# Pharmacological Neuroprotective Therapy for Acute Spinal Cord Injury: State of the Art

S. Martiñón and A. Ibarra*

*Unidad de Investigación Médica en Enfermedades Neurológicas, HE, CMN Siglo XXI, IMSS, Av. Cuauhtemoc No. 330, Col. Doctores, C.P. 06720, México City, México; Proyecto CAMINA A.C. Tlalpan No. 4430 Col. Toriello Guerra, C.P. 14050, México city, México*

**Abstract:** After spinal cord injury, a number of destructive events developed immediately after the primary insult increase tissue damage.

Several therapeutic approaches are directed to neutralize these phenomena. The present manuscript revises diverse pharmacological treatments used to promote neuroprotection, both in clinical and experimental acute spinal cord injuries.

**Key Words:** Neuroprotection, neuroprotective drugs, paraplegia.

## 1. INTRODUCTION

Spinal cord (SC) injury is a complex disease that causes severe neurological disabilities. The victims are partially or totally impaired to reincorporate to their customary activities, so they are strongly disturbed in their physical, emotional and economical stability.

Even in specialized centers, SC injury is a disease with a high morbi-mortality [1-5]. The incidence of this pathology fluctuates between 10.4 and 83.0 per million inhabitants per year. One-third of patients are reported to be tetraplegic and 50% have complete lesion. The mean age is 33 years, and the men/women ratio is of 3.8 [5].

In spite of its important impact, the availability of useful therapies is very limited at the moment, since no effective treatment exists either to diminish damage or to promote functional recovery. It is interesting to remind the great optimism generated by methylprednisolone (MP) and its supposed beneficial effects in patients with acute SC injury [6, 7].

It seemed that the problem was partially solved for these patients. Nevertheless, the failure to replicate the supposed positive effect has caused an important decrease in such enthusiasm; therefore, a wide range of other pharmacological interventions should be evaluated. That is why, some anti-inflammatory agents (COX inhibitors), immunophilin ligands (cyclosporine A, FK506), antioxidants (peroxynitrite scavengers) or neurosteroids (progesterone) have been tested in different experimental models of CNS damage. In some cases, the studies have provided promising results.

The purpose of this review is to describe some of these pharmacological therapies used in both clinical and experimental acute spinal cord injuries.

*Address correspondence to this author at the Unidad de Investigación Médica en Enfermedades Neurológicas, HE, CMN Siglo XXI, IMSS, Av. Cuauhtemoc No. 330, Col. Doctores, C.P. 06720, México City, México; Tel: 52 55 55780240; Fax: 52 55 55735545;
E-mail: iantonio65@yahoo.com

## 2. PATHOPHYSIOLOGY OF SPINAL CORD INJURY

After injury, SC damage is caused by two events: i) the mechanism of the lesion by itself (i.e. contusion or compression) which causes the primary injury; and ii) the self-destructive phenomena developed as a consequence of the initial lesion, which produce a secondary injury [8].

Primary injury causes disruption of neural tissue (mainly axons) and blood vessels [9]. As a result, both cells and axons are elongated or disrupted causing an irreversible and diffuse structural damage. Myelin breakdown is one of the most deleterious consequences of primary lesion, especially that of highly myelinated axons [10]. Primary injury is also associated with the rupture of several blood vessels causing an extensive hemorrhagic zone mainly localized in the gray matter, which is highly vascularized [8, 11].

Secondary injury is caused by several self-destructive phenomena which increase the damaged area towards healthy tissue as a centrifuge craneo-caudal wave, from the epicenter of injury [12]. During the primary lesion, the damage inflicted to the blood vessels limits or even prevents, blood flow [8]. This ischemic condition causes the failure of important metabolic mechanisms (i.e. glycolysis and oxidative phosphorylation) thus promoting loss of cellular energy and activating necrotic processes; including loss of membrane permeability and lysosome rupture. That way, ischemia also induces the activation of proteases, phospholipases, ATPases and endonucleases which degrade cytoplasmic membranes as well as nuclear and cytoskeleton components [11].

As a result of the ischemia-reperfusion phenomenon, a wide range of reactive oxygen species (ROS), i.e. $ROO^{\bullet}$, $RO^{\bullet}$, $OH^{\bullet}$, are produced. They attack different cellular components (i.e. lipids, proteins and nucleic acids) and contribute to cellular death. Peroxidation of membrane lipids is in fact the most harmful damage causing mechanism.

ROS attack unsaturated fatty acids (mainly polyunsaturated) causing a chain reaction which supplies a continuous provision of free radicals. This process is known as lipid peroxidation [13].

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Excitotoxicity due to an excessive release of neurotransmitters is another harmful event developing after SC injury. A continuous increase in glutamate concentrations [14], especially in a hypoxic environment [15], produces an overstimulation of ionotropic receptors [N-metil-D-aspartate (NMDA), α-amino-3-hidroxi-5-metil-4-isoxazolepropionic (AMPA) and kainate] and activates the voltage-dependent sodium channels causing an extensive depolarization and a marked increase in intracellular sodium concentration [16]. This ion imbalance produces an important chloride inflow to the cell, which increases the osmotic intracellular conditions and thus induces secondary cellular lysis.

Excitotoxicity also produces an increase in intracellular calcium concentrations, which activate a wide range of proteases and lipases that degrade diverse cellular constituents including proteins, cell membranes and neurofilaments [16].

From hours to days after injury, a cellular inflammatory response also contributes to SC damage. Neutrophils and macrophages can produce reactive oxygen species and then contribute to LP. As early as 1 h after lesion, neutrophils reach the area [17], then their number increases, peaking at 24 h after injury [18]. Peripheral macrophages can be observed 24 h after lesion and then they multiply until they reach a peak between days four and seven [18, 19]. They may persist in the injured area even at chronic stages [20]. Microglia (resident macrophages) are activated within the epicenter of the lesion between three and seven days post-injury [21]. All these cells have been correlated with the amount of damaged tissue after injury [18].

Another harmful event developed after the primary lesion is the apoptotic cascade. This event can be triggered by cytokines, inflammatory injury, free radical damage and excitotoxicity [22, 23].

Apoptosis occurs *via* Fas ligand/Fas receptor, nitric oxide, direct caspase-3 proenzyme activation or mitochondrial damage [8, 24]. This event greatly contributes to cell loss, which has an important negative impact on the neurological outcome.

Finally, the primary insult to the SC also disturbs the ability of the mitochondria to carry out cellular respiration, oxidative phosphorylation and respiration-dependent $Ca^{2+}$ uptake/sequestration. The latter disturbs intracellular $Ca^{2+}$ homeostasis and induces permeability changes in the mitochondrial inner membrane which contribute to mitochondrial lysis.

All these alterations together, significantly increase cellular death and thereby aggravate injury. The secondary mechanisms of damage are currently the target of pharmacological therapy.

## 3. CYCLOOXYGENASE INHIBITORS

Cyclooxygenase (COX) is an enzyme that contributes to the formation of prostanoids (i.e. prostaglandins, prostacyclin and thromboxane) which importantly participate in the inflammatory processes.

Three *COX* isoenzymes are known at present: *COX-1*, *COX-2* and *COX-3* (also called *COX-1b* or *COX-1 variant* (*COX-1v*) [25]. Since these enzymes play an important role in the development of inflammatory reactions, some therapeutic approaches for acute SC injury have been directed to inhibit the function of these molecules.

Some selective or non-selective COX inhibitors have been proven for their potential to promote SC-neuroprotection.

### 3.1. Indomethacin

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) used for fever symptoms relief, pain, stiffness, and swelling; especially when there is an inflammatory component. Indometacin is a methylated indole derivative and a member of the arylalkanoic acid class of NSAIDs [26]. This compound works through the inhibition of both COX-1 and COX-2 enzymes [27].

Indomethacin directly inhibits motility and activity of polymorphonuclear leucocytes as well [28]. The anti-inflammatory effects exerted by this compound prompted to evaluate its neuroprotective action in animal models of acute SC injury. Preliminary studies showed that indomethacin is capable of reducing the severity of tissue damage, attenuating the alteration of spinal cord evoked potentials and diminishing edema formation. At the same time, this drug also improves blood flow and neurological function after SC injury [29-31].

More recently, Pantovic and co-workers [32] also reported an improved motor recovery when indomethacin was administered to SC injured rabbits. In spite of these interesting results, administration of indomethacin has also been reported ineffective or even deleterious for SC injury [33, 34].

Regarding the latter, it was observed that administration of 3 mg/kg of indomethacin (the minimum dosage used in other studies for neuroprotection) induced lipid peroxidation, a process strongly related with secondary damage after SC injury. Such disparity in observations reflects the lack of reliability and limits the clinical usefulness of this compound.

### 3.2. Selective COX2 Inhibitors

*COX-1* and *COX-2* are isoenzymes with a 60% amino acid sequence homology and near-identical catalytic sites.

The most significant difference between them, which allows selective inhibition, is the substitution of isoleucine (in COX-1) with valine (in COX-2*)* at position 523 [35]. This substitution allows access to a hydrophobic side-pocket in COX-2.

Some drugs, such as DuP-697 and the coxibs derived from it, bind to this alternative site and are considered to be selective inhibitors of *COX-2* [36]. Even though both catalyze identical chemical reactions, COX-2 can be activated by hydroperoxide concentrations that are approximately ten times lower than those that activate COX-1; this raises the possibility that under limiting concentrations of peroxide, COX-2 may be fully active whereas COX-1 is not [37].

Furthermore, COX-2 efficiently oxidizes ester and amide derivatives of arachidonic acid whereas COX-1 does not [35].

After SC injury a significant up-regulation of COX-2 has been reported [38, 39]. This over expression is postulated to be an active component of the inflammatory reaction observed [40, 41]. Therefore it could be expected that selective inhibition of COX-2 activity would promote neuroprotection.

Preliminary studies with celebocid, an oral COX-2 inhibitor, showed only a modest protective effect after acute SC injury [42]. The partial failure of this drug, could be due to its non-optimal absorption as a consequence of the alterations induced by SC injury upon gastrointestinal function [43-45]. Therefore, the outcome of parenteral formulations such as NS-398, prompted to test these compounds again.

Hains and co-workers [46], demonstrated a significant reduction in locomotor alterations in SC-injured animals treated with NS-398.

More recently Lopez- Vales and co-workers [47], also reported the protective effect of this compound; however, they observed that the combination of this drug with olfactory ensheathing cell grafts rather than increasing the positive effect, decreased it. Although the available data suggest a promising usefulness for this compound, the reduced number of studies on the field demands more experimental investigation.

It would also be important to evaluate the risk presented by these compounds for cardiovascular pathologies [48], summated to the intrinsic alterations of SC-injured patients [49].

## 4. IMMUNOPHILIN LIGANDS

Immunophilins (IPs), are an evolutionary conserved, but structurally heterogeneous family of proteins that share a common enzymatic activity and pharmacological profile [50]. IPs are up to 50 times more abundant in the nervous system than in immune tissues [51] and some of them are receptors for immunosuppressive drugs like cyclosporine A ( CsA), FK506, rapamycin and their non-immunosuppressive analogs which are collectively referred to as "immunophilin ligands" (IPLs) [50].

CsA and FK506 are the more commonly used IPLs for treating experimental acute SC injury. Cyclosporin A binds to cyclophilin A (CyPA) whereas the receptor for FK506 is the FK506-12 binding protein (FK-12BP). The link of these compounds to IPs, inhibit the peptidil-prolyl *cis-trans* isomerase (rotamase) activity of these molecules. Besides, the resulting drug-IP complex, binds and inhibits the activity of calcineurin, a calcium-dependent phosphoserine/ phosphothreonine protein phosphatase [51-53]. These actions can promote a wide range of neuroprotective effects.

### 4.1. Cyclosporine A

Cyclosporine A is a cyclic and lypophilyc undecapeptide that inhibits T helper lymphocyte proliferation and as a consequence, depresses both cellular and humoral immune responses.

By inhibiting calcineurin, CsA interferes with some immunological mechanisms such as cytokine production [53, 54] and neutrophil cytoskeleton motility [55]. It also inhibits non-immunological phenomena, like the expression and activation of nitric oxide synthase (NOS) [56, 57].

By these means CsA could inhibit both the immune response (in part the inflammatory reaction) and the NO overproduction. CsA may also exert other actions. After injury, this compound could inhibit phospholipase A2 [58] and cyclooxigenase [59]. That way, by a calcineurin-independent mechanism, CsA inhibits the expression [59, 60] and activation [61] of the inducible NOS (iNOS), an enzyme related with NO overproduction and proinflammatory effects.

Finally, binding of CsA to CyPA inhibits the "romatase activity" of this IP, promoting neuroprotection and probably neuroregeneration [50]. After injury, CsA is capable of diminishing LP [62] even to the same extent as MP but without the deleterious effects of the latter [63]. The beneficial effect of CsA on LP was also associated with a significant decrease in the demyelination process, an enhanced survival of neurons and a greater recovery of function in SC injured rats [62, 64].

These data are in fact the result of a rationally designed and implemented dosing regimen based on the knowledge of population-specific pharmacokinetic behavior [65] and support the usefulness of this drug to protect neural tissue from a traumatic insult.

Rabchevsky and co-workers [66] failed to demonstrate a beneficial effect for CsA following acute SC injury; however, different dosing regimens and experimental models were used, and this could explain the disparity in results.

Therapy with CsA could also induce neuroregeneration which makes the use of this drug more attractive [67-69].

### 4.2. FK506

FK506 (also Tracolimus) is a FDA-approved macrolide immunosuppressant compound which is mainly used to reduce rejection after allogenic transplant. The actions of this drug are similar to those of CsA: FK506 reduces peptidyl-prolyl isomerase activity by binding to the immunophilin FKBP-12; thus, creating a new complex [70]. This FKBP12-FK506 complex interacts with and inhibits calcineurin [71].

These actions are of relevance for inducing neuroprotection. FK506 could also exert calcineurin-independent actions such as leukotriene and arachidonic acid inhibition [72-74] or heat shock proteins up-regulation [75, 76].

Studies performed in models of SC injury have shown the beneficial effect of this drug to reduce LP [77], GFAP and COX-2 reactivity [78] or caspase-3 activation [79]. In the same way, FK506 improves axonal and motor neuron survival [80, 81], motor evoked potentials [78] and neurological function recovery [78, 81].

The combination of this compound with olfactory ensheathing cells has also demonstrated the promotion of additive protection and SC injuries repair [82]. FK506 by itself is also able of inducing neuroregeneration [80, 83, 84].

Immunophilin ligands constitute a promising therapy for acute SC injury; thereby, the enforcement of further experimental investigation and even the beginning of preclinical

studies are encouraged in order to be able to formulate the best strategy.

## 5. ANTIOXIDANTS

Oxygen radical-induced LP is perhaps the most important detrimental phenomenon developed after SC injury. Therefore, several therapeutic strategies are directed to neutralize the harmful effect of this process [85]. In this section only those antioxidants that according to diverse experimental or clinical studies have provided promising results will be mentioned.

### 5.1. Methylprednisolone and Lazaroids

Glucocorticoid steroids have been extensively employed in the clinical treatment of SC injury. Initially, the mechanistic rationale for their use was centered on the expectation that they would reduce post-traumatic spinal cord edema. Nevertheless, the attention was later focused on the possibility that these compounds could inhibit LP as a result of their high lipid solubility and ability to intercalate between polyunsaturated fatty acids; a mechanism that would limit LP propagation [86, 87].

Methylprednisolone (MP), a synthetic glucocorticoid, is at the moment the only available drug for acute SC injury in humans. This compound is capable of inhibiting LP, calpain-mediated neurofilament loss [88], phospholipase A2 and lactate accumulation, inflammation and post-traumatic ischemia [89]. Likewise, MP improves ATP and intracellular calcium [90, 91].

Studies performed in animals with SC injury have supported a beneficial effect of MP on neurological recovery [92, 93]. Furthermore, positive results in SC injured humans treated with MP have also been found in clinical trials (National Acute Spinal Cord Injury Studies, NACIS II, and III).

In spite of these results, a strong controversy exists regarding the beneficial effect of this drug [94-97]. It has been reported that MP therapy is associated with a 2.6-fold increase in the incidence of pneumonia [98]. Besides, the beneficial effect of MP on neurological recovery has not been conclusively proven and the NACIS II and III trials have been severely criticized [7, 94, 99-103]. Thus, the use of this drug for acute SC injury merits a careful reappraisal.

Lazaroids (also 21-aminosteroids) also emerged as very promising therapeutic agents. These compounds were obtained by modifying the steroid molecule to enhance the anti-LP effect and to eliminate the glucocorticoid actions [87]. Lazaroids do not present the glucocorticoid receptor-mediated side effects that limit the clinical use of MP. One of these, tirilazad, was tested in the NACIS III trial. In this study, tirilazad-treated patients presented a slightly but not significantly better neurological recovery than those treated with MP [104].

Although tirilazad may induce the apparent positive effects of MP without the same side effects, the ultimate approval of this compound for SC injury in humans requires at least another trial comparing it against placebo in order to be registered by the FDA. [87]. At the moment, the scenario in which tirilazad could be approved is not apparent since no more studies have been reported.

### 5.2. Peroxynitrite Scavengers

Peroxynitrite is a product of the reaction resulting from the superoxide radical combined with nitric oxide. This compound is the most critical ROS generated during acute SC injury, and LP is undoubtedly its key mechanism of damage [105, 106].

Tempol (4-Hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl) is a membrane-permeable, metal-independent SOD mimetic that is superoxide anion specific. Therefore, by scavenging $O_2^-$, Tempol inhibits the formation of peroxynitrite. A recent study already demonstrated the neuroprotective effect of this drug after SC injury. Tempol significantly improved motor recovery and neural tissue sparing in SC injured animals even when the drug was administered 48h after injury [107]. This preliminary data should encourage more experimental studies to support it and detail its use.

Inhibition of NO production could also diminish the formation of peroxynitrite. In this line, some iNOS inhibitors are protective in acute SC injury.

Aminoguanidine (AG) is a selective iNOS inhibitor that can prevent both NO production and LP in SC tissue. It can also improve the functional status of SC injured animals [108-110].

ONO-1714, another selective inhibitor of iNOS, attenuates the increase of apoptosis and improves the functional outcome of animals with traumatic SC injury [110, 111].

Finally, agmatine, an iNOS inhibitor and selective NMDA receptor antagonist, is a drug that has generated interesting expectations. It has been shown to reduce tissue damage and to improve motor function of SC-injured rats [112, 113].

Additional studies about the role of these drugs are needed before they can be claimed helpful to improve treatment of patients with SC injuries.

## 6. CALPAIN INHIBITORS

Calpain, a calcium-dependent cysteine protease, is another candidate for neuroprotective intervention since this enzyme mediates the degradation of many cytoskeletal and membrane proteins in the course of neuronal death. Besides, in conjunction with caspases, calpain can also cause neural cell apoptosis following trauma [114].

Substantial research effort has been focused upon the development of highly specific inhibitors of calpain for therapeutic use. Administration of cell permeable and specific calpain inhibitors in models of SC injury has provided significant neuroprotection. The mechanism of action of these compounds involves a covalent interaction between the –SH of the active site Cys108 of calpain, and an electrophilic center of the inhibitor.

Two classes of such inhibitors are the oxiranes and the aldehydes. E-64-d, is a cell permeable oxirane which is highly selective for calpain [114]. Preliminary studies have demonstrated its neuroprotective effects in animals with acute SC injury [9, 115-117].

Leupeptin, an aldehyde that, not only inhibits calpain but also other cysteine and serine proteases, has also shown neuroprotective ability in models of SC injury [118].

MDL28170 is an aldehyde which has been synthesized and tested for calpain inhibition. This compound lacks charged groups, and is thus capable of penetrating the cell membrane by passive diffusion [114]. MDL28170 also has neuroprotective properties and has even shown the ability to improve the neurological function after SC injury [119, 120].

Together, these observations suggest that calpain inhibitors may be of benefit in treating acute SC injury; however, additional data are required to evaluate the effectiveness of these drugs.

## 7. APOPTOSIS INHIBITORS

Apoptosis is one of the most important forms of cell death seen in SC injury [22, 121]. This phenomenon occurs *via* mediators known as caspases which could be therapy targets; that is why, a number of strategies are based on the use of competitive caspase inhibitors with similar amino acid sequences to those of the natural substrates [87].

Caspases 3 and 9 are key molecules in the apoptotic cascade; thereby caspase inhibitors that block these molecules could promote apoptosis inhibition and thus neuroprotection.

zDEVD-fmk is a caspase 3 inhibitor that reduces secondary tissue injury and improves motor function after local administration in animals with SC injury [122]. Similarly, z-LEHD-fmk a caspase-9 inhibitor has a beneficial effect after SC injury [123].

Another interesting target to inhibit apoptosis is the molecule known as P38 mitogen-activated protein kinase (MAPK). The application of SB203580, a selective inhibitor of MAPK, reduced the number of apoptotic cells and the magnitude of myelin degeneration in SC injured animals. At the same time, it promoted a better neurological function as compared to the one observed in non-treated animals [124].

In spite of the above mentioned positive results, other studies have reported unsupportive evidence about the beneficial effects of anti-apoptosis drugs [118, 125]. Therefore, it is difficult to determine the efficacy of these compounds in the treatment of acute SC injury at present, and further studies are necessary.

Minocyline is a tetracycline that crosses the blood-brain barrier and prevents caspase up-regulation, thus preventing the apoptotic phenomenon [126]. Among other things, this drug may also diminish cytokine expression, mitochondrial cytochrome c release and reactive microgliosis [127-130]. These multifaceted effects have also yielded a significant motor recovery after acute SC-injury [128, 131, 132]. Among anti-apoptotic compounds, minocycline is perhaps the one with the most possibilities to be tested in clinical trials.

## 8. STEROID HORMONES

Due to its lipidic structure, steroid hormones can traverse the cell membrane and get into the nucleus quite easily. Two of these hormones have been extensively used as neuroprotective agents: progesterone and estrogen.

These two hormones have been reported to reduce the consequences of injury by enhancing anti-oxidant mechanisms, axonal remyelinization, synaptogenesis and dendritic arborization. Aside from these affects they could also reduce apoptotic cell death, excitotoxicity and immune inflammation [133-141].

Progesterone (PROG), has shown beneficial effects upon motor recovery and tissue sparing in acute SC-injury [142]. Nevertheless, failure of this drug to display significant benefit in locomotive function has been reported [143]. It should be mentioned that in this study a significant effect on spared tissue was observed when PROG was administered for a longer time and at higher concentrations.

Estrogens have also been employed as neuroprotective agents in experimental models of SC injury. Administration of 17-beta-estradiol to rats, improved hind-limb locomotion recovery, increased white matter sparing, and decreased apoptosis [144, 145]. According to the present data, the use of steroid hormones in acute SC injury is a promising strategy; however, further carefully planned studies are necessary to establish the efficacy of these drugs.

## 8. SODIUM CHANNEL BLOCKERS

Accumulation of intracellular sodium is another deleterious phenomenon developed after SC injury. Therefore, drugs specialized in blocking sodium channels could be useful for promoting neuroprotection. The use of tetrodotoxin, a potent sodium channel blocker that binds to the pores of the voltage-gated, fast sodium channels in nerve cell membranes, induced significant tissue sparing and motor recovery in rats with acute SC-injury [146-148].

QX-314, another sodium channel blocker, was also evaluated in rats with acute SC-injury, but in this case, it was not capable of promoting a significant motor recovery after injury, even though it induced some tissue preservation [149].

Another sodium channel blocker that has been evaluated is riluzole. Significant evidence has been provided about the usefulness of this drug. Besides sodium channels, riluzole blocks glutamatergic neurotransmission, attenuates ischemia-induced necrosis and apoptosis, diminishes cytoskeletal proteolysis, reduces lipid peroxidation and reestablishes somatosensory evoked potentials [150]. Administration of this drug has provided significant neuroprotection resulting in sparing of both gray and white matter and in improvement of motor recovery in acute SC injury [151-154]. As a consequence of these data, riluzole has been considered as a therapy with a very promising potential [155]. However, at the moment, there is not enough convincing data supporting its efficacy.

## 10. NMDA AND AMPA-KAINATE RECEPTOR ANTAGONISTS

As a result of the intense release of excitatory amino acids observed immediately after injury, NMDA and AMPA/Kainate receptor antagonists have been proposed as possible neuroprotective agents for acute SC-injury. These compounds can exert competitive (by glutamate recognition site binding) or non-competitive (by combination to the NMDA-associated ion channel) antagonistic actions [156, 157].

Memantine, a non-competitive NMDA receptor antagonist, was evaluated in two different models of SC injury [158]. In this study, memantine was not capable of promot-

ing neuroprotection maybe as a consequence of its low affinity for NMDA receptors in the SC. Nevertheless, in a different model (SC injury in rabbits), memantine significantly reduced neurological damage [159].

MK 801, another non-competitive NMDA antagonist agent, has demonstrated no consistent positive effects either. Although some authors have reported neuroprotective effects in this drug [160-165], others have not been able to demonstrate any beneficial action [166-168].

Another similar antagonist, gacyclidine, provided optimistic data in experimental studies [167, 169, 170], however, once it was tested in clinical trials the results were disappointing [171]. The use of NBQX, a highly selective antagonist of AMPA-kainate receptors, showed consistent neuroprotective effects upon neural tissue; however, its effect on functional recovery has not been convincing [172-178].

Analyzed together, the present data are not conclusive; besides, as these agents tend to be toxic in therapeutic doses, their use has not been contemplated for the near future.

## 11. OTHER THERAPIES

Erythropoietin (EPO) is a glycoprotein hormone and a cytokine for erythrocyte precursors in the bone marrow. Recent studies have suggested that EPO activates the CREB transcription pathway and increases BDNF expression and production [179]. It also decreases myeloperoxidase and caspase-3 activity, prevents apoptosis and reduces lipid peroxidation after SC injury [180]. Studies performed in experimental models suggest that the protective effects of this drug are exerted through EpoR and betacR receptors [181].

Gorio and co-workers demonstrated that, recombinant human EPO (rhEPO) provokes early recovery of function, especially after SC compression, as well as longer anti-inflammatory and anti-apoptosis functions [182]. More recently, several experimental studies have also provided evidence about the beneficial effects of this drug on motor recovery of animals with acute SC injury [179, 183-187]. Furthermore, Loblaw and co-workers reported improvement in the neurological function of patients with malignant extradural spinal cord compression [188]. Thus, this compound holds promise in treatment of acute SC injury and available data encourage further clinical trials.

Thyrotropin-releasing hormone (TRH) and its analogs, also appear to be useful for acute SC injury. TRH is a tripeptide that can act as a physiological antagonist of opiate receptor activation by injury-induced endorphin release [189]. This hormone can also be able to neutralize some of the harmful compounds released after injury. For instance, TRH antagonizes platelet activation factor and excitatory amino acids [190, 191]. Additionally, this compound could also enhance SC blood flow and restore ionic balances and somatosensory evoked potentials after SC injury [190, 192-194].

Administration of TRH has been shown to improve tissue sparing and neurological recovery in cats and rats with SC injury [195-201]. This drug has also been preliminary tested in a Phase II safety trial in a small number of SC injured patients [202].

After 4 months of follow up, TRH treatment was associated with significantly better motor and sensory functions than placebo. Despite these encouraging data, the results must be interpreted with considerable caution because of the small number of patients.

Some TRH analogs with improved pharmaceutical properties have also demonstrated to be beneficial in experimental models [203, 204]. For instance, CG3509 and YM14673 induced significant recovery of neurological function in animals with SC injury [195, 198, 204].

Although the use of TRH and its analogs remains an intuitive therapeutic strategy, additional research is necessary to further evaluate the potential benefits of these drugs.

Other less known agents have also been studied. The beta2-adrenoreceptor agonist, clenbuterol, has been shown to induce spinal cord tissue preservation and enhance locomotor recovery in an experimental model of SC contusion [205]. According to recent studies the positive effects of this drug are glutathione dependent [206].

Taurine is a sulfur amino acid found endogenously in humans. It has been suggested that taurine and its analogs exert protective action through scavenging ROS and down regulating several other inflammatory mediators like tumor necrosis factor-alpha (TNF-$\alpha$) [207, 208]. In rats, these agents favor restoration of motor function after SC trauma and significantly decrease fatality in animals [209].

Another recently evaluated drug is citicoline, which is an essential intermediate in the biosynthetic pathway of cell membrane structural phospholipids; particularly phosphatidylcholine. This compound crosses the blood-brain barrier and reaches the central nervous system, where it is incorporated into the membrane and microsomal phospholipid fraction. Citicoline activates the biosynthesis of structural phospholipids of neuronal membranes, increases brain metabolism, and acts on the levels of different neurotransmitters.

In addition, citicoline has been shown to restore the activity of mitochondrial ATPase and membrane Na+/K+ATPase, it inhibits activation of certain phospholipases, accelerates reabsorption of cerebral edema and inhibits apoptosis [210]. In studies conducted in SC injured animals, citicoline attenuated LP and significantly improved motor recovery [211, 212]. Clearly, all these compounds merit further investigation in order to be proven successful.

## CONCLUSION

SC injury triggers a complex cascade of secondary neurodegenerative phenomena that are set on by the primary injury. These secondary events include neurogenic shock, vascular insults such as hemorrhage and ischemia-reperfusion, lipid peroxidation, inflammation, excitotoxicity, intracellular calcium increment, apoptosis, and disturbance of mitochondrial function. They contribute to extend the damage to the surrounding neural tissue; thereby, they should be targets for therapeutic strategies.

A number of pharmacological neuroprotective therapies targeting one or more of these secondary events have been extensively studied. In particular, MP has been suggested as

the drug of choice for acute SC injury in humans. However, its beneficial effect on the neurological recovery of patients has not been conclusively proven.

Therefore, a variety of other pharmacological interventions including cyclooxygenase inhibitors, immunophilin ligads, antioxidants, calpain and apoptosis inhibitors, steroid hormones, sodium channel blockers, NMDA and AMPA-Kainate receptor antagonists, erythropoietin, and thyrotropin-releasing hormone have been evaluated. Some of them have shown benefit in experimental and even in clinical trials; however, they must be subjected to additional rigorous evaluation and exact determination of optimal dosages before being readily adopted in the management of patients with acute SC injury.

Future studies should evaluate the combination of diverse strategies with the goal of elucidating potential additive, synergistic or antagonistic effects. In spite of the substantial progress in the area, SC injury remains as a significant health problem. The hope of recovery for a great number of patients suffering from this disease should be enough to encourage our continued efforts to develop safe and effective neuroprotective therapies for acute SC injury.

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