteroidal anti-inflammatory (NSAID) drug, acts as a nonselective cyclooxygenase inhibitor. It has shown that it inhibits the synthesis of prostaglandins and ameliorates the effects of secondary injuries like tissue necrosis in SCI [55–57]. RhoA is a convergent intracellular pathway that limits axonal growth; its inhibition with indomethacin prevents oligodendrocyte loss and induces myelination across damaged white matter [58]. Nevertheless, the administration of nonselective cyclooxygenase inhibitors is a controversial issue since these compounds could inhibit platelet aggregation and may produce gastrointestinal ulceration [55]. Moreover, there is evidence that a single injection of indomethacin in SCI had a minimal effect on functional recovery and anatomical repair [57].

3.1.6.1.2 Meloxicam

Meloxicam is a drug derived from enolic acid, which inhibits prostaglandin biosynthesis under inflammatory conditions via the inhibition of COX-2. It has minimal gastric toxicity. Meloxicam has shown to reduce SCI-induced oxidative stress and exert neuroprotection by inhibiting LPO, GSH depletion, and DNA fragmentation [59, 60]. Despite these interesting results, meloxicam has not been further studied. Therefore, more studies are needed to know about its clinical management in SCI.

3.1.7 Immunophilin ligands

3.1.7.1 Cyclosporine A

Cyclosporine A (CsA) is an immunosuppressant agent compound formed by 11 amino cyclic peptides, and it is obtained from *Tolypocladium inflatum*. CsA inhibits T-helper lymphocytes, cytotoxic and inflammatory responses in macrophages, inducible nitric oxide synthase (iNOs) expression avoiding the formation of nitric oxide (NO)-derived cytotoxic species, Cox-2 mRNA accumulation, tumor necrosis factor (TNF α) production and reduces cytokines and interleukins production (IL-1, IL-2, and IL-6). Also, CsA reduced the apoptosis of SC cells and increased the protein expression levels of cyclophilin-D (Cyp-D) and apoptosis-inducing factor (AIF) [61, 62]. This compound is capable of inducing motor recovery after SCI [63].

3.1.7.2 Tacrolimus

Tacrolimus or FK506 is an immunosuppressant macrolide drug, isolated from *Streptomyces tsukubaensis*, and it is approved by The Food and Drug Administration (FDA) [64, 65]. An indirect neuroprotective effect results from its immunosuppressant action on T-cells that infiltrate SCI, and this action modulates inflammation. On the other hand, FK506 inhibits caspase-3 and NF-kB, improving functional recovery with the increase of rostral axonal sparing and oligodendroglial survival [66, 67]. Additionally, this compound is capable of reducing FR and thereby LPO. These neuroprotective effects improve if the administration of FK506 is during the first 30 min after injury [65]. The studies suggest that FK506 might be a good drug for treating SCI in humans.

3.1.8 With neural derived peptides

Immunization with neural derived peptides (INDP) such as A91, a peptide derived from the 87–99 immunogenic sequence of myelin basic protein has shown to induce neuroprotection and motor recovery after SCI [68]. Its mechanism of action is related to the activation of T-lymphocytes inducing an anti-inflammatory Th2 response that allows microglia to differentiate into a M2 phenotype. Th2 response is capable of producing brain-derived neurotrophic factor (BDNF), a molecule strongly related to tissue protection [69]. INDP has shown that anti-A91 T-lymphocytes promote tissue protection by inhibiting the expression of iNOS, reducing ON production [68] and decrease LPO after SCI [70]. On the other hand, it has been shown that all these beneficial effects contribute to the preservation of neural tissue by preventing apoptosis [71], the survival of neurons in rubrospinal tract [72] and promoting a better neurological recovery in models of SCI [46]. Studies suggest that A91 might be an immune modulating treatment for SCI.

3.1.9 Metformin

Metformin is a hypoglycemic agent used for therapy of type 2 diabetes mellitus; it is an AMP-activated protein kinase (AMPK) agonist. Metformin also acts through signaling pathway of mTOR and p70S6K causing an inhibition of apoptosis and inflammation. This drug is also capable of stimulating autophagy and reducing expression of NF-kB-mediated inflammation [73, 74]. Studies indicate that long-term use of metformin has been proved effective as a pharmacological treatment for some CNS disorders like Parkinson's disease, Huntington's disease, and ischemic brain injury. Using a rat model of traumatic SCI, the administration of metformin helps restoring the dysfunctional autophagy-lysosome pathways providing neuroprotection, decreasing neuronal death and mitigating apoptosis [75, 76]. The immediate administration of metformin after the injury showed diminishing complications, reflecting a decrease on histopathological signs of neuroinflammation, including TNF α and IL-1 β inflammatory cytokines in the SC [73]. Although these outcomes are promising, subsequent studies are required to determine the risk ad optimal doses for the use of metformin on clinical studies.

3.1.10 Gonadal hormones

Androgens and estrogens are multi-active steroidal hormones that have neuroprotective effects in neural injuries; both testosterone and estradiol improve safeguard against apoptosis and promote motor and sensitive recovery. Also, reduce inflammation and FR generation and have been involved in regulating the expression of cytoskeletal proteins, promoting them as an increasing in neurite outgrowth [77, 78]. Studies in rats treated with estradiol have shown a reduction in the lesion size, an increase in white matter sparing, and an improving in motor function [77, 79, 80]. On the other hand, testosterone has shown to exert similar but not identical effects; it is neuroprotective against apoptosis in oxidative stress [77, 78]. A study with young adult female rats implanted with testosterone-filled silastic capsules reported regressive changes in motoneuron and muscle morphology after a SCI providing the possibility of improving motor function [81]. A study with administration of progesterone in rats improves neurological deficits and reduces inflammatory response. Prevents degeneration of motor neurons and reestablishes proliferation and differentiation of oligodendrocytes [82]. At the moment, investigations on the field conclude that gonadal hormones could be an effective alternative after SCI.

3.2 Clinical pharmacological therapies

Methylprednisolone, minocycline, GM-1-ganglioside, and glyburide are some of the most investigated pharmacological therapies in clinical settings.

3.2.1 Methylprednisolone

Methylprednisolone (MP) is a synthetic glucocorticoid, with anti-inflammatory and anti-oxidant effects [83, 84]. MP blocks the inflammatory cascade and disrupts neuron regeneration by inhibiting immunological cells [85, 86]. The potential neuroprotective effects of MP have been reported especially in the acute phase of SCI. According to some investigations, MP is capable of reducing FR production, Ca⁺² influx, excitotoxicity, and immune-mediated phagocytosis over the course of hypoperfusion of SCI [87]. In addition, MP appears to have effect in apoptosis and autophagy regulation; however, the mechanisms are not clear [84]. While it remains the only option for acute SCI treatment in clinical settings, a debate regarding optimal dose, time of administration, efficacy, and adverse effects has dominated the field for years. There are three National Acute SCI Studies (NASCIS) and other clinical or biomedical investigations, in which the safety and efficacy of MP were assessed (**Table 2**) [88]. Despite the intense investigation, currently there is an important controversy regarding the real utility of this drug.

3.2.2 Minocycline

Minocycline is a second generation tetracycline, a semi-synthetic antibiotic able to cross blood brain barrier, and it can be used to treat rheumatoid arthritis [95, 96]. Minocycline has neuroprotective effects when administered during the acute neural trauma. Current data suggest that minocycline has anti-inflammatory, immunomodulatory, and neuroprotective effects. These beneficial actions are achieved as a result of the inhibition of iNOS matrix metalloproteinases (MMPs), PLA2, TNF- α , caspase-1, and caspase-3. Moreover, minocycline enhances Bcl-2 and thus, reduces apoptosis, also, it decreases p38 mitogen-activated protein kinase (MAPK) phosphorylation and inhibits PARP-1 [97–100]. Other studies report that minocycline can bind to Ca⁺² and Mg⁺, reduces reactive astrocytes to increase oligodendrocyte viability in white matter, and inhibits the activation of microglial cells [101, 102]. A multi-center phase II trial was performed to explore the neuroprotective effect of minocycline; however, the results of the study did not establish a real improvement in SCI. Authors suggest further investigations in a multi-center phase III trial [103].

Treatment outcome	Ref.
NASCIS I: Treatment with a dose 1.0 g daily promotes neurological recovery. The morbidity and mortality is increased.	[89]
NASCIS II: Administration of (30 mg/kg intravenous bolus plus 23 hour infusion of 5.4 mg/kg) during the first 8 hours after injury causes neurological recovery seen from 6 weeks after the SCI.	[86]
NASCIS III: Administration within 8 hours from the SCI, should maintain the administration for 48 hours to improve neurological function.	[90]
Combination of riluzole and MP improves functional recovery and tissue sparing. In addition, beneficial effects on oxidative stress were observed.	[91]
MP may cause acute corticosteroid myopathy, at doses recommended by the NASCIS.	[92]
High-dose MP inhibits glucocorticoid receptors as well as having effects in LPO; however, their beneficial effects are independent of LPO inhibition.	[55]
Administration of MP for treatment of SCI is not recommended. There is evidence that high-dose steroids are associated with harmful side effects including death.	[93]
A comparative study of MP vs. A91-immunization showed that A91-immunization has a better efficiency promoting motor recovery. Combining MP with A91-immunization allowed to observe that MP has a transient immunosuppressive effect that eliminated the beneficial actions of A91-immunization.	[94]

Table 2.

Effects of methylprednisolone in spinal cord injury.

3.2.3 GM-1-ganglioside

Gangliosides (GM-1) are sialic acid-containing glycosphingolipids, present in cell membranes of CNS cells, specifically in the external leaflet of plasma membranes. They participate in the repair and maintenance of CNS [104, 105]. A randomized placebo-controlled (Phase II) trial with administration of GM-1 within 24 hours after injury was realized in 37 patients with SCI. The results of this study showed that GM-1 enhances the recovery of neurologic function after 1 year [104]. Further studies should be designed in order to provide more evidence about the efficacy of GM-1.

3.2.4 Glyburide

Glyburide (glibenclamide) is a FDA approved sulfonylurea drug widely used to treat type 2 diabetes; it has the ability to target receptor (SUR1) regulated Ca⁺² activated [ATP] cation (NCCa-ATP) channels [96, 106]. After SCI, there are small hemorrhagic lesions at the epicenter of gray matter. Glyburide diminishes the progressive hemorrhage necrosis by jamming the interaction between SUR-1 and preforming subunits of NCCa-ATP channels located in endothelial cells. In addition, improves neurological function [107]. Actually, a phase I/II clinical trial is currently under way to test the safety and neuroprotective effectiveness of glyburide in patients with SCI [88].

4. Nonpharmacological therapies (preclinical interventions)

The most common preclinical nonpharmacological therapies in the acute phase of SCI are antioxidants, growth factors, and transplant of cultured cells like neural stem cells (NSCs), bone marrow stem cells (BMSCs), olfactory ensheathing cells (OECs), and Schwann cells (SCs).

4.1 Antioxidants

First damage in the acute phase of injury is generated in membranes, membranes which are susceptible to the attack of ROS and reactive nitrogen species (RNS). ROS are produced in metabolic and physiological processes of cells; however, they are overproduced by inflammatory response. ROS and RNS induce LPO, which leads to demyelinating processes. Among the nonpharmacological therapies to prevent damage from FR are nonenzymatic antioxidants like vitamins.

4.1.1 Vitamins

Vitamins are one of the main natural antioxidants. **Table 3** shows some vitamins and their neuroprotective effect after SCI.

4.1.2 Resveratrol

Resveratrol is a natural polyphenolic compound that has exhibited beneficial health properties as well as antioxidant, anti-inflammatory, and antitumor effects. Resveratrol exerts a neuroprotective effect by regulating apoptosis [118]. Studies have shown that the anti-inflammatory effects of resveratrol are mediated mainly by sirtuin (SIRT) 1 [119, 120]. Resveratrol enhances locomotor recovery [121–123]. Furthermore, resveratrol increases nuclear factor erythroid 2-related factor (Nrf-2) activation, providing antioxidant effects [121]. Further investigation is needed in order to provide more evidence about the efficacy of this treatment.

Treatment	Neuroprotection mechanism	Ref.
Vitamin E	Increases functional recovery. Reduces cavitation and decreases FR, LPO, and glutathione peroxidase and improves functional recovery.	[108–112]
Vitamin C	Stops lipid hydroperoxyides formation and decreases membrane damage. Reduces necrotic tissues and improves functional recovery in rats. Inhibits ROS generation and LPO. Decreases levels of proteins like NF-kB, iNOS, and COX-2. Down-regulates the levels of TNF α and IL-1 β . Modulates antioxidant status and MPO activity	[113, 114]
Vitamin C + fluoxetine	Co-treatment with vitamin C + fluoxetine inhibits the blood-SC barrier disruption after SCI. Inhibits capillary fragmentation by reducing mRNA levels of MMP-9. Prevents degradation of tight-junction proteins, inhibits infiltration of neutrophils and macrophages. Inhibits apoptotic cell death and improves functional recovery.	[115]
Vitamin A	Increases the expression of IL-1 β , IL-6, and TNF α after SCI. Systemic administration reduces early transcript levels of IL-1 β , IL-6, and TNF α . Reduces blood-SC-barrier permeability and improves functional recovery	[116]
	Decreases levels of β-catenin, P120 catenin, occluding, and claudin5. Inhibits endocytoplasmic reticulum stress and caspase-12 expression.	[117]

4.2 Growth factors

The use of growth factors like BDNF, transforming growth factor- β (TGF- β), and insulin-like growth factor-1 (IGF-1) as a therapy to improve morphological and behavioral outcomes after SCI has been topic of study of many investigations.

4.2.1 Brain-derived neurotrophic factor

BDNF exerts a relevant function in the repair of neural tissue and plasticity in CNS [124, 125]. Nevertheless, recent studies have also shown that BDNF is capable of exerting neuroprotective effects. In acute phases of injury, several reports indicate that both, BDNF alone [126, 127] or in any combination [128, 129] has improved functional recovery, neuronal survival, and tissue preservation. Moreover, BDNF has potent antioxidant effects and may be involved in regulation of immune responses after an SCI [130]. BDNF after SCI requires careful selection to consider the location, mode, and time of application after an injury.

4.2.2 Transforming growth factor- β

TGF- β is a pleiotropic molecule with specific key functions in cell differentiation, proliferation, migration, immunosuppression, and extracellular matrix metabolism [131]. TGF- β could also be contributing to neuroprotective mechanisms

Therapy	Neuroprotective effects	Ref.
NSCs	Increase functional recovery. Reduction in neutrophils and M1 macrophages. Downregulation of TNF α , IL-1 β , IL-6, and IL-12. Improve functional recovery and reduce neuronal apoptosis, microglia activation, reduce pro-inflammatory cytokines like TNF α , IL-1 β , and IL-6. Improve locomotor and sensory function and increase mRNA expression of BDNF.	[141–144]
BMSCs	Improve locomotor function and tissue protection. Increase the neurotrophic growth factor. Stimulate M2 macrophage activation. Reduce cystic cavities size and suppress glial scar formation.	[145–148]
BMSCs + SCs	Reduce the formation of the glial scar, remyelinate the injured axons, and promote functional recovery	[149]
BMSCs + IGF-1	Induce modulation of inflammatory cytokines and oxidative stress. Increase functional recovery and reduce activation of glial fibrillary acidic protein and increase myelination 4 weeks following SCI.	[150]
BMSCs + OECs	Reduce apoptosis and increase locomotor recovery.	[151]
OECs	Reduce cavity size, increase the neurofilaments sprouting and serotonin axons, and improve functionality.	[152]
OECs + SCs	Diminish astrocyte number, microglia/macrophage infiltration and expression of CCL2 and CCL3.	[153]
SCs	Upregulate the expression of NOS, activate the NO-dependent cyclic-GMP pathway, which enhances neuronal survival. Stimulate the expression of neural growth factor and BDNF. Reduce inflammatory cytokines and ROS.	[154, 155]
SCs + NSCs	Promote neuronal differentiation, increase axonal regeneration/ myelination, reduce neuronal loss, and improve functional recovery.	[156]

Table 4.

Stem cell therapy in spinal cord injury.

after SCI since it participates in the regulation of neuronal survival and orchestrates repairing processes in the CNS [132]. It has been previously observed that TGF- β administration reduces microglial activation and increases neuronal survival [133]. The early induction of TGF- β after SCI modulates the acute immune response, the formation of glial scar and improves functional recovery [134].

4.2.3 Insulin-like growth factor-1

IGF-1 belongs to the family of insulin-related peptides, and it is the mediator of the anabolic and mitogenic activity of the growth hormone [135]. Aside from this, IGF-1 acts as a strong antioxidant [136] and pro-survival [137] factor in the CNS since it diminishes caspase-9 and elevates Bcl2 [138]. Experimental studies have shown that IGF-1 reduces edema and the upregulation of iNOS after SCI [139]. In the same way, it has been suggested that IGF-1 and erythropoietin protect against ischemic SCI in rabbits [140]. Therefore, the beneficial properties of IGF-1 make this molecule an interesting neuroprotective strategy in the acute phase of SCI.

4.3 Stem cells

Stem cells have also been the focus of several investigations. **Table 4** summarizes some of the neuroprotective effects exerted by stem cells like NSCs, BMSCs, OECs, and SCs.

5. Nonpharmacological therapies (clinical trials)

Nonpharmacological therapies with clinical studies are hence limited in acute phases of the injury.

5.1 Stem cells neural stem cells

Pilot studies cover the acute phase of SCI.

5.1.1 Neural stem cells

Transplants with human NSCs in phase I/IIa assessed the safety and neurological effects after SCI. Of 19 treated subjects, 17 were sensorimotor complete and two were motor complete and sensory incomplete. They demonstrated that 1 year after cell transplantation, there was no evidence of SC damage, syrinx or tumor formation, neurological deterioration, and exacerbating neuropathic pain or spasticity [157]. Additional studies should be designed in order to afford more evidence about the efficacy of NSCs.

5.1.2 Bone marrow stem cells

Regarding bone marrow stem cells (BMSC), an interesting study reported data from 20 patients with complete SCI who received transplants of BMSC. They showed improvement in motor and sensory functions [158]. In addition, a study with autologous BMSCs in three patients in the sub-acute phase of injury (<6 months of disease) demonstrated that, these cells could be safely administered through intrathecal injection in SCI patients [159]. Other study showed that 45.5% of transplanted patients presented improved neurological function. They showed some degree of improvement in sensitivity and motor function as well as in sexual function. In two patients, neuropathic pain disappeared and bladder and bowel control increased [160]. Nevertheless,

more investigation through clinical trials is required with a larger population of patients before further conclusions can be drawn.

5.1.3 Olfactory ensheathing cells

Transplants with autologous OECs in three patients indicated that there were no adverse effects 1 year after transplantation. The neurosurgical process did not lead to any negative sequelae either during the operation or postoperatively. Additionally, they demonstrated the possibility of taking a nasal biopsy and reliably generating enough cells for transplantation within 4 weeks [161]. These observations suggest that autologous transplantation is safe but further researches are needed.

5.1.4 Schwann cells

A Phase I clinical trial with autologous human SCs was conducted to evaluate the safety of transplantation into the injury of six subjects with subacute SCI. There was no evidence of additional SC damage, mass lesion or syrinx formation. They conclude that it is feasible to identify eligible candidates, appropriately obtain informed consent, perform a peripheral nerve harvest to obtain SCs within 5–30 days of injury, and perform intra-spinal transplantation of highly purified autologous SCs within 4–7 weeks of injury [162]. Studies in acute phases using SCs are very few: therefore, more studies are needed in this area.

5.2 Physical therapy

Timing as a specific prognostic factor in rehabilitation results and confirms that early specific rehabilitation treatment is associated with greater improvement. Several studies investigate the early rehabilitation as a therapeutic strategy to improve locomotor function, some of them have even shown physical functional independence [163–165]. Other studies indicated that in acute SCI physical therapy of body weight support on a treadmill and defined overground mobility therapy did not produce different results [166]. Further studies are required to afford conclusive results.

6. Conclusions

In conclusion, there are several pharmacological and nonpharmacological treatments that have been tested in preclinical and clinical phases. However, so far have not yielded fully satisfactory results; even using combined therapies. Further studies are needed in order to identify novel therapeutic targets and strategies that provide a better medical care avoiding complications.

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Conflict of interest

The authors declare no conflict of interest.

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