

# An Overview of Pharmacological Approaches for Management and Repair of Spinal Cord Injuries

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Spinal cord injury (SCI) leads to loss of nervous tissue and consequently to catastrophic neurological deficits. Up to now there is no definite treatment available that restores the loss of function to a degree that an independent life can be guaranteed.

This justifies the cost of research into the new modalities for a treatment of SCIs. In current paper, recent developments and new approaches in pharmacological therapy have been reviewed

**Key words:** Medication therapy management, Spinal cord injury

*Iran J Psychiatry 2010; 5:119-127*

**S**pinal cord injury (SCI) results in devastating neurological deficits and disabilities. The annual incidence of SCI in developed countries varies from 11.5 to 53.4 per million populations (1-3). As the life expectancy of survivors is increasing, information on the prevalence of SCI is becoming more important, but few prevalence studies are available.

Prevalence rate ranged from 11 to 112 per 100000 populations (4-7).

The social and economic impact of SCI extends to involve, not just the patient and the immediate family, but also the community and society at large (8, 9).

In 1990, it was estimated that the cost of managing all SCIs in the United States was 4 billion dollars annually.

Therefore, it seems rational to invest for the development of new treatment modalities that improve the condition of these patients.

(10).

## PATHOPHYSIOLOGY

There are two types of injury that may cause damage to the spinal cord. These include primary and secondary injuries (8). Primary injuries occur at the time of mechanical trauma to the spinal cord. Secondary injuries are caused by a series of cellular and biochemical reactions that are provoked by the primary injuries (11). Among these are hypoxia, accumulation of excitatory neurotransmitters, hyperthermia, imbalance in intracellular electrolytes, increased level

of opioid (dynorphins) at the site of injury, free radical formation and lipid peroxidation, microvascular alteration, anemia, activation of inflammatory cells associated with cytokines and activation of calpain and caspases and apoptosis (12, 13).

Inhibitory elements in the CNS inhibit damaged nerve fibers to exhibit regenerative sprouting. Nogo-A (neurite out growth inhibitor), MAG (myelin-associated glycoprotein), OMgp (oligodendrocyte-myelin glycoprotein), chondroitin sulfate proteoglycan which are exposed after the injury, are proteins that play such a role (14-16).

## APPROACH TO TREATMENT

Surgical decompression of the cord and restoration of its normal alignment, together with stabilization of the spine when indicated, accompanied by physical and occupation therapy, and managing psychologic, urologic and proctologic problems are the standard managing methods for spinal cord injury patients (17, 18).

Several attempts have been made to modulate the mechanisms leading to the secondary injury. These are: pharmacological interventions, neutralization of the inhibitory proteins, cell therapy, and gene therapy (19-22).

Considering the key pathophysiological mechanisms that contribute to neurological deficits after SCI, it seems that promising drug-based therapeutic approaches (that we explain in this paper), including

regenerative strategies to neutralize myelin-mediated neurite outgrowth inhibition, neuroprotective strategies to reduce apoptotic triggers, targeting of cationic/glutamatergic toxicity, anti-inflammatory strategies and the use of approaches that stabilize disrupted cell membranes could be considered effective ways to prevent further damage to the spinal cord and promote its repair(23, 24).

## PHARMACOLOGICAL INTERVENTION

### *Methylprednisolone*

Methylprednisolone (MP) has been used to treat different neurological impairments. Its mechanism of action has been explained by anti-inflammatory and antioxidant properties in addition to inhibitory effects on lipid peroxidation (25). It has been suggested that MP selectively inhibits oligodendrocytes but not neuronal cell death via a receptor-mediated action and may be a mechanism for its limited protective effect after SCI (26). MP has been used together with olfactory ensheathing cells and Nogo-A monoclonal antibody after producing SCI in rat models; and improvement in axonal re-growth and neuroprotection have been observed(27, 28).

Efficacy has also been examined in a multi-centre double blind RCT by comparing high doses of MP (1000mg bolus and 1000mg daily thereafter for 10 days) with that of a standard dose (100mg bolus and 100 mg daily

thereafter for 10 days). No significant difference was observed in neurological recovery 1 year after SCI between the two treatment groups (29). There is also no evidence of the benefit of its simultaneous use with nimodipine in the SCI (30).

### *Atorvastatin*

Anti-inflammatory properties and immunomodulatory activities of statins have been reported in the animal model previously (31). Atorvastatin treatment attenuated the SCI-induced inducible nitric oxide synthase (inos), tumor necrosis factor alpha (TNF-alpha), and interleukin 1beta (IL-beta) expression. Atorvastatin also provided protection against SCI-induced tissue necrosis, neuronal and oligodendrocyte apoptosis, demyelination, and reactive gliosis. Studies report beneficial effect of atorvastatin for the treatment of SCI-related pathology and disability.

### *Omega-3 Poly Unsaturated Fatty Acid (PUFA)*

It has been suggested that PUFA could target some of the pathological mechanisms that underlie damage after SCI (32). Reports indicated that omega-3 PUFA  $\alpha$ -linolenic acid and docosahexaenoic acid (DHA) injected 30 min after injury significantly improved locomotor performance and neuroprotection, including a decrease in lesion size and apoptosis and an increase in neuronal and oligodendrocyte survival. In contrast, animals treated with arachidonic acid (AA), and omega-6 PUFA, had a significantly worse outcome than controls (33).

### *Fenretinide*

Fenretinide (4-hydroxy (phenyl)retinamide) (INN) is a synthetic retinoid derivative. Retinoids are substances related to vitamin A, and they have been investigated for potential use in the treatment of cancer (34). Researches have shown that daily oral administration of fenretinide after spinal cord contusion injury led to a significant decrease in AA and increase in DHA levels in plasma and in the injured spinal cord tissue. This was accompanied by a significant reduction in tissue damage and improvement in locomotor recovery. Fenretinide also reduces the expression of proinflammatory genes and the levels of oxidative stress markers after SCI. In addition, vitro studies demonstrated that fenretinide reduces TNF- $\alpha$  expression by reactive microglia (35). These beneficial effects may be mediated via the ability of fenretinide to modulate PUFA hemostasis. Since fenretinide is currently in clinical trials for the treatment of cancers, this drug might be a good candidate for the treatment of acute SCI in humans.

### *Erythropoietin*

Cytokine erythropoietin (EPO) is a glycoprotein mediating cytoprotection in a variety of tissues, including brain and spinal cord, through activation of multiple signaling pathways (36, 37). Uninjured spinal cord expresses a high density of EPO receptor (EPOR) in the basal state (38). It has been reported that EPO exerts its beneficial effects by apoptosis blockage, reduction of inflammation, and restoration of vascular integrity. Neuronal

regeneration has also been suggested (39). Moreover, administration of EPO or other recently generated EPO analogues such as asialo-EPO and carbamylated-EPO demonstrate exceptional preclinical characteristics, rendering the evaluation of this tissue-protective agents imperative in human clinical trials (40).

### *Progesteron*

Reports show that progesteron (Prog) has neuroprotective and promyelinating effects in lesions of the spinal cord(41). These effects may be due to regulation of myelin synthesis in glial cells and also to direct actions on neuronal function (42). When SCI is produced, several genes become sensitive to Prog. in the region caudal to the lesion site.

Neurotrophins, their receptors, and signaling cascades might be part of the molecules involved in the process of neuroprotection. It has been shown that in rats with SCI, a 3-day course of Prog. treatment increases the mRNA of brain-derived neurotrophic factor(BDNF) and BDNF immunoreactivity in perikaryon and processes of motoneurons, whereas chromotolysis is strongly prevented(43). Increased expression of BDNF is correlated with increased immunoreactivity of the BDNF receptor TrkB and of phosphorelated CAMP responsive element binding in motoneurons. In the same SCI model, Prog. restored myelination, according to measurements of myelin

basic protein (MBP) and mRNA levels, and further increased the density of NG2+positive oligodendrocyte progenitors. These cells might be involved in remyelination of the damaged spinal cord.

**Estrogen**

Estrogen is a steroid that processes antiinflammatory and antioxidant effects (44).It may also modulate intracellular Ca(2+), attenuate apoptosis, and inhibit activation and activity of calpain and caspase-3(45, 46).

Treatment of SCI rats with estrogen (4mg/kg) at 15min and 24hr post-injury reduced edema and decreased inflammation and myelin loss in the lesion, suggesting its potential as a therapeutic agent (47).

**Inosine**

Inosine, a naturally occurring metabolite has been shown to induce axon outgrowth from primary neurons in culture through a direct intracellular mechanism(48).It can significantly reduce the spread of secondary degeneration and the cell death following SCI(48, 49). Inosine applied with a minipump to the rat sensorimotor cortex stimulated intact pyramidal cells to undergo extensive sprouting of their axons into the denervated spinal cord white matter and adjacent neuropil (50, 51). Thus, inosine, a purin nucleoside without known side effects ,might help to restore essential circuitry after injury to the CNS.

**Rho Inhibitors (Cethrin-BA210)**

Axons of the adult CNS have limited ability to regenerate after injury .This may be, at least partly, attributable to myelin-derived proteins, Nogo and oligodendrocyte myelin glycoprotein. Recent evidences suggest that these proteins inhibit neurite outgrowth by activation Rho (an intracellular GTPase) through the neurotrophin receptorP75NTR/Nogo receptor complex (52). Following SCI in vivo, massive activation of Rho is observed in the injured neurites (53-56). Application of Rho antagonist (c3-05) reversed Rho activation and reduced cell death after CNS injury. It also blocked the increase in P75NTR expression (57-59). Cethrine is a recombinant protein drug intended to facilitate the re-growth of axon during the critical period immediately after a major SCI (phase

II trial is now going on). It can be delivered topically onto the dura matter (and diffuses into the spinal cord) during decompression/stabilization surgery (60, 61). Cethrin is known as an orphan drug by FDA.

**cAMP-Rolipram**

Elevation of intracellular cyclic AMP (C AMP) is one of the most successful strategies that enable axons to suppress inhibitory proteins that are made after SCI (62, 63). Intracellular cAMP levels can be increased through a peripheral conditioning lesion, administration of cAMP analogues, priming with neurotrophins or treatment with the phosphodiesterase inhibitor rolipram (64).

**Fingolimod (FTY720)**

FTY720, a sphingosine receptor modulator that sequesters lymphocytes in secondary lymphoid organs, has been shown to be effective in the treatment of a variety of experimental autoimmune disorders (65, 66). Accordingly, by reducing lymphocyte infiltration into the spinal cord following SCI, this novel immunomodulator may enhance tissue preservation and functional recovery(67). Collectively, results demonstrate the neuroprotective potential of FTY720 after experimental SCI (68).

**Chondroitinase ABC (Ch ABC)**

For successful regeneration, long injured axons must overcome their poor intrinsic growth potential as well as the inhibitory environment of the glial scar established around the lesion site (69). Recent animal studies have shown that ch ABC can enhance plasticity in the adult nervous system by cleaving inhibitory chondroitin sulfate proteoglycans (CSPGs) in the scar matrix (70, 71). There are evidences indicating that CSPGs have two faces in spinal cord repair. Inhibition of CSGPs synthesis immediately after injury, impairs functional motor recovery and increases tissue loss. It causes a dramatic effect on the spatial organization of the infiltrating myeloid cells around the lesion site, decreases insulin-like growth factor 1 (IGF-1) production by microglia/macrophages, and increases TNF-α levels. In contrast, delayed inhibition, allowing CSPGs synthesis during the first two days following injury, with subsequent inhibition, improves recovery (72). The distinction between the beneficial role of CSPGs during the acute stage and its deleterious effect at later stages emphasizes the need to retain the endogenous potential of this molecule in repair by controlling its levels at different stages of post-injury repair.

**Sialidase**

MAG, one of the inhibitor proteins, binds to sialoglycans and other receptors on axons. MAG inhibition of axon outgrowth in some neurons is reversed by treatment with sialidase, an enzyme that hydrolyzes sialic acids and eliminates MAG-sialoglycan binding. Neurotrophin-induced TrK tyrosin kinase receptor activation and neuronal cell survival responses have been reported to be under the control of a membrane associated sialidase(73).Reports show that sialidase delivered intrathecally to rats following SCI significantly enhances hindlimb motofunction, improves autonomic reflexes and increases axon sprouting (74, 75).

**Calpain Inhibitor**

Calpains are a family of calcium-dependent, non-lysosomal cysteine proteases (proteolytic enzymes) (76,77).One factor potentially limiting the efficacy of transplanted Schwann cells is poor cell survival. It has been demonstrated that SCs die within 24 hours after

transplantation. Calpain inhibitor, MDL28170, enhances Schwann cell survival both in vitro in response to oxidative stress and in vivo following delayed transplantation into the injured spinal cord (78). The results support the use of calpain inhibitors as a promising new treatment for promoting the survival of transplanted cells(79).

#### ***Scutellaria Baicalensis (EESB)***

EESB significantly inhibits lipopolysaccharide-induced expression of inflammatory mediators such as TNF- $\alpha$ , IL-1 $\beta$ , il-6, cyclooxygenase-2, and inducible nitric oxide synthase. Additionally, reactive oxygen species and nitric oxide production are also significantly attenuated. In vivo study on rats with SCI that had orally received EESB, it was revealed that expression of proinflammatory factors and protein carbonylation and nitration were inhibited (80). Furthermore, EESB significantly inhibited apoptotic cell death of neurons and oligodendrocytes and improved functional recovery after SCI.

#### ***Folic acid***

Reports demonstrate a crucial role for folate in the regeneration of afferent spinal neurons after injury. Findings show that axonal regeneration relies upon the integrity of DNA methylation pathways (81). It has been found that intraperitoneal treatment of adult rats with folic acid significantly improves the re-growth of sensory spinal axons into a grafted segment of peripheral nerve in vivo. The results show that the effects of folic acid supplementation on CNS growth processes are not restricted to the embryonic period, but can also be effective for enhancing growth, repair, and recovery in injured adults CNS (82).

#### ***Pioglitazone***

Peroxisome proliferation activated receptors (PPAR) are widely expressed nuclear receptors whose activation have led to diminished pro-inflammatory cascades in several CNS disorders. Based on this fact, efficacy of the PPAR agonist pioglitazone injected I.P in a rodent SCI model has been examined. Stereological measurement throughout the lesion revealed a significant increase in rostral spared white matter in pioglitazone treatment groups. Spinal cord from the high dose group also had significantly more gray matter sparing and motor neurons rostral and caudal to epicenter (83). These results suggest that clinical treatment with pioglitazone, an FDA approved drug used currently for diabetes, may be a feasible and promising strategy for promoting anatomical and functional repair after SCI (84).

#### ***Anti- CD11d Integrin Antibody***

Acute inflammatory response is a process that damages descending pathways after SCI. Neuropathic pain and motor dysfunction associated with SCI may be due to increases in serotonergic fiber density in spinal segments rostral and decreases caudal to the lesion.

Restricting the acute inflammatory response by a monoclonal antibody to the CD11d subunit of the leukocyte CD11d/CD18 integrin, limits the trafficking of neutrophils and macrophages into the SCI site. After treatment, the typically increased serotonin immunoreactivity rostral to injury was reduced, whereas that caudal to the lesion increased toward normal. Increased serotonergic fiber density below the lesion also occurred in the intermediolateral cell column and ventral horn of treated rats, relative to controls. Improved locomotor recovery paralleled this increased serotonin (85, 86).

#### ***Nigella Sativa (Black Seed)***

*Nigella sativa* (NS) is a plant, native to southwest Asia. It grows to 20-30 cm tall, with finely divided, linear leaves. NS has been used for medicinal purposes for centuries, as a herb and it was also pressed into oil, in Asia, middle East and Africa (87-89). Possible beneficial effects of NS have been investigated on experimental SCI in rats. Malondialdehyde (MDA) and protein carbonylation (PC) levels are increased in SCI, whereas, superoxide dismutase (SOD), glutathion peroxidase (GSH-PX), and catalase (CAT) enzyme activities decreased. NS treatment decreased tissue MDA and PC levels and prevented inhibition of SOD, GSH-PX and CAT enzymes in the tissue. The morphology of neurons in NS-treated groups was well protected. As a result, NS treatment might be helpful in SCI and therefore shows a potential for clinical implication (90-92).

#### ***Sodium Channel Blockers (Riluzole, Phenytoin, Mexiletine)***

Influx of Na (+) ions into cells have been postulated to be a key early event in the pathogenesis of secondary traumatic and ischemic CNS injury. Pharmacological blockade of Na (+) channels can attenuate secondary pathophysiology and reduce functional deficits acutely. In an experimental model of rats with SCI riluzole, injected I.P significantly enhanced residual tissue area at the injury epicenter compared with controls. Riluzole (a drug used to treat ALS, preferentially blocks tetrodotoxin sensitive sodium channels, which are associated with damaged neurons) (93, 94) significantly reduced tissue loss in rostro caudal regions surrounding the epicenter, with overall sparing of gray matter and selective sparing of white matter(95, 96).

Animal experiments with phenytoin also showed decreased MDA levels in rats with SCI. Phenytoin appears to protect spinal cord against injury by decreasing lipidperoxidation and lessening neural damage associated with SCI in rats(97-99). Some studies reveal better results with riluzole and mexiletine than phenytoin (95, 100).

#### ***Hydralazine (Acrolein Scavenger Drug)***

Acrolein, a lipid peroxidation byproduct, is significantly increased following SCI in vivo, and that

exposure to neuronal cells results in oxidative stress, mitochondrial dysfunction, increased membrane permeability, impaired axonal conductivity and eventually cell death (101). Acrolein thus may be a key player in the pathogenesis of SCI, where lipid peroxidation is known to be involved (102). Acrolein is capable of depleting endogenous antioxidants such as glutathione, generating free radicals, and damaging proteins and DNA (103).

Acrolein has a significantly longer half-life than the transient free radicals, and thus may represent a potentially better target of therapeutic intervention to attenuate oxidative stress. Animal studies demonstrate that the Acrolein scavenger hydralazine protects against not only Acrolein-mediated injury, but also compression in SCI. It can significantly alleviate Acrolein-induced superoxide production, glutathione depletion, mitochondrial dysfunction, loss of membrane integrity and reduced compound action potential conduction (104). These findings suggest that Acrolein scavenging drugs such as hydralazine may represent a novel therapy to effectively reduce oxidative stress in SCI.

#### **Minocycline (An Antibiotic Drug)**

After SCI, pro-nerve growth factor (proNGF) plays a central role in apoptosis of oligodendrocytes. It has been shown that minocycline improves functional recovery after SCI in part by reducing apoptosis of oligodendrocytes via inhibition of pro NGF production in macroglia (105). Minocycline treatment significantly reduces production in microglia in vitro and in vivo by inhibition of the phosphorylation of p38MAKP (a protein kinase) (106). Minocycline treatment significantly reduces a number of terminal deoxynucleotidyle transferase (TdT)-mediated deoxyuridine triphosphate-biotin nick end labeling (TUNEL)-positive cells 24h after SCI as compared to that of the vehicle control(107). In addition, minocycline treatment significantly reduces the specific caspase-3 activity after SCI. It also decreases TNF- $\alpha$  expression. Furthermore, minocycline treatment inhibits p75 neurotrophin receptor expression and Rho A activation after injury. These data suggest that after SCI, minocycline treatment modulated expression of cytokines, attenuated cell death and the size of lesion, and improved functional recovery in injured rats.

#### **GHRELIN**

Ghrelin, an acylated peptide, synthesized primarily in stomach and is the endogenous ligand for the growth hormone secretagogue receptor (GHS-R), stimulates both food intake and GH secretion (108, 109). Ghrelin is not detected in normal, uninjured spinal cord, but spinal cord neurons and oligodendrocytes express the Ghrelin receptor (110). Ghrelin significantly inhibits apoptotic cell death of neurons and oligodendrocytes, release of mitochondrial cytochrome-C and activation of caspase-3 after moderate contusive SCI. Ghrelin also significantly increases the level of phosphorylated ERK (protein kinase) but decreases the level of

phosphorylated p38MAPK. In addition, ghrelin increases the level of ERK-dependant brain-derived neurotrophic factor expression and decreases the level of pronerve growth factor expression. The neuroprotective effects of ghrelin are mediated through the ghrelin receptor. Eventually, ghrelin significantly improves functional recovery and reduces the size of lesion volume and the loss of axons and myelin after injury(111).

#### **4-Aminopyridine (4-AP) and Its Derivatives**

4-AP is a potassium (k+) channel blocking agent that has been shown to reduce the latency and increases the amplitude of motor evoked potentials (MEPS) elicited with transcranial magnetic stimulation (TMS) in patients

with chronic SCI (112). It has been shown to improve neurological motor and sensory function in both animal and human studies, and it has a more effect on conduction after stretch injury than compression (113, 114). The drug is safe, however, after starting 4-AP therapy, patients must be carefully monitored for the possible occurrence of peripheral vasospasm (which may be the most hazardous complication of this therapy) (115, 116).

Since the maximal tolerated level of 4-AP in humans is 100 times lower than the optimal dose in animal studies, structurally distinct pyridine based blocker with fewer side effects have been synthesized(117). One of these derivatives named (4-AP-3-MeOH) is 10 times more potent than 4-AP in restoring axonal conduction (118).

#### **Conclusion**

The complicated and sometimes confusing mechanisms of SCI had caused therapeutic interventions to improve very slowly for many years. However, in recent years, rapid progress that has occurred in understanding the pathophysiology of SCI, opened up the way for new pharmacologic therapies. These new strategies in addition to other treatment approaches (cell therapy, gene therapy, immunomodulatory therapy and bioscaffolds) have shown promising results to help patients with SCI.

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