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Chemical priming for spinal cord injury: a review of the literature. Part I—factors involved

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Abstract
Introduction There are significant differences between the propensity of neural regeneration between the central and peripheral nervous systems.
Materials and methods Following a review of the literature, we describe the role of growth factors, guiding factors, and neurite outgrowth inhibitors in the physiology and development of the nervous system as well as the pathophysiology of the spinal cord. We also detail their therapeutic role as well as those of other chemical substances that have recently been found to modify regrowth following cord injury.
Conclusions Multiple factors appear to have promising futures for the possibility of improving spinal cord injury following injury.

Keywords Spinal cord · Injury · Experimental · Trauma · Treatment

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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 systems, and chemical status around them into a destructive environment for neuronal function and regeneration. Priming entails putting a cell into 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 the sciatic nerve that leads to robust activation of Schwann cells. Parallel to mechanical priming, chemical priming can also be performed. Any chemical substance that can modify a cell can be a chemical primer.

Differences between the central and peripheral nervous systems

In the injured peripheral nerve, the initial neurite outgrowth often continues, leading to regeneration. Schwann cells have shown some promising results not only in the maintenance of the initial peripheral neurite outgrowth but also when used in the central nervous system (CNS) environment [1]. To obviate some characteristics and differences of the regeneration in the peripheral nervous system (PNS) and the CNS, implantation of PNS in PNS, PNS in CNS, and CNS in PNS has been studied.

To test the growth-promoting capabilities of PNS in PNS, allogenic and xenogenic nerve segments or in vitro preparations of Schwann cells have been implanted in

transected sciatic nerve of immune-suppressed mice where they ensheathed and myelinated axons regenerating from the host nerve [2]. When the immune suppression was discontinued after the regeneration, the allogenic and xenogenic cells of the implanted nerve segment were rejected and the segments of nerve by the original graft became ensheathed by Schwann cells migrating from the host [2–4].

Growth of PNS in CNS with reinnervation of peripheral nerve segments grafted into the spinal cord has been demonstrated by several authors [5–8], but until recently, it was unclear if the axons within these grafts originally were derived from the intrinsic spinal neurons or from regrowing neighboring spinal roots. This question was answered when a segment of the thoracic spinal cord was resected and replaced by a 1-cm long autologous sciatic nerve graft, showing that all grafts of more than 3 weeks' duration were richly innervated with myelinated and unmyelinated axons, even if the dorsal spinal roots entering the graft site and their ganglia had been avulsed [9]. It must be mentioned that there is a possibility that axons regenerate along the pial connection in cases of avulsed nerves with intact pia [10].

To investigate implantation of CNS in PNS, a 5-mm long segment of optic nerve has been transplanted into the sciatic nerve showing that the majority of axons arising from the proximal stump of the recipient sciatic nerve bypassed the transplant and reentered the distal stump. The glial transplants were penetrated by some peripheral axons that became ensheathed by astrocytic processes and were occasionally myelinated by oligodendrocytes but the longitudinal growth was at most 1 mm with only a few axons reaching the distal end of the graft [11, 12].

Hence, CNS transplants are less receptive to regeneration in the PNS but the PNS transplants are more likely to regenerate, both in the PNS and the CNS. There are also separate observations demonstrating that injured dorsal root axons regenerate as far as the PNS–CNS junction. Carlstedt et al. showed though that damaging the astrocyte-rich transitional zone makes this boundary less inhibitory [10]. Further studies have, however, shown that following spinal cord injury (SCI), Schwann cells of peripheral nerve origin can migrate along the dorsal and ventral spinal roots and invade the cord parenchyma where they may proliferate and be involved in remyelination of CNS axons and axonal guidance [13–18].

Growth-promoting substances

The differences in the innate abilities of the adult CNS and PNS have at least partially been postulated as being dependent on various neurotrophic factors. This is demonstrated by the fact that there is an innate CNS ability for regeneration following trauma, which is lost with age. Injured CNS neurons fail to reexpress at least some of the growth-associated proteins that are expressed during development and during successful regeneration [19]. Levels of fetal cyclic adenosine monophosphate (cAMP) have been shown to drop by birth and application of cAMP analog, dibutyryl cAMP, has shown promoting effects on neural regeneration [20]. cAMP seems to be involved in inducing transcription of regeneration-associated genes and subsequently, the synthesis of polyamines important in spontaneous regeneration. Their presence and interaction with the damaged neurons are substantially changed in the damaged SCI environment. Some axonal regrowth has been shown to occur after spinal cord injury early in development [21–23]. This capacity of regrowth decreases as the age of the animal [24, 25]. As the CNS matures, there is decreased expression of growth-associated genes in neurons [26, 27]. Still, there are studies showing that some of the growth-associated molecules in the early development are still expressed in a regenerating adult CNS [28]. There is significant literature not only on the effects of neurotrophic factors on regeneration, BDGF, NGF, GDNF, VEGF, IGF, CNTF, NT-3, aFGF, and bFGF, but also on the growth-related proteins actin, myosin, and GAP -43 as well as transcription factors [29–32] and guidance molecules semaphorins and slits [33]. Schwann cells have proven to be one of the major sources of neurotrophic factors, [34] particularly those relating to the survival of motoneurons, such as CNTF [35–37] and BDGF (see Table 1) [38].

Growth-inhibitory substances

We know that there is some initial neurite outgrowth following SCI that soon stops due to many factors. The inability to continue the initial regeneration has been postulated not only being due to loss of inherent inability of the adult CNS, but also due to the inhibitory effects of myelin-associated molecules. Alterations both in the intrinsic properties of neurons and in the environment of the injury contribute to the decreased regrowth capacity. Due to the oligodendrocyte injury, the myelin-associated molecules on the myelin–glial interface become exposed. Several molecules have been identified by multiple groups, e.g., Nogo-A, myelin-associated glycoprotein (MAG), and oligodendrocyte-myelin glycoprotein (OMgp) [39–45].

Nogo-A is the most extensively studied. It possesses two inhibitory domains, Amino-Nogo and Nogo-66, that function by independent mechanisms. Amino-Nogo is a nonspecific neuronal and non-neuronal inhibitor. Nogo-66 is a neuron-specific inhibitor and a Nogo-66 receptor on the axonal surface has also been identified. The Nogo-66

Table 1 Level of evidence for clinical studies using steroids for SCI

Author/year	Design	Level	Agent	Result
Bracken et al./1984 [112]	Prospective, randomized, double-blind	I	Methylprednisolone	Negative
Bracken et al./1990 and 1992 [113, 114]	Prospective, randomized, double-blind	I	Methylprednisolone	Positive
Bracken et al./1997 and 1998 [115, 116]	Prospective, randomized, double-blind	I	Methylprednisolone/tirilizad	Positive
Otani et al./1994 [117]	Prospective, randomized, not blinded	I	Methylprednisolone	Positive
Pointillart et al./2000 [118]	Prospective, randomized, blinded	I	Methylprednisolone/nimodipine	Negative
George et al./1995 [119]	Retrospective, historical case control	II-3	Methylprednisolone	Negative
Gerhart et al./1995 [120]	Retrospective, historical case control	II-3	Methylprednisolone	Negative
Kiwerski/1993 [121]	Retrospective, concurrent case control	II-2	Dexamethasone	Positive
Poynton et al./1997 [122]	Retrospective, concurrent case control	II-2	Methylprednisolone	Negative
Prendergast et al./1994 [123]	Retrospective, historical case control	II-3	Methylprednisolone	Negative

receptor includes the family NgR1/NgR2/NgR3. It does not have an intracellular domain and is dependent on the intracellular p75-molecule, expressing its second messenger activities. In the CNS, p75 is not so abundant and instead TROY (TAJ) is, and it performs similar functions. The second messenger activity is through either RhoA, which is a neural intracellular GTPase, or a Ca-dependent EGFR, which destabilizes actin cytoskeleton by depolymerizing it, thus, leading to collapse of the initial growth cones [46–49].

Similarly, the MAG has affinity not only to NgR1 and NgR2, but also to OMgp. OMgp likewise not only has affinity to NgR1, but also to MAG [50]. Hence, it is important to understand that some of these molecules can simultaneously act as ligand and receptor on neuronal, oligodendrocyte, and glial cell surface. For instance, Nogo-A, MAG, and OMgp, and also a Nogo-A-related molecule (RTN-3) are represented on the glial surface, meanwhile NgR1, NgR2, and again OMgp are represented on the neuronal cell membrane interacting with those on the glial cell membrane (see Table 2).

In order to decrease the effect of Nogos, a Nogo inhibitor monoclonal antibody, called mAB IN-1, has been applied to both intact and hemisected rats. It not only caused increased aberrant corticospinal tract projections, i.e., sensory fibers projecting into the ventral horn and motor fibers projecting dorsally in the intact spinal cord, but also caused progressive reorganization of the sprouting of the remaining corticospinal tract across the midline

Table 2 Neurite outgrowth inhibitors, their receptors and antagonists

Inhibitory molecule	Receptor	Antagonist
Nogo-A (Nogo-66/Amino-Nogo)	NgR/NgR1 [124]	mAB IN-1 [125]
	Co-receptors: p75/LINGO [58]	NgR(310)ecto-Fc [124]
	LINGO/TROY(TAJ) [58, 59]	NEP1-40 [55] Clostridium Botulinum C3Tr [55]
	2nd messenger:	Y27632 [55]
	-Rho[60]	C3-05 [61]
	-Ca-dependent EGFR [127]	TACE(TNF-a-convert enzyme) [126]
		LINGO-1-Fc [128]
		LINGO-1-antibody [128]
		Schwann cell-derived factor [127]
MAG	NgR1/NgR2/OMgp [58, 127]	Trisaccharide substrate 13 [129]
OMgp	NgR1/MAG [127]	NgR(310)ecto-Fc [128]
Semaphorin 4D	Plexin B1 [65, 130]	SB269970 [130]
Ephrins	Eph [66–68]	TNYL-RAW [131]
Tenascin R	$GABA_B$-receptor [133]	HNK-1-antibody [132]
Slits	Rig-1/Robo3[a] [133, 134]	Stromal cell-derived factor-1 [135]
Nitric oxide	Sgc [136]	ONO-1714 [137]
Chondroitin sulfate	Annexin 6 [138]	Chondroitinase ABC [139]

[a] Present in precerebellar fetal neurons

towards the hemisected site. Interestingly, within the spinal cord, the mAB IN-1 treatment that was only supposed to inhibit Nogo was also associated with upregulation of BDGF, VEGF, actin, myosin, GAP -43 [28], and STATs whereas in pyramidotomy, induced enhanced expression of guidance molecules (semaphorins and slits) as well as BDGF, IGF, and BMP was seen [31]. This is interesting since it may put a connection between Nogos and neurotrophic factors as separate but parallel factors. Other studies have shown similar results [52, 53], and in regard to Nogo, similar results have been shown with Nogo antibody in chronic SCI [54].

Systemic deletion of Nogo improves regenerative and plastic responses after SCI [55] although one study found lack of enhanced spinal regeneration in Nogo-deficient mice [56].

Some other inhibitory molecules have also been identified, e.g., LINGO (leucine-rich repeat) and Ig-domain-containing Nogo receptor-interacting protein) and TROY [57]. These seem to be part of the Nogo receptor complex and rather have a co-ligand or co-receptor function. For instance, LINGO-1 binds to NgR1 and at the same time is needed in the complex that transmits the effects of Nogo A. TROY (also known as TAJ) is a TNF receptor family member, selectively expressed in adult CNS, which can form a functional receptor complex together with NgR/LINGO to mediate the effects of Nogo. This molecule seems to activate the non-p75 receptor complexes responsible for Nogo/MAG/OMgp's effects [58–60]. Rho, being involved in the intracellular second messenger system of Nogo, has also been shown to have a role in apoptosis [61].

Alteration in the extracellular matrix with exposure of chondroitin sulfate proteoglycan [51, 62], as well as interactions between the growth guidance molecules and their receptors, Semaphorin 4D, Ephrin B3, Arretin, Tenascin-R, and Versican, have also a modulatory effect on regeneration [63, 64]. Some of these have also been visualized [65]. Semaphorin 4D, activating its receptor, Plexin B1, induces growth cone collapse through a second messenger system [65].

Ephrins are guidance molecules with their receptor family Eph (erythropoietin-producing hepatocellular) that are another source of inhibitory action on the neurite outgrowth in brain and spinal cord. These control migration in the fetal spinal cord and they have been shown to be involved in migration after spinal cord injury [66–68]. However, in another study, conflicting results showed that the ligand–receptor activity might be involved in promoting sprouting although it was not the only determinant [69]. The protein previously called Arretin is now believed to predominantly consist of OMgp [70].

Tenascin R has been postulated as having mostly inhibitory effects although some works have indicated that there may be cooperation with other extracellular molecules that promote formation of microprocesses in the brain neurons [71, 72]. The tenascin family constitutes a group of extracellular matrix proteins with similar structure. Of these, tenascin-R (TNR) appears to be restricted to the CNS. TNR is synthesized by oligodendrocytes during myelination [73–75] and by subsets of CNS neurons in the spinal cord, retina, cerebellum, and hippocampus where TNR is particularly enriched in perineuronal nets surrounding inhibitory interneurons [75–78]. Tenascins seem to be among early molecules expressed after the spinal cord injury [79]. Versicans are chondrotine sulfate proteoglycans, which are similar to Tenascins, have inhibitory properties during the development [80–84].

STATs are mediators past the ligand–receptor system that are involved in CNS development [85]. Slits are mRNAs involved in inhibition of sprouting after CNS injury [86].

In both vertebrates and invertebrates, the attractant protein netrin serves to guide commissural axons towards the midline. In *Drosophila*, axonal projections away from the midline depend on the presence at the midline of the repellent molecule Slit, which binds axonal Robo receptors [87, 88]. As they approach the midline, axons are attracted by netrin and express only a low level of Robo.

Application of the chondroitin sulfate inhibitor, chondroitinase ABC, has been shown to promote functional recovery after SCI [89, 90]. There are some paradoxical studies on nitric oxide's role in regeneration. One study has indicated its role in regeneration as implantation of PNS grafts has shown inhibition of neuronal nitric oxide synthase (NOS) and enhanced survival of spinal motoneurons following root avulsion, indicating that induction of NOS in avulsed motoneurons may result from the deprivation of neurotrophic factors produced by the PNS component [91], while other contradicting studies have shown that expression of nitric oxide synthase is beneficial to the axonal regeneration of the injured spinal motoneurons although the rate of axonal regeneration was not affected [92]. In summary, there are multiple extracellular inhibitory molecules. Some of these have been studied extensively and their mechanism is shown by multiple independent groups (see Table 3).

From acute inflammation to scar tissue formation

The acute and subacute inflammatory reactions subside eventually and glial scar tissue forms. Approximately 4 weeks after the SCI, the glial scar tissue is well developed and a central cyst forms [93]. This scar tissue is another obstacle for neurite outgrowth. There are studies demonstrating that the connective tissue that forms at the margins of the grafts is not an impenetrable barrier to axon growth because some axons enter the PNS glial grafts [94]. Due to

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

Author/year	Design	Level	Agent	Result
Geisler et al./1991 [100]	Prospective, randomized, double-blind	I	GM-1 gangliocyte	Positive
Geisler et al./2001 [140]	Prospective, randomized, double-blind	I	GM-1 gangliocyte	Negative
Bracken et al./1990 and 1992 [113, 114]	Prospective, randomized, double-blind	I	Naloxone	Negative
Flamm et al./1985 [141]	Prospective feasibility/safety study	III	Naloxone	N/A
Pitts et al./1995 [142]	Prospective, randomized, double-blind	I	Thyrotropin-releasing hormone	Positive
Tadie et al./1999	Prospective, randomized, double-blind	–	Gacyclidine	Negative
Pointillart et al./2000 [118]	Prospective, randomized, blinded	I	Nimodipine	Negative

the subsiding inflammatory reaction in the acute phase, a controlled study has shown dramatically increasing supraspinal pathway recovery 2–4 weeks after the SCI when fetal cell transplants together with NT-3 were implanted, compared to the acute phase. Growth below the lesion was shown only in the NT-3 groups [95]. This obviates the negative non-permissive effect of the post-injury acute inflammatory reaction to the initiating regrowth.

Although astrocytes have been postulated as being the major finding in non-permissive scar tissue, there are studies, although in the brain and not in the spinal cord, that suggest reactive intracerebral astrocytes acting as substrates for growing axons, but only in the presence of elevated levels of NGF [96]. Reactive astrocytes together with macrophages have also shown some promising results in optic nerve in vitro studies [97].

An interesting addition to the aforementioned is that local application of human Schwann cells together with methylprednisolone have shown some regeneration beyond the implant and some modest motor recovery in rats [98], indicating the neurotrophic and scaffolding properties of Schwann cells together with the known anti-inflammatory effect of the steroids.

Deficit and recovery

The clinical consequences of the injury depend on the location and extent of the SCI. One important observation is the finding of some degree of continuity at the lesion site even in cases with clinical complete lesion [99]. Motor roots have an increased vulnerability to injury and decreased capacity for recovery than sensory roots [15]. The surrounding zone of the acute immediate ischemia, the penumbra, carries cells and tracts that remain viable for a period of time and with persisting ischemia and inflammation, will also be damaged.

The gray matter has a higher metabolic rate than the white matter [100]. Therefore, it seems that acute micro-intervention is to be directed at salvaging the immediate ischemia and directing treatment towards the gray matter, and secondary micro-intervention can be directed towards the white matter. Even small numbers of cells and tracts can be the difference between function and non-function as we know that there is persistence of only 12% of the normal number of axons following clip compression injury in rats [101]. Another study showed that a lesion extending for even as much as 90% of the transverse plane of the spinal cord may not produce paraplegia in rats [102].

In the incomplete SCI, there is some improvement of function after the initial injury, which has been postulated as being due to recruitment of collateral tracts and plasticity of the remaining neurons and tracts [103–106] rather than neurite outgrowth and connection. Recruiting collaterals means that the CNS rostral to the lesion attempts to maintain its contact with the spinal cord caudal to the lesion via collaterals in the undamaged parts of the level that has been damaged. Plasticity demonstrates that a certain nerve that typically has contact with a certain end-organ (neuron, glia, or muscle cell) expands its contact with more end-organs which, prior to the SCI, were supplied by the damaged cord and its related nerves. It also means that the surviving neurons develop more synapses with other neurons. In these cases, visible regeneration is not seen despite improvement of clinical and electrophysiological results.

Another important factor is not only regrowth but also an organized regrowth connecting correct structures to respective end-organs [107]. There is an array of various extra- and intracellular molecules, dependent and independent of the above mentioned growth factors, involved in promoting regeneration [30–33]. Hence, after the SCI, there is cell loss, tract disruption, ischemia, inflammation, neurite outgrowth inhibition, lack of nerve growth factors, scar tissue formation, and physical gap between the two ends of the damaged region, and therefore, a suboptimal environment for the initial regrowth.

In the PNS, the same factors can occur, but the neurite regrowth usually persists as long as there is physical contact between the ends or at least a scaffold that supports regrowth.

Schwann cells of peripheral nerve origin can migrate along the dorsal and ventral spinal roots and invade the cord parenchyma where they may proliferate and be involved in remyelination of CNS axons and axonal guidance [13–18]. Their ability to encapusulate and myelinate axons is entirely dependent on deposition of the basal lamina and the components that they synthesize and secrete, namely, laminin, heparin sulfate proteoglycans, type IV collagen, and some more components of the basal lamina [18, 108]. Prevention of the basal lamina formation by, for instance, ascorbic acid deficiency, which impairs collagen production, inhibits myelination [108]. Surviving oligodendrocytes can extend their cytoplasmic processes to remyelinate adjacent axons [16]. Ependymal cells have functioned as a scaffold in lower animals [109]. A self-renewing population of mitotically active multipotent neural stem cells has been recovered from the central canal of the adult mammalian spinal cord [110]. In one study in rats, it was shown that grade of the functional recovery is correlated to distribution and number of regenerated fibers [111].

Conclusions

In summary, the final grade of neurological deficit following SCI is dependent on multiple cellular and sub-cellular factors, but one very important fact remains, and that is that the CNS has enormous capacity to remodulate and to maintain its function despite major trauma. This shows that even a few neurons, and especially axons, can be the difference between function and non-function, and every effort should be aimed at preserving as many neurons and axons as possible and to promote their regeneration.

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