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ORIGINAL PAPER

Chemical priming for spinal cord injury: a review of the literature part II—potential therapeutics

Martin M. Mortazavi · Ketan Verma · Aman Deep · Fatemeh B. Esfahani · Patrick R. Pritchard · R. Shane Tubbs · Nicholas Theodore

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Abstract
Introduction Spinal cord injury is a complex cascade of reactions secondary to the initial mechanical trauma that puts into action the innate properties of the injured cells, the circulatory, inflammatory, and chemical status around them, into a non-permissive and destructive environment for neuronal function and regeneration. Priming means putting a cell, in a state of "arousal" towards better function. Priming can be mechanical as trauma is known to enhance activity in cells.
Materials and methods A comprehensive review of the literature was performed to better understand the possible chemical primers used for spinal cord injuries.
Conclusions Taken together, many studies have shown various promising results using the substances outlined herein for treating SCI.

Keywords Spinal cord · Injury · Experimental · Trauma · Treatment

Introduction

Spinal cord injury is a complex cascade of reactions secondary to the initial mechanical trauma that puts into action the innate properties of the injured cells, the circulatory, inflammatory, and chemical status around them, into a non-permissive and destructive environment for neuronal function and regeneration. Priming means putting a cell, in a state of "arousal" towards better function. Priming can be mechanical as trauma is known to enhance activity in cells. A good example of this is moderate compression of sciatic nerve that leads to robust activation of the Schwann cells. Parallel to mechanical priming, chemical priming can also be applied. Any chemical substance that can modify a cell can be a chemical primer. Here we describe first, the differences between the innate properties of central nervous system (CNS) and peripheral nervous system (PNS) in terms of their reaction to trauma and potential for regeneration. We describe the role of growth factors, guiding factors, and inhibitors and neurite outgrowth inhibitors in the physiology and development of the nervous system as well as the pathophysiology of the spinal cord. We also look into their therapeutic role in detail. We also describe the time frame past the acute inflammation and until a scar tissue is formed. We finally make a detailed review of all the other chemical substances that have been found to modify the final spinal cord injury and the regenerative possibilities for it.

M. M. Mortazavi · N. Theodore
Department of Neurosurgery, Barrow Neurological Institute, Phoenix, AR, USA

K. Verma · A. Deep · F. B. Esfahani · R. S. Tubbs (✉)
Pediatric Neurosurgery, Children's Hospital, 1600 7th Avenue South ACC 400, Birmingham, AL 35233, USA
e-mail: shane.tubbs@chsys.org

P. R. Pritchard
Division of Neurosurgery, Birmingham, AL, USA

Treatment strategies

Growth stimulatory factors

In terms of the growth stimulatory factors effects on the nervous system, it is important to differ between effects on axonal/dendritic growth versus the neuronal cell body, effects on motor/sensory/autonomic nervous system, as well as their effect on the non-neural parts of the nervous system like vascularization. It is also important to differentiate their specific effects on the PNS versus CNS.

Some of the growth factors have specifically effect on corticospinal tract, as neurotropin 3 (NT-3), and some on the sensory tracts, as NGF. Some affect both the motor neurons and the motor tracts as brain-derived neurotrophic factor (BDNF). Some have effects only in CNS, as BDGF, and some may have effects both in CNS and PNS, as FGF and ciliary neurotrophic factor (CNTF). Some may have specific stimulatory effect on non-neuronal systems, for instance FGF's promoting effect on revascularization (see Table 1).

cAMP

Cyclic adenosine monophosphate (cAMP) levels are greatly elevated in young neurons and decrease after birth. The improved regenerative capacity of embryonic neurons in vitro can be blocked by the use of the cAMP antagonist, cAMP-analog dibutyryl-cAMP, which is able to mimic the effect of neurotrophin. cAMP has been shown to increase growth with or without the presence of Nogo [1].

NT-3

Neurotropin 3 promotes growth of sensory axons in the dorsal column into and beyond spinal cord injury (SCI) but not all the way to the nucleus gracilis [2]. Nakahara et al. have also demonstrated some role in the sensory system [3]. For the motor pathways, e.g., corticospinal tracts, NT-3 is a potent neurotrophic factor [4]. NT-3's effect on neuron survival has also been shown when NT-3 transplants showed no significant neuron loss in rat's Clarke's nucleus 2 months after T8 hemisection. This survival has been postulated through interaction with trkC receptors [5]. In summary, NT-3 is probably the only neurotrophic factor that has consecutively been identified to promote growth of the corticospinal axons after SCI [6, 7]. Furthermore, it not only stimulates the motor neurons, but also has some promoting effects on sensory tracts.

aFGF/bFGF

In rats, alpha-fibroblast growth factor (aFGF) is mostly localized in the cytoplasm of ventral motor neurons and sensory fibers in the dorsal columns. Beta-fibroblast growth factor (bFGF) is primarily restricted to astrocyte nuclei and the cytoplasm of a few neurons in the intermediate gray matter. The levels of bFGF increase markedly after SCI suggesting a role in regeneration [8]. bFGF's role in the sensory system has been demonstrated by Nakahara et al. [3]. aFGF and bFGF were previously named EDGF-2 and EDGF-1, respectively [5]. Also, following peripheral nerve lesioning, FGF levels increase in the DRG and spinal cord astrocytes, suggesting a possible neurotrophic role [9]. FGF binding protein (FGF-BP) is a secreted protein that mobilizes FGF from the extracellular matrix, protects it from degradation, and enhances its biologic activity. In a SCI-hemisection model, increased levels were observed in the fibers and cell bodies ipsilateral but not contralateral to the lesion, with a peak 4 days post trauma. Use of exogemous FGF-BP increased the capacity of FGFs to stimulate neurite outgrowth and to increase cell survival. Thus, these results suggest FGF-BP may be an early response gene after SCI and its agonism may provide neurite promoting means [10]. The neuroprotective role of this family has further been demonstrated by Cuevas et al. [11]. Local administration of aFGF and bFGF 24 h after a spinal cord contusion protected autonomic preganglionic neurons in the intermediolateral column (IML) and somatic motor neurons in the ventral horn (VH). Furthermore, there was enhanced choline acetyltransferase immuno-reactivity in surviving IML and VH neurons suggesting an improved status [12].

Table 1 Growth factor effects on different parts of the nervous system

Growth factor	Motor neurons	Sensory neurons	Autanomic neurons	Motor tracts	Sensory tracts	Autanomic neurons and tracts	CNS effect	PNS effect	Non-neurol effects
NT-3	Yes	–	–	Yes	Yes	–	Yes	–	–
FGF	Yes	–	Yes	Yes (a)	Yes	Yes	Yes	Yes	Yes
NGF	–	–	–	–	Yes	–	Yes	–	–
GDNF	–	–	–	–	DREZ	–	DREZ	DREZ	–
BDNF	Yes	Yes	–	Yes	Yes	–	Yes	–	–
VEGF	–	–	–	Yes	–	–	Yes	–	–
CNTF	Yes	–	–	Yes	–	–	Yes	Yes	–
IGF	Yes	–	–	–	–	–	Yes	–	Anti-inflammatory

aFGF has shown growth promoting effects on both motor and sensory axon regeneration in peripheral nerve injuries as well [13]. Intrathecal bFGF has shown positive functional and morphological effects after moderate SCI contusion but only positive functional effects after severe SCI [14]. There is work showing that it also increases long-term survival of spinal motor neurons and improves respiratory function after SCI [15]. FGF is so far the only growth factor that stimulates revascularization [16]. FGF may be down-regulated by heparan sulfate [17].

NGF

Nerve growth factor (NGF) has moderate effects on neuron survival in certain nuclei, as NGF-expressing transplants in Clarke's nucleus produced partial rescue compared with hemisection alone, 2 months after T8 hemisection [5]. There are further reports on NGFs' stimulatory effects on the sensory fibers into the spinal cord white matter after SCI [3, 18–21]. NGF has been shown to promote growth of sensory axons into the dorsal column of the white matter [18, 19, 22]. However, no effect on corticospinal motor axons is noted after SCI [23].

GDNF

Glial-derived neurotrophic factor (GDNF) is up-regulated following SCI [24].

Dolbaere et al. have shown neuroprotective effects, by administering GDNF in the cervical hemisection showing significant decrease in the extent of axonal retraction. They have also shown regenerative effects by applying GDNF 1 month post injury [25]. An interesting study is when a certain basement membrane component (Matrigel) was transplanted in to a T9 hemisection. In this group, limited axonal growth was observed after 1 month. When Schwann cells (SC) were added, consistent axonal ingrowth containing both myelinated and unmyelinated axons was observed. The addition of GDNF alone without SC, resulted in substantial ingrowth of unmyelinated axons as well as reduced extent of reactive gliosis, infiltration of activated macrophages/microglia and cystic cavitation [26].

Although GDNF has shown no promoting effect on the sensory dorsal column axons in some studies [2], it has however, been shown to promote growth of sensory axons into the dorsal column of the white matter in others [18, 19, 22]. However, GDNF has proven to be the most effective neurotrophic factor in stimulating axonal growth across the dorsal root entry zone in the spinal cord white matter [7, 22]. GDNF's association with a specific inhibitor of nitric oxide synthase, ONO-1714 has been shown to diminish the early stage production of GDNF after SCI [27]. Experiments have confirmed that the GDNF mRNA levels, rather than the reduction of NO synthase could be correlated with the restoration of activity of locomotor function and also suggests that more inflammation may lead to a greater degree of repair through GDNF produced by activated macrophages/microglia [28].

BDNF

Brain-derived neurotrophic factor is shown to reduce the necrotic zone and to support neuronal survival after SCI [29]. It also promotes connections of corticospinal neurons onto spared descending interneurons in SCI [30]. However, BDNF has no promoting effect on sensory dorsal column axons [2]. Nakahara et al. have also shown no growth response in the sensory system [3]. However, BDGF has been shown to promote growth of sensory axons into the dorsal columns [24–26]. In another study, bone marrow stromal cells transduced with BDNF not only demonstrated a significant increase in the extent and diversity of host axonal growth, enhancing the growth of serotonergic and coerulospinal tracts, but also dorsal column sensory axons. In this study, no functional recovery was observed [29, 31]. BDNF has shown promising results in promoting axonal regeneration from supraspinal neurons following chronic SCI [32]. BDNF's effects seem to be restricted to the CNS [33]. In another study, when BDNF was continuously maintained for 14 days after a T3 SCI, it showed more regeneration in the red nucleus and sensorimotor cortex [34].

VEGF

Vascular endothelial growth factor (VEGF) is not only a promotor of angiogenesis but also has been shown to promote regeneration of corticospinal tracts [35].

CNTF

Ciliary neurotrophic factor has shown promising effects on motoneurons in the PNS [36–39]. Intrathecal infusion of exogenous CNTF following SCI may significantly reduce tissue damage and protect the rubrospinal descending tracts and enhances functional recovery [40].

After application to the cervical SCI, it promotes regeneration to most of the brain regions but not the motor cortex [41].

IGF

Insulin-like growth factor (IGF)-1 has shown some promising result in multiple studies. In a recent study, IGF-1 promoted

growth of corticospinal motor neurons. The corticospinal tract was not studied [42]. In another study in rats, IGF-1 was given systemically and showed a decreased inflammatory response in terms of decreased microglia and astrocyte activation, but also demonstrated decreased neuronal loss and increased functional recovery [43].

Combined growth factors

cAMP and NT-3

In one study, priming sensory neurons by injecting cAMP into the L4 dorsal root ganglia and injecting NT-3 within and beyond a cervical spinal cord lesion site grafted with autologous bone marrow stromal cells was performed. One to 3 months later, dorsal column sensory axons regenerated into and beyond the lesion. Regeneration beyond the lesion did not occur with cAMP or NT-3 alone [44].

NT-3 and BDGF

Local administration of NT-3 and BDGF together with a peripheral nerve graft has induced robust regeneration of spinal cord neurons into the graft [45]. This shows that the regulatory mechanisms for neuronal survival and growth may differ from those for axonal regeneration and that the survival of one system is not a prerequisite for survival of the other. However, delayed grafting of NT-3 and BDGF producing fibroblasts into SCI stimulated sprouting in partially rescued axotomized red nucleus neurons and provided some regeneration [20].

BDNF and GDNF

Local application of BDNF or GDNF alone 30 min after right dorsal horn injury at T10–11 has significantly improved motor function and reduced blood-spinal cord barrier, edema formation, and cell injury. These effect were markedly absent when administered separately either 60 or 90 min after injury. However, combined application 60 or 90 min after injury resulted in significant reduction in motor dysfunction and spinal cord pathology [21].

Sonic hedgehog glycoprotein

Sonic hedgehog glycoprotein has shown an effect on innate neural precursor cells of the spinal cord, as well as implanted oligodendrocytes, after spinal cord injury [44–46].

Inhibition of neurite outgrowth inhibitors

Nogos are new and as their signaling mechanisms are being documented, more and more molecules involved in theses complex reactions are being demonstrated. As discussed earlier, the Nogo-A, MAG, and OM-gp seem to affect a receptor family Nogo receptor (NgR) that is dependent on co-factors. These co-factors can differ in different tissues. p75 is a prominent one but most often, it is dependent on leucine-rich repeat and Ig domain containing 1 (LINGO-1). In most of the CNS, p75 is absent and the NgR receptor is needed for the co-factor TROY (TAJ), or the complex LINGO-1/TROY (TAJ). The second messenger of all of these is Rho or epidermal growth factor receptor (EGFR). Hence antagonism of the inhibitory molecules can be done on multiple levels. It can be done by blocking the Nogo-A itself, its binding to NgR, or by blocking the co-factors, as well as Rho/EGFR. Nogo-inhibition directly or at its receptor is by anti Nogo A antibody (mAB NT-1), NgR-ecto, NEP 1-40, and inhibition of Nogo's intracellular second messenger Rho, such as clostridium botulinum C3 transferase, and Y27632, have all been shown to promote neurite outgrowth [47].

Schwann cells have been shown to disinhibit the growth inhibition by multiple factors interfering with the NogoA/NgR-connection and with the Nogo-A/NgR/TROY-complex [48]. Rho kinase inhibition promotes regeneration [49] and the Rho inhibitor C3-05 has shown some promising results in decreasing the post-traumatic apoptosis in SCI [50]. One study combined NT-3 with mAb IN-1 resulting in transected corticospinal axons retaining the ability to regenerate at least for a few weeks after injury [51]. Chondroitinase ABC removes the major neuronal inhibitory glycosaminoglycan chains of chondroitin phosphate and promotes regeneration (see Table 2) [52].

Other neuroprotective chemical approaches

Inhibition of ischemia; opiate antagonists

The opiate Dynorphin decreases microcirculatory blood flow in the spinal cord [50].

Animal studies have shown release of endogenous opioids after SCI [53].

Opiate receptor antagonists improve blood pressure and survival following traumatic shock [54]. Inhibition of the circulatory collapse and ischemia has been postulated to limit spinal cord injury. Three substances have shown neuroprotective effects in animal models: thyrotropin-releasing hormone (TRH), naloxone, nalmefene (see Table 3) [55–59]. In humans, naloxone has shown some minor effects that need further investigation [60, 61]. Also in humans, TRH has been used in one small study showing no effects in complete injury but significant motor effects in incomplete injuries [62].

Table 2 Neurite outgrowth inhibitors, their receptors and antagonists

Inhibitory molecule	Receptor	Antagonist
Nogo-A (Nogo-66/Amino-Nogo)	NgR/NgR1 [64]	mAB IN-1 [98]
	Co-receptors: p75/LINGO [99]	NgR(310)ecto-Fc [64, 100]
	LINGO/TROY(TAJ) [99, 101]	NEP1-40 [47] Clostridium Botulinum C3Tr [47]
		Y27632 [47]
	2_{nd} messenger:	C3-05 [50]
	-Rho[102]	TACE(TNF-a-Convert Enzyme) [103]
	-Ca-dependent EGFR [48]	LINGO-1-Fc [104]
		LINGO-1-antibody [104]
		Schwann cell-derived factor [48]
MAG	NgR1/NgR2/OMgp [48, 99, 100]	Trisaccharide Substrate 13 [105]
OMgp	NgR1/MAG [48, 100]	NgR(310)ecto-Fc [104]
Semaphorin 4D	Plexin B1 [106, 107]	SB269970 [107]
Ephrins	Eph [108–110]	TNYL-RAW [111]
Tenascin R	$GABA_B$-receptor [112]	HNK-1-antibody [113]
Slits	Rig-1/Robo3[a] [112, 114]	Stromal cell-derived factor-1 [115]
Nitric oxide	Sgc [116]	ONO-1714 [27]
Chondroitin sulfate	Annexin 6 [117]	Chondroitinase ABC [118]

[a] Present in precerebellar fetal neurons

Inhibition of increased cytosolic calcium

Calcium channel blockers

Calcium channel blockers effects can be divided in two groups: those related to relaxing of perivascular smooth muscle and causing increased blood flow and hypotension, and those related to their effect in the cytosolic calcium also causes vasodilatation. In animal studies, there has been controversy, as some studies have shown increased blood flow to the spinal cord [62, 63] and some none [64–67]. Some studies have shown positive results [68, 69] while others have shown inconclusive results [66, 67, 70–72]. In humans, when nimodipine was compared to methylprednisolone, a cocktail of both and a placebo showed that there was no difference (see Tables 3 and 4) [73]. However, epinephrine and nimodipine together showed increased spinal cord flow after SCI. Calcium channel blockers have though, shown some promising results on cochlear and facial nerve function after vestibular schwannoma surgery [74].

EAA antagonism

EAA increase is short, transient and is probably over only 2 h after SCI [75–77]. Another problem is that glutamate is ubiquitous excitatory transmitter in the CNS and antagonism of it would give serious adverse effects. Animal studies have shown some positive results [78, 79] but in humans, gacyclidine, a NMDA antagonist, showed no significant positive results, although it showed some positive trends in incomplete SCI (see Table 3) [62, 80].

Table 3 Level of evidence for clinical studies using non-steroid medications for SCI

Author/year	Design	Level	Agent	Result
Geisler et al./1991 [119]	Prospective, randomized, double-blind	I	GM-1 Gangliocyte	Positive
Geisler et al./2001 [120]	Prospective, randomized, double-blind	I	GM-1 Gangliocyte	Negative
Bracken et al./1990 and 1992 [121, 122]	Prospective, randomized, double-blind	I	Naloxone	Negative
Flamm et al./1985 [120]	Prospective feasibility/safety study	III	Naloxone	N/A
Pitts et al./1995 [123]	Prospective, randomized, double-blind	I	Thyrotropin-releasing hormone	Positive
Tadie et al./1999 [124]	Prospective, randomized, double-blind	–	Gacyclidine	Negative
Pointillart et al./2000 [125]	Prospective, randomized, blinded	I	Nimodipine	Negative

Table 4 Level of evidence for clinical studies using steroids for SCI

Author/year	Design	Level	Agent	Result
Bracken et al./1984 [126]	Prospective, randomized, double-blind	I	Methylprednisolone	Negative
Bracken et al./1990 and 1992 [121, 122]	Prospective, randomized, double-blind	I	Methylprednisolone	Positive
Bracken et al./1997 and 1998 [127, 128]	Prospective, randomized, double-blind	I	Methylprednisolone/Tirilizad	Positive
Otani et al./1994 [129]	Prospective, randomized, not blinded	I	Methylprednisolone	Positive
Pointillart et al./2000 [125]	Prospective, randomized, blinded	I	Methylprednisolone/Nimodipine	Negative
George et al./1995 [130]	Retrospective, historical case control	II-3	Methylprednisolone	Negative
Gerhart et al./1995 [131]	Retrospective, historical case control	II-3	Methylprednisolone	Negative
Kiwerski/1993 [132]	Retrospective, concurrent case control	II-2	Dexamethasone	Positive
Poynton et al./1997 [133]	Retrospective, concurrent case control	II-2	Methylprednisolone	Negative
Prendergast et al./1994 [134]	Retrospective, historical case control	II-3	Methylprednisolone	Negative

Inhibition of the inflammatory cascade

Methylprednisolone

Controlling the inflammatory cascade has been one of the milestones of SCI research. The precise role of previously widely used steroids in the acute phase of SCI is unclear but probably has to do with their overall inhibitory effect on the immune system. Several studies have shown contrasting results but the most beneficial effect has been some small but significant improvements in motor outcome if administered within 3–8 h post SCI, and continued for 24–48 h. However, 48 h study showed six times greater risk of death due to respiratory compromise compared to the 24-h study, therefore, steroid use has been abandoned at many institutions (see Table 4) [81–97].

Antioxidants

Methylprednisolone actions are likely to be due to the inhibition of peroxidation and hence free radical production, but its efficacy has not been convincing. Tirilazad mesylate, which inhibits iron-dependent lipid peroxidation in CNS has been studied together with methylprednisolone (see Table 4) [82]. The endogenous free radical scavengers; ascorbic acid, and glutathione-analog still have unclear results [88–90].

Complement inhibition

There are also studies showing complement that inhibitory protein factor H and Clusterin limit the inflammatory reaction in the injured spinal cord [83] as well as complement inhibitor CR2-Cry showing improved pathological and clinical outcomes [88].

Inflammatory cell modulation

Activated autologous macrophages have shown some partial neurological recovery of paraplegic rats with improved clinical motor function and reduced cyst formation in some studies. The postulated mechanism is activation of T-cells, increased BDNF and removal of inhibitory myelin debris but more uncertain regarding axonal regeneration [84, 85, 89, 90]. Their role is still not convincing since other unpublished studies has shown contradictory results. Also there have been different types of this approach. One is ex vivo activation and local implantation which initially was very promising but that now is about to be abandoned as further trials have been contradictory. Activated dendritic cells have shown both functional and NPC-promotional effects as well [85, 86].

GM-1 ganglioside

Gangliosides are glycophosphingolipids being located in the neuronal cell membrane especially close to the synapses. GM-1 ganglioside has been studied in two trials. In the first smaller one, it showed significant positive effects [87], but in the larger one, it showed some trends towards positive [88]. Worth of note is that they were administered together with methylprednisolone (see Table 3).

Statins

Statins have shown attenuation of the post SCI inflammatory response, promotion of neurite outgrowth, prevention of endothelial dysfunction, and promotion of motor recovery in animal models [89–91]. Together with their neuroprotective role in vasospasm and subarachnoid hemorrhage, they are strong candidates of neuroprotection in SCI.

Uric acid

Uric acid has shown some protection against secondary damage after SCI but needs further investigation [92].

Lithium

Lithium has shown enhancement of proliferation and differentiation of neural progenitor cells in vitro and in vivo after transplantation into the rat spinal cord [93].

Conclusions

Taken together, many studies have shown various promising results using the substances outlined herein for treating SCI.

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