Review

Repair of chronic spinal cord injury

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Abstract

Advances in medical and rehabilitative care now allow the 10–12,000 individuals who suffer spinal cord injuries each year in the United States to lead productive lives of nearly normal life expectancy, so that the numbers of those with chronic injuries will approximate 300,000 at the end of the next decade. This signals an urgent need for new treatments that will improve repair and recovery after longstanding injuries. In the present report we consider the characteristics of the chronically injured spinal cord that make it an even more challenging setting in which to elicit regeneration than the acutely injured spinal cord and review the treatments that have been designed to enhance axon growth. When applied in the first 2 weeks after experimental spinal cord injury, transplants, usually in combination with supplementary neurotrophic factors, and possibly modifications of the inhibitory central nervous system environment, have produced limited long-distance axon regeneration and behavioral recovery. When applied to injuries older than 4 weeks, the same treatments have almost invariably failed to overcome the obstacles posed by the neurons’ diminished capacity for regeneration and by the increasing hostility to growth of the terrain at and beyond the injury site. Novel treatments that have stimulated regeneration after acute injuries have not yet been applied to chronic injuries. A therapeutic strategy that combines rehabilitation training and pharmacological modulation of neurotransmitters appears to be a particularly promising approach to increasing recovery after longstanding injury. Identifying patients with no hope of useful recovery in the early days after injury will allow these treatments to be administered as early as possible.

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Introduction

During the First World War soldiers with complete spinal cord injuries did not survive; 80 percent of British soldiers with traumatic paraplegia are estimated to have died within 3 years of injury. Survivors were chronically ill and dependent, and, because their prospects were so dismal, programs of aggressive rehabilitation were not established. Even through the early years of World War II most soldiers and civilians with spinal cord injuries died within 2–3 years from sepsis due to infections of the bladder and kidneys and infected pressure sores, which were considered to be inevitable consequences of their injuries (reviewed by Guttmann, 1976). Now, however, nearly 94 percent of patients with spinal cord injuries survive the first year after their injury and, of those that survive their initial hospitalization in specialized units, 93 percent are sufficiently independent to be discharged back into the community (DeVivo, 2002). The life expectancy of the estimated 11,000 annual victims of traumatic spinal cord injuries in the United States has improved in recent years, and this improved survival is projected to increase the prevalence rate in the United States to nearly 280,000 by 2014 (DeVivo, 2002). Many of these individuals remain healthy and productive thanks to programs designed to prevent the debilitating long-term effects of their injuries.

While these advances in care are dramatic, there remains a pressing need for treatments that will improve repair processes and recovery in individuals with longstanding spinal cord injuries. Christopher Reeve has described the daily exertions required for severely injured people to main-
tient physical and psychological well-being (Reeve, 1998). These individuals remain eager, even desperate, for treatments that will improve autonomic function, diminish neuropathic pain, and restore walking. Particularly for those who were injured recently, progress in treating injuries in the laboratory has made treatments in the clinic seem tantalizingly close. Patients with chronic injuries are also of research interest because they provide a potentially attractive population for the initial clinical application of experimental therapies. Because deficits of chronic patients are stable, treatments will not interfere with spontaneous recovery and spontaneous recovery will not confound the results of treatments.

**Acutely injured central axons can regenerate**

Prior to 1980 the prevailing view was that damage to the mature central nervous system (CNS) was permanent, without the possibility of repair. At best there would be local sprouting from adjacent, uninjured axons but sprouting was thought to be as likely to cause maladaptive responses, such as spasticity, autonomic dysreflexia, and pain, as to contribute to recovery. Failure of injured axons to achieve long distance regrowth was blamed on the inability of adult CNS neurons to maintain a regenerative mode (Ramón y Cajal, 1928), in contrast with the response to peripheral nerve injuries, where structural and functional repair frequently occurred (reviewed in Fu and Gordon, 1997). These observations suggested that the environmental milieu of peripheral nerves was as important for axon regrowth as the innate ability of neurons to regenerate and that the composition of the injured CNS played a prominent role in restricting long distance axon extension. The classic experiments from Aguayo’s laboratory using peripheral nerve grafts to bridge injured regions of the brain and spinal cord illustrated the considerable potential of adult CNS neurons to regenerate their axons when provided with a suitable environment or substratum (Aguayo et al., 1979; Benfey and Aguayo, 1982; David and Aguayo, 1981; Richardson et al., 1980). Axons have also been reported to grow from a peripheral nerve graft back into the CNS and to form synaptic contacts with host neurons, but growth has been limited to a small number of axons found in regions immediately adjacent to the graft end (Carter et al., 1989; Kierstead et al., 1989; Vidal-Sanz et al., 1987).

At about the same time as the initial studies of peripheral nerve grafts, several groups reported encouraging results after transplanting fetal spinal cord tissue into an acute spinal cord lesion cavity (Das, 1983; Reier et al., 1986). The transplants integrated with adjacent host spinal cord and rescued injured supraspinal neurons in the neonatal brainstem (Bregman and Reier, 1986). Fetal spinal cord transplants alone are not very effective in eliciting regeneration in adult hosts; the perikarya of the few CNS axons that grow into these transplants are generally located within 1 mm of the grafts and the axons do not traverse the grafts to enter host spinal cord (Jakeman and Reier, 1991). Diverse neural and nonneural tissues have therefore served as intraspinal transplants in attempts to promote axon growth across a lesion (reviewed in Murray and Fischer, 2001; Bunge, 2001). Several different types of grafts, including olfactory ensheathing cells, (Li et al., 1998; Ramón-Cueto et al., 1998) embryonic stem cells (McDonald et al., 1999), and Schwann cells (Xu et al., 1995), enable a small number of axons to regenerate across a lesion site and into the host. This limited response indicates that additional treatments are necessary to enhance the number and length of axons growing across a lesion.

Repair strategies can target different regions of the neuraxis (reviewed by Bregman, 1998; Horner and Gage, 2000; Behar et al., 2000; Murray and Fischer, 2001). For example, treatments might target the cellular and matrix changes that occur at the injury site (Akiyama et al., 2001), the regenerative perikaryal responses that occur in injured neurons (Bregman, 1994), or the reactions of neuronal and nonneuronal cells located beyond the lesion (Beattie et al., 1997). Interventions that have been combined with transplants to promote repair and/or recovery include the application of neurotrophic or growth factors (Bregman et al., 1997; Kim et al., 1999; Oudega and Hagg, 1999; Oudega et al., 1999), pharmacological agents that mimic the action of neurotransmitters (Robinson and Goldberger, 1986; Barbeau and Rossignol, 1991), anti-apoptotic agents (Takahashi et al., 1999; Shibata et al., 2000), agents that interfere with inhibitors of growing axons (Schwab, 2001; Strittmatter, 2002), and physical rehabilitation and training (Edgerton et al., 1991, 2001). Grafts have also been applied within a polymer scaffold that allows directed growth of regenerating axons (Teng et al., 2002). Additional modifications that supply supplementary neurotrophic factors or antagonize inhibitory components in the CNS may make artificial bridges even more supportive of axon growth (reviewed by Geller and Fawcett, 2002). For the most part these combination therapies have been directed toward repair of the acutely injured spinal cord and provide insight into intrinsic and extrinsic factors affecting the regeneration of injured axons. An acute injury is an unstable environment with progressive changes occurring over days to months (Fitch et al., 1999). Several studies suggest that a short delay (~2 weeks, subchronic) between injury and intervention is more favorable for axon regeneration and behavioral recovery than immediate treatment at the time of injury (Coumans et al., 2001; Reier and Stokes, 1992). Some neurons remain responsive to supplementary neurotrophic factors at considerably longer postinjury periods (Kwon et al., 2002a; Tobias et al., 2001), encouraging the search for effective repair strategies that can be administered long after the initial injury. In many respects the chronic injury is a more challenging condition in which to encourage repair but, because the vast majority of spinal cord injury patients have chronic injuries, it has begun to attract much needed investigation.
What is a chronic injury?

There appears to be no generally agreed upon definition of what constitutes a chronic injury of the mammalian spinal cord. “Chronic” implies a stable injury that is undergoing little additional change, but the time at which an injury stabilizes differs depending on whether it is based on pathological or behavioral criteria. Contusion injuries in the rat continue to show development of pathology until 14 weeks (Hill et al., 2001), whereas recovery based on an open field rating score (BBB score) reaches a plateau at ~4 weeks (Basso et al., 1995). Other measures of autonomic and locomotor performance become stable at times in between. It would therefore appear reasonable to define a chronic injury in the contused rat as one that is at least 4 weeks old since before this time both structural and functional measures are changing actively. Intervals at which other types of injuries stabilize may differ from a contusion lesion, but this has not been systemically investigated. Similar considerations vex the classification of human spinal cord injuries as chronic, because pathology and spontaneous recovery also evolve at different rates. One review of human injuries adopted an operational definition, in which patients are considered to have chronic injuries upon discharge from their initial hospitalization (Ditunno and Formal, 1994). The time of discharge, however, is determined primarily by third-party payers and in the Model Systems SCI Care System it has shortened progressively from ~140 days in 1974 to ~60 days in 1999 (www.spinalcord.uab.edu).

In the present review we focus on interventions that have shown the potential to enhance recovery when applied to experimental spinal cord injuries in rodents after a delay of at least 4 weeks. Our emphasis is on treatments designed to elicit axon growth and functional recovery. We consider the evolving responses of injured neurons and the features of the environment at the site of injury and beyond, and how these changing conditions may affect the success of treatments that have been reported to enhance regeneration and recovery when applied to the acutely injured spinal cord. For the most part we consider experimental injuries in rats, but we also attempt to relate these studies to chronic spinal cord injuries in humans when appropriate.

Lessons from chronic peripheral nerve injuries

The prognosis is good for most peripheral nerve injuries in which the endoneurial tubes remain intact. The damaged neurons increase their expression of growth-associated molecules and the region of the injury is filled by an influx of growth-promoting Schwann cells, macrophages, and fibroblasts. The distal nerve stump provides a favorable environment for axon regrowth due to the rapid phagocytosis of degenerating myelin and increased synthesis of neurotrophic factors and substrate molecules by proliferating Schwann cells in the endoneurial tubes, which guide regenerating axons back to their denervated targets (reviewed by Fu and Gordon, 1997). Recovery is much poorer after injuries that lead to prolonged denervation of the distal nerve segment and target muscle, including proximal injuries and injuries in which lengthy delays precede repair. Although exceptional clinical case reports have documented effective functional recovery when injured peripheral nerves are surgically repaired years after injury, in general the prospects for recovery decline progressively, particularly if the delay exceeds 6 months (reviewed by Sunderland, 1991).

The failure of regeneration after proximal injuries and late secondary suture has traditionally been attributed to both degenerative changes below the lesion and to exhaustion of the neuron’s regenerative response (Seddon, 1972; Sunderland, 1991). When surgical repair using a cross suture paradigm was delayed for 6–12 months, Gordon and colleagues (Fu and Gordon, 1995) recorded motor unit forces that indicated a threefold reduction in numbers of tibial nerve motor neurons whose axons regenerated to form functional connections with the tibialis anterior muscle, consistent with the idea that prolonged axotomy reduces the capacity of motor neurons to regenerate (Fu and Gordon, 1995). Preliminary evidence has suggested that the response of chronically injured motor neurons to a second injury resembles the response to a single injury, including upregulation of cytoskeletal proteins and GAP-43 and downregulation of neurofilament protein, but that the regenerative response to a second injury is not sustained (Gordon and Fu, 1997; Fernandes and Tetzlaff, 2001). When freshly cut tibialis motor neurons were surgically ligated to denervated common peroneal nerve stumps, the denervated stump provided a favorable terrain for regeneration for about 4 weeks after the initial injury. Prolonged denervation of the distal nerve stump and terminal nerve sheaths within the target muscle gradually reduces the numbers of successfully regenerating axons to an even greater extent than with delayed reapposition (Sulaiman and Gordon, 2000). The development of an unfavorable environment is related temporarily to a progressive decrease in the numbers of Schwann cells, which leads to a disappearance of endoneurial tubes and basement membrane, and a decline in their expression of regeneration-associated molecules, including glial derived neurotrophic factor (GDNF) (Sulaiman and Gordon, 2000; Hoke et al., 2002). Both a decline in the regenerative capacity of chronically axotomized neurons and a deterioration of the milieu of the chronically denervated nerve stump therefore appear to contribute to the failure of peripheral nerves to regenerate after chronic injury. Thus peripheral nerve regeneration after chronic injury faces obstacles similar to those affecting attempts to repair a chronic spinal cord injury.

The chronically injured spinal cord presents additional challenges

The chronic lesion challenges efforts to enhance regeneration in ways that acute injuries do not, in part because an
increasingly inhospitable environment develops at the injury site and beyond (overview in Fig. 1). In the most common pattern of closed spinal cord injury, swelling and hemorrhagic necrosis appear within hours of the contusion in the gray matter and adjacent white matter of the injury site. Neurons, astrocytes, and oligodendrocytes die as the lesion expands over several spinal cord segments (Beattie and Bresnahan, 2000). In humans a cascade of secondary changes results within a few weeks in the formation of a mature cystic cavity surrounded by a thick astrocytic scar; the lesion subsequently evolves over months and years into a multilobular cystic structure whose walls are formed by glia (Kakulas and Taylor, 1992). If the injury has interrupted the pia, the density of the scar is increased further by acellular collagenous tissue originating in the meninges (Hughes, 1966). Axons do not grow across cavities and the scar imposes a physical and chemical barrier to regenerating axons (reviewed by Geller and Fawcett, 2002). Among the inhibitors present in the scar are chondroitin sulfate proteoglycans and tenascin produced by astrocytes (Niederost et al., 1999; Fawcett, 1997) and Semaphorin 3A associated with fibroblast-like cells (Pasterkamp et al., 1999). Although closed contusion injuries usually spare axons in the subpial white matter of the impact site (Kakulas; 1999; Bunge et al., 1993), injury to axons and oligodendrocytes causes demyelination (Kakulas and Taylor, 1992) and exposure of voltage-gated potassium channels at the inter-

**Experimental Interventions To Promote Repair of Chronic Spinal Cord Injury**

<table>
<thead>
<tr>
<th>Transplanted Tissue</th>
<th>Type of Injury and Delay before Treatment</th>
<th>Source of Re-growing Axons</th>
<th>Behavioral Improvement</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal Spinal Cord</td>
<td>L.1 Hx, 5 wks</td>
<td>5-HT</td>
<td>Not Studied</td>
<td>Houle and Reier, '88</td>
</tr>
<tr>
<td>Fetal Spinal Cord with Neurotrophins</td>
<td>T 6-8 Tx, 2 or 4 wks</td>
<td>CST, 5-HT</td>
<td>Weight Supported Stepping</td>
<td>Coumans et al., '01</td>
</tr>
<tr>
<td>with NGF-Nitrocellulose</td>
<td>L.1 Tx, 5 wks</td>
<td>CGRP</td>
<td>Not Studied</td>
<td>Houle and Ziegler, '94</td>
</tr>
<tr>
<td>with Hind Limb Exercise</td>
<td>T 10 Tx, 4 wks</td>
<td>5-HT</td>
<td>Restore Muscle Size</td>
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</tr>
<tr>
<td>Human Fetal Spinal Cord</td>
<td>L.1 Hx, 6 wks</td>
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<td>No Sign. Change in Open Field Score (BBB)</td>
<td>Akesson et al., '01</td>
</tr>
<tr>
<td>Transfected Fibroblasts Secreting Neurotrophins</td>
<td>T7 Dorsal Hx, 1-3 mos</td>
<td>DBH, DLF</td>
<td>Not Studied</td>
<td>Grill et al., '97</td>
</tr>
<tr>
<td>C3 Hx, 5 wks</td>
<td>5-HT</td>
<td>Bilateral Forepaw Use</td>
<td>Bilateral Forepaw Use</td>
<td>Jin et al., '00; Jin et al., '02</td>
</tr>
<tr>
<td>C3 Hx, 5 wks</td>
<td>RST, VST, ReST</td>
<td>BBB Increase from 1 to 4.3</td>
<td>BBB Increase from 4.5 to 5.4</td>
<td>Lu et al., '02; Woerly et al., '01</td>
</tr>
<tr>
<td>Olfactory Ensheathing Glia</td>
<td>T10 Tx, 4 wks</td>
<td>5-HT</td>
<td>Not Studied</td>
<td>Grill et al., '97</td>
</tr>
<tr>
<td>Neuregul™</td>
<td>T8 Balloon Cr, 14 wks</td>
<td>Propriospinal</td>
<td>Placing Response</td>
<td>VonMayenburg et al., '98</td>
</tr>
<tr>
<td>Antibodies to Myelin Inhibitory Proteins and Neurotrophins</td>
<td>T8 Dorsal Hx, 2 or 8 wks</td>
<td>RST</td>
<td>Not Studied</td>
<td>Grill et al., '97</td>
</tr>
</tbody>
</table>

Hx = Hemisection, Tx = Complete Transection, Cr = Crush

Spinal Pathways: Corticospinal (CST), Rubrospinal (RST), Vestibulospinal (VST), Reticulospinal (ReST), Raphespinal (5-HT), Coeruleospinal (DBH), Ascending Sensory (CGRP, DLF)

Fig. 1. Summary of experimental treatments of the chronically injured spinal cord. Recent studies have shown that neural tissue transplants alone or combined with neurotrophic factors support axonal growth from most chronically injured supraspinal neurons. In many studies marked behavioral improvement has been recorded although anatomical correlation with these results has not been strong.

increasingly inhospitable environment develops at the injury site and beyond (overview in Fig. 1). In the most common pattern of closed spinal cord injury, swelling and hemorrhagic necrosis appear within hours of the contusion in the gray matter and adjacent white matter of the injury site. Neurons, astrocytes, and oligodendrocytes die as the lesion expands over several spinal cord segments (Beattie and Bresnahan, 2000). In humans a cascade of secondary changes results within a few weeks in the formation of a mature cystic cavity surrounded by a thick astrocytic scar; the lesion subsequently evolves over months and years into a multilobular cystic structure whose walls are formed by glia (Kakulas and Taylor, 1992). If the injury has interrupted the pia, the density of the scar is increased further by acellular collagenous tissue originating in the meninges (Hughes, 1966). Axons do not grow across cavities and the scar imposes a physical and chemical barrier to regenerating axons (reviewed by Geller and Fawcett, 2002). Among the inhibitors present in the scar are chondroitin sulfate proteoglycans and tenascin produced by astrocytes (Niederost et al., 1999; Fawcett, 1997) and Semaphorin 3A associated with fibroblast-like cells (Pasterkamp et al., 1999). Although closed contusion injuries usually spare axons in the subpial white matter of the impact site (Kakulas, 1999; Bunge et al., 1993), injury to axons and oligodendrocytes causes demyelination (Kakulas and Taylor, 1992) and exposure of voltage-gated potassium channels at the inter-

nodes (Nashmi and Fehlings, 2001) that may produce malfunction in surviving axons.

The spinal cord beyond the injury site also poses formidable obstacles to axon regeneration and recovery. For example, myelin remnants produced by anterograde degeneration remain in the human spinal cord for years (Hughes, 1966). Components of degenerating CNS myelin, including Nogo-A (Bandtlow and Schwab, 2000; Caroni and Schwab, 1988; Shen et al., 2000; GrandPre et al., 2000), myelin-associated glycoprotein (McKerracher et al., 1994; Mukhopadhyay et al., 1994; Tang et al., 1997), and oligodendrocyte-myelin glycoprotein (Wang et al., 2002) are important contributors to regeneration failure (David and Ousman, 2002; Huang et al., 1999) by directly inhibiting axonal growth. The progression of anterograde degeneration in white matter tracts is accompanied temporally and spatially by the apoptotic death of oligodendrocytes (Emery et al., 1998; Liu et al., 1997; Shuman et al., 1997). Loss of trophic factors derived from axons that are degenerating, harmful cytokines secreted by infiltrating cells, and a paradoxical effect of neurotrophins acting on the p75 receptor are among the possible mechanisms responsible for this cellular reaction (reviewed by Beattie et al., 2000). The death of oligodendrocytes can have two deleterious consequences for recovery. (1) Because oligodendrocytes ensheathe multiple CNS axons, their loss can amplify the functional deficits of spinal cord injury by impairing conduction through...
denuded axons that survive the injury. (2) Their death can impede regeneration by exposing axons to inhibitors such as Nogo, much of which is normally sequestered within the cytoplasm of intact oligodendrocytes and neurons and in the myelin sheath (Huber et al., 2002).

The chronically injured spinal cord also may lack the molecular cues that guide axons to their targets during development (reviewed by Jacob et al., 2001; Geller and Fawcett, 2002). Some evidence suggests that these cues persist or are reexpressed after acute CNS injury and that regenerating axons can recognize them. For example, following induction of apoptotic degeneration of corticothalamic neurons in layer VI of the anterior cortex of adult mice, new neurons differentiate from endogenous neural precursors and reform appropriate corticothalamic projections (Magavi et al., 2000). In acutely injured spinal cord, the cut corticospinal tract axons that regenerate after vaccination with myelin components (Huang et al., 1999) and rubrospinal tract axons that regenerate in response to brain derived neurotrophic factor (BDNF)-expressing fibroblast grafts (Liu et al., 1999) continue to grow in their normal locations in the caudal host spinal cord and the grafts contribute to recovery of locomotor function. Furthermore, fetal raphe tissue transplanted into the spinal cord distal to a transection lesion shows remarkable axon growth through both gray and white matter to appropriate targets in the upper lumbar spinal cord (Privat et al., 1989) where initiation of hind limb locomotor activity occurs (Feraboli-Lohnherr et al., 1997; Giménez y Ribotta et al., 2000; Yakoleff et al., 1995). Embryonic and adult rat retinal ganglion cell axons recognize membrane-associated guidance activities that continue to be expressed in the adult rat superior colliculus for at least 220 days after optic nerve section (Wizenmann et al., 1993), suggesting long-term maintenance of guidance cues after CNS injury. Axon growth from grafted dorsal root ganglion (DRG) neurons within degenerating dorsal column white matter supports the idea that this environment is not completely refractory to regeneration, even with a delay of 3 months between spinal cord injury and transplantation (Davies et al., 1999). Axons of these transplanted DRG neurons did not grow into appropriate terminal areas by 10 days after transplantation, which was the longest survival period studied, so it remains to be shown whether effective guidance cues persist in the chronically injured spinal cord.

The complexities that follow chronic spinal cord injuries

Retrograde degeneration: death, atrophy, and metabolic failure

Strategies designed to promote regeneration after long-standing injuries assume that neurons survive and remain responsive to treatment. Axotomized rubrospinal tract neu-
(NT-3) to an acute injury site has little effect on lesion size but reduces significantly the formation of terminal clubs by injured corticospinal tract axons, which may facilitate axonal regrowth under appropriate conditions (Sayer et al., 2002). Extensive debridement of the wound in preparation for transplantation may therefore reinjure many descending and ascending axons, but transplantation procedures should bring treatments applied to the lesion site close to most of their axon terminals.

Neurotrophic molecules applied to a lesion site can act on injured neurons only if they express the appropriate specific receptors and if the bound ligand is then transported retrogradely to the neuronal soma, where specific cell signaling pathways are activated (Ceresa and Schmid, 2000; Schlessinger, 2000). Disruption of either neurotrophic factor binding or retrograde transport will impair the ability of neurons to respond to neurotrophins applied to the lesion site. Retrograde transport has been reported to be diminished or absent in Red nucleus neurons 3 days after a T10 hemisection (Tseng et al., 1995). The observation that Red nucleus neurons show a diminished regenerative response to basic fibroblast growth factor (FGF2) provided at 8 weeks compared to treatment 4 weeks after a cervical hemisection suggests a decline in either ligand transport or receptor expression during this interval (Houle and Ye, 1997). In contrast, ciliary neurotrophic factor (CNTF) applied to the lesion site 8 weeks after injury elicits as robust a regenerative response from Red nucleus neurons as treatment at 1 or 4 weeks (Houle and Ye, 1997), indicating that impairment of responsiveness is likely to be ligand specific. Reports of changes in the expression of trk B mRNA in supraspinal neurons following spinal cord injury are also conflicting. Two studies reported a 30% decline in trk B expression in Red nucleus neurons by 7 days after cervical hemisection, which persisted for at least 28 days (Kobayashi et al., 1997; Novikova et al., 2000). In contrast, Liebel et al. (2001) found no significant change in trk B or trk C mRNA expression in either Red nucleus or corticospinal tract neurons at 1, 7, or 42 days following a thoracic contusion injury. This discrepancy likely reflects the varying response of these neurons to the different types and levels of injury examined in the two studies, as some types of contusion injury might not affect the rubrospinal tract. Infusion of BDNF either directly into the Red nucleus (Kobayashi et al., 1997) or into the lumbar subarachnoid space (Novikova et al., 2000) prevented the decline in trk B mRNA expression. Whether BDNF directly applied to a lesion site would act similarly is unknown, but its effectiveness may depend on whether it is applied at the time of injury or after a delay. Delayed administration to the lesion site may be less effective in promoting repair than acute treatment because the truncated form of trk B overexpressed by components of the glial scar may bind most of the BDNF and sequester it from axons (Liebel et al., 2001; Frisen et al., 1993). It also is possible that, although persisting in the cell bodies of chronically injured Red nucleus neurons, levels of trk B receptors greatly diminish at the terminal end of rubrospinal axons (Kwon, B.W., Tetzlaff, W., personal communication).

Environmental differences

Endogenous neurotrophin mRNA is expressed after spinal cord injury, but the transient upregulation may not be sufficient to offset the deleterious effects of a long-term injury. Levels of BDNF mRNA expression in tissue surrounding an injury reach a peak by 24 h and return to control levels within 3 days of injury. The initial increase in BDNF expression due to neurons and astrocytes is followed at 3 days by expression by invading macrophages (Ikeda et al., 2001). GDNF and CNTF mRNA expression also is upregulated at 1 day; significantly higher levels of GDNF mRNA persist for 2 days and of CNTF mRNA for 4 days (Nakamura and Bregman, 2001). In the chronically injured spinal cord a second injury leads to a different pattern of neurotrophin mRNA expression than after an acute injury (Houle and Eckenstein, 2002). By 6 h after reinjury there is a significant increase in the expression of nerve growth factor and GDNF mRNA, which persists for 3 days. In contrast to the response reported following an acute injury, the expression of CNTF mRNA does not appear to change at any time following the second injury. Distinct differences in the cell and tissue responses between acute and chronic injury sites are likely to contribute to the challenge of eliciting regeneration following long-term injuries and the use of exogenous neurotrophins appears necessary to supplement a limited local production immediately after injury.

Strategies for promoting recovery from chronic injuries

The encouraging results found with acute transplantation of fetal spinal cord (FSC) tissue led to investigations to determine whether these transplants would survive in a chronic lesion site and whether neurons that had been injured for several weeks to months retained the ability to regenerate their axons, if provided an appropriate substrate. The initial studies compared survival, differentiation, and integration of FSC tissue grafted into a lumbar hemisection cavity 2 or 7 weeks after the initial injury (Houle and Reier, 1988). The transplantation procedure left the cavity wall undisturbed. Most of the transplants grew to fill the cavity, established an interface with the host spinal cord, and contained host serotonergic bulbospinal axons and calcitonin gene-related peptide-immunoreactive primary afferent axons (Houle and Reier, 1989). Despite the presence of an established glial scar at the time of transplantation, regions of the transplant-host interface lacked obvious scarring, demonstrating that the transplants had reduced an established scar formation. This effect of FSC tissue transplantation was subsequently confirmed by measuring the extent of glial scarring at the transplant-host interface when
established scar tissue was removed just prior to transplantation (Houle, 1992). The results of this study confirmed that FSC tissue not only reduced the continuity of an established glial scar but also limited scar reformation. Both of these actions would ensure that regions of possible interaction between the transplant and host spinal cord persisted.

Whether axon growth into delayed FSC transplants represented regeneration by chronically injured neurons or collateral sprouting by uninjured axons remained an issue in the early 1990s. The report that cut axons of retinal ganglion cell neurons grew into a peripheral nerve graft placed 1–6 weeks after optic nerve injury provided the first convincing demonstration of regeneration by chronically injured neurons (Thanos and Vanselow, 1989). The propensity of retinal ganglion cell neurons to regenerate progressively decreased as the postinjury period before transplantation increased, with optimal regrowth occurring with a delay of less than 3 weeks between injury and transplantation. In our laboratory a double-labeling strategy was devised in which neurons that had been axotomized by a spinal cord injury in the early 1990s. The report that cut axons of retinal ganglion cell neurons grew into a peripheral nerve graft placed 1–6 weeks after optic nerve injury provided the first convincing demonstration of regeneration by chronically injured neurons (Thanos and Vanselow, 1989). The propensity of retinal ganglion cell neurons to regenerate progressively decreased as the postinjury period before transplantation increased, with optimal regrowth occurring with a delay of less than 3 weeks between injury and transplantation. In our laboratory a double-labeling strategy was devised in which neurons that had been axotomized by a spinal cord injury in the early 1990s. The report that cut axons of retinal ganglion cell neurons grew into a peripheral nerve graft placed 1–6 weeks after optic nerve injury provided the first convincing demonstration of regeneration by chronically injured neurons (Thanos and Vanselow, 1989). The propensity of retinal ganglion cell neurons to regenerate progressively decreased as the postinjury period before transplantation increased, with optimal regrowth occurring with a delay of less than 3 weeks between injury and transplantation. In our laboratory a double-labeling strategy was devised in which neurons that had been axotomized by a spinal cord injury

Present information indicates that for some types of neurons therapy is most effective after a short delay, whereas for others the extent of growth is similar even if treatment is delayed for weeks to months. For example, FSC tissue grafted into a contusion site 10 days after injury survives, integrates with the host spinal cord, and promotes partial recovery of certain gait parameters indicative of a return of fine motor behavior (Stokes and Reier, 1992). Axons of fetal serotonergic neurons grow to a comparable extent when the neurons are grafted caudal to a spinal transection at the time of injury or 7–10 or 30 days later, suggesting that the host spinal cord remains receptive to growing axons for extended periods after injury (Reier et al., 1992). Coelurospinal and primary afferent axons grow robustly into fibroblasts genetically modified to express nerve growth factor whether the transplants are grafted into a dorsal hemisection site after a delay of 1–3 months or acutely (Grill et al., 1997). In contrast, the extent of regenerative sprouting of CST axons caudal to a thoracic dorsal hemisection lesion elicited by placing NT-3 saturated gel foam at the lesion site and hybridoma cells releasing IN-1 antibodies into the cerebral cortex differed depending on whether treatment was initiated 2 or 7 weeks after injury (von Mayenburg et al., 1998). Axons extended in spinal cord beneath the lesion in both groups, but their number and length significantly decreased with a longer delay before intervention. Studies comparing growth into transplanted bone marrow stem cells (Hofstetter et al., 2002) or FSC tissue grafts (Coumans et al., 2001) placed acutely or 1–2 weeks after injury found that the relatively short delay enhanced host axon growth into and through the transplants. Axon growth into FSC transplants decreased with a longer delay (4 weeks) before grafting, however, and axons did not grow through transplants under any of these conditions without supplementary neurotrophic factors. These studies support the idea that regeneration may be most extensive following a short delay between injury and treatment, but other data (Fig. 2) indicate that a substantial regenerative response is possible after a delay of several months (Grill et al., 1997; Jin et al., 2000, 2002) and even 1 year after spinal cord injury (Kwon et al., 2002a).

Attempts to repair the chronically injured spinal cord have applied transplantation procedures similar to those that achieved some success after acute injury. In nearly all cases some type of tissue or synthetic matrix has been grafted into the lesion site and most have included exogenous trophic factors to enhance regeneration (Fig. 1). The general outcome has been regrowth of both descending and ascending axons within the graft, regardless of the interval between injury and transplantation. The one study that reported robust axon regeneration into the spinal cord beyond the transplant found maximum growth after a 2-week delay (Coumans et al., 2001). This investigation also indicated that the extent of behavioral recovery exceeded that of regeneration, suggesting that specific reconnection across a lesion is not necessary for some level of functional recovery. Our own studies using fibroblasts genetically modified
to secrete BDNF made similar observations (Jin et al., 2000, 2002); sparse regeneration of bulbospinal axons into the spinal cord caudal to the grafts could not account for the observed recovery of bilateral fore limb use after a cervical hemisection.

Reports of recovery range from the return of more normal fore limb or hind limb use (Coumans et al., 2001; Jin et al., 2000, 2002), to significantly increased open field rating scores (Lu et al., 2002; Woerly et al., 2001). None of these studies of chronic injuries observed a good correlation between the functional measures used for rating behavioral outcome and axonal regrowth/synaptic connectivity across the lesion. It is possible that, as after some instances of acute injuries, recovery is more closely related to sprouting of uninjured axons than to regeneration. For example, spontaneously sprouting ventral corticospinal tract axons (Weidner et al., 1999) and corticospinal (Thallmair et al., 1998) and rubrospinal axons (Raineteau et al., 1999) sprouting in response to neutralization of Nogo-A likely contribute to recovery of fine motor performance after specific tract lesions. Few studies have examined whether sprouting of uninjured axons contributes to recovery after chronic injuries. However, preliminary results demonstrate that undamaged vestibulospinal axons grow into NT-3 and BDNF-expressing fibroblasts transplanted into a contralateral cervical hemisection 5 weeks after the initial injury (Tobias et al., 2001). These fibroblast transplants also induce an increase in GAP-43 expression in uninjured corticospinal axons, suggestive of sprouting. The sprouting is associated with recovery of sensorimotor function in the absence of regeneration of any specific descending pathway.

Additional investigations using electrophysiological techniques are necessary both to document recovery and to clarify the mechanisms by which recovery occurs. For example, electromyographic recordings from hind limb muscles, showing an increase in amplitude and decreased overlap of flexor and extensor muscle activity, have documented spontaneous recovery after a thoracic dorsal hemisection injury (Kaegi et al., 2002). Magnuson and colleagues have shown that improvements in open field test scores following spinal cord contusion or kainic acid injection correlate with changes in the latency of transcranial magnetic motor evoked potentials, suggesting that descending motor pathways contribute to the recovery (Magnuson et al., 1999; Loy et al., 2002). Transcranial magnetic motor evoked potential appears to offer a relatively straightforward, noninvasive technique that can be easily replicated within different laboratories. Intracellular and extracellular recording from transplant neurons and adjacent host ventral motoneurons has also been used to demonstrate that dorsal roots that have

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**Fig. 2.** Conditions that influence regeneration by chronically injured neurons. A variety of factors have positive or negative effects on axonal regrowth by chronically injured neurons. In this illustration the balance is shifted toward regeneration based upon the evidence that a combination of interventions have been shown to blunt some of the adverse effects of glial scarring, axonal reinjury, and so on. There remain several unknowns centered above the injured neuron that can affect this balance and it is the goal of future research to determine how these unknowns can be modulated to promote axonal regeneration. There also is a cautionary note that not all neurons will respond to the same intervention to the same extent, suggesting that individual treatment programs for different types of neurons may need to be devised.
regenerated into FSC transplants establish synapses that are functional by conventional electrophysiological criteria (Houle et al., 1996; Itoh et al., 1996).

Combination therapies that include transplants have rescued axotomized neurons in chronically injured animals and promoted axon regeneration and recovery of general and more specific behavioral tasks (Fig. 2). Whether comparable results will be attained in the treatment of human chronic spinal cord injury remains to be demonstrated. Intraspinal transplants have been shown to be feasible in chronically injured patients suffering from the expansion of cystic cavities (posttraumatic syringomyelia) (Reier et al., 2001). In many of the seven cases reported, fetal spinal cord transplants reduced the preoperative cavitation observed by magnetic resonance imaging without producing adverse neurological signs or symptoms.

**Neuronal response to a second injury**

Studies designed to enhance chronically injured axon regeneration emphasize the importance of removing glial scar tissue to optimize integration of host and graft tissues (Grill et al., 1997; Houle, 1991). Because sectioned supraspinal axons remain relatively close to the lesion (see above), removal of scar tissue will subject many of them to a second injury. The observation that the regenerative response of some supraspinal neurons diminishes with an increased interval between initial injury and intervention (Houle and Ye, 1997) suggests that neurons have become more sensitive to a second injury. Thus, resection of scar tissue, while necessary to expose axons to beneficial factors and/or cells placed into a lesion site, may preclude an effective regenerative effort. Following reinjury 4 weeks after an initial cervical hemisection, expression of GAP-43 and βII-tubulin mRNA in Red nucleus neurons increases more rapidly (6 h) than after an acute injury (24–72 h) (Storer and Houle, 2002). This response contrasts with the absence of amplified expression of regeneration associated gene mRNA following a second lesion of the facial nerve (Fernandes and Tetzlaff, 2001). Also suggesting an initially robust metabolic response is the absence of Red nucleus neuron shrinkage during the first 7 days after reinjury (Storer and Houle, 2002). Another indicator of the neuronal response to reinjury is the expression of the inducible transcription factor, c-Jun, which is involved in both neurodegeneration and neuroprotection. Acutely injured Red nucleus neurons initially increase their expression of c-Jun, but there is a significant decrease between 4 and 8 weeks (Houle et al., 1998). A second injury 4 weeks after the initial injury combined with treatment with CNTF significantly increases the number of neurons expressing c-Jun. The response to this combination of second injury and trophic factor treatment correlates with the known neuroprotective and regeneration promoting effects of exogenous CNTF treatment. In a separate experiment to test if a second injury would affect neuron survival, neurons were labeled with True Blue at the time of the first injury (C3 hemisection), reinjured after 4 weeks, and counted 4 weeks later (Houle and Ye, 1997). The number of labeled neurons in the Red nucleus and in the lateral vestibular nucleus decreased significantly after a second injury, but treatment with CNTF prevented the neuron loss. CNTF treatment also rescued neurons reinjured 8 weeks after the initial injury, but delays of 14 or 22 weeks between the two injuries led to significant neuron death that could not be prevented by any of the factors tested (CNTF, BDNF, or FGF2). The demonstration of neuronal cell death following a second injury as long as 1 year after the initial injury illustrates the continued susceptibility of neurons to further perturbation (Kwon et al., 2002b). These results highlight the vulnerability of chronically injured neurons, but also demonstrate the potential for maintaining a relatively stable number of reinjured neurons by a straightforward, short-term application of trophic factors to the lesion site immediately after a second injury.

**Changes in the lumbar cord may facilitate recovery**

Cervical and thoracic spinal cord injuries spare most caudal ventral horn neurons (Kaelan et al., 1988; Bjugn et al., 1997) and produce alterations in lumbar segments that may contribute to spontaneous recovery and be exploited therapeutically to enhance recovery after chronic injuries. One alteration that may serve as a therapeutic target is upregulation of receptors for neurotransmitters that initiate and/or cells placed into a lesion site, may preclude an effective regenerative effort. Following reinjury 4 weeks after an initial cervical hemisection, expression of GAP-43 and βII-tubulin mRNA in Red nucleus neurons increases more rapidly (6 h) than after an acute injury (24–72 h) (Storer and Houle, 2002). This response contrasts with the absence of amplified expression of regeneration associated gene mRNA following a second lesion of the facial nerve (Fernandes and Tetzlaff, 2001). Also suggesting an initially robust metabolic response is the absence of Red nucleus neuron shrinkage during the first 7 days after reinjury (Storer and Houle, 2002). Another indicator of the neuronal response to reinjury is the expression of the inducible transcription factor, c-Jun, which is involved in both neurodegeneration and neuroprotection. Acutely injured Red nucleus neurons initially increase their expression of c-Jun, but there is a significant decrease between 4 and 8 weeks (Houle et al., 1998). A second injury 4 weeks after the initial injury combined with treatment with CNTF significantly increases the number of neurons expressing c-Jun. The response to this combination of second injury and trophic factor treatment correlates with the known neuroprotective and regeneration promoting effects of exogenous CNTF treatment. In a separate experiment to test if a second injury would affect neuron survival, neurons were labeled with True Blue at the time of the first injury (C3 hemisection), reinjured after 4 weeks, and counted 4 weeks later (Houle and Ye, 1997). The number of labeled neurons in the Red nucleus and in the lateral vestibular nucleus decreased significantly after a second injury, but treatment with CNTF prevented the neuron loss. CNTF treatment also rescued neurons reinjured 8 weeks after the initial injury, but delays of 14 or 22 weeks between the two injuries led to significant neuron death that could not be prevented by any of the factors tested (CNTF, BDNF, or FGF2). The demonstration of neuronal cell death following a second injury as long as 1 year after the initial injury illustrates the continued susceptibility of neurons to further perturbation (Kwon et al., 2002b). These results highlight the vulnerability of chronically injured neurons, but also demonstrate the potential for maintaining a relatively stable number of reinjured neurons by a straightforward, short-term application of trophic factors to the lesion site immediately after a second injury.

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strength of the monosynaptic Ia stretch reflex (reviewed by Wolpaw and Tennissen, 2001). The training, which appears to depend on the integrity of the corticospinal tract (Chen and Wolpaw, 2001), elicits changes in motor neuron membrane properties and synaptic composition on the side of the trained reflex (reviewed by Wolpaw and Tennissen, 2001). The spinal cord can also acquire more complex motor behaviors. Daily training modifies the residual pathways that control hind limb flexion and extension and enables cats with complete spinal cord transections at a low thoracic level to step or stand on a moving treadmill (reviewed by Barbeau and Rossignol, 1987; Lovely et al., 1990). The effect is activity specific because cats that are trained to stand do not acquire the ability to step and cats trained to step do not acquire the ability to stand. Training also produces activity-specific biochemical changes in local inhibitory pathways (Tillakaratne et al., 2002). Levels of the GABA synthesizing enzyme GAD 67 and its mRNA increase following transection in the lumbar cord of untrained cats and of cats trained to stand, whereas step training returns GAD 67 levels toward normal. These results indicate that diverse patterns of proprioceptive and cutaneous input from the leg produce specific effects on the intraspinal synthesis of a major inhibitory neurotransmitter and suggest that an appropriate training regimen can promote recovery in part by modulating neurotransmitter expression in this pathway.

The application of similar training principles provides one of the most promising approaches to the rehabilitation of patients with longstanding spinal cord injuries. In a particularly encouraging report, patients with incomplete spinal cord injuries were trained to walk on a treadmill for 30 min once or twice a day, 5 times/week, with body weight support (BWS) provided by a harness and passive movements of the limbs provided by therapists if necessary (Wernig et al., 1999). Training began from 5.5 months to 15 years after injury, when the patients had completed standard rehabilitation therapy. Of 25 patients who were confined to a wheelchair, 20 became independent walkers after a mean of 12 weeks of BWS therapy and only one of these patients failed to maintain improvement when reassessed from 0.5 to 6.5 years later. Because the patients were motor incomplete, the effects of the BWS training may have been mediated at spinal or supraspinal levels. A multicenter prospective trial already in progress will test the efficacy of BWS training in larger numbers of patients with complete and incomplete injuries.

We anticipate that treatments based on additional synergies between transplantation, pharmacological, and rehabilitative training techniques will eventually improve recovery after chronic spinal cord injury. For example, we have found that fetal tissue transplantation combined with hind limb exercise 1 month after a complete transection of adult rat spinal cord leads to significant changes in atrophied muscles (Peterson et al., 2000). This includes a return to near normal size of affected myofibers, reexpression of specific myosin heavy chain isoforms, and a return of normal levels of succinate dehydrogenase. The combination of these interventions was significantly more effective than either alone, suggesting a synergistic action between exercise and transplantation.

**Concluding remarks**

With one exception (Coumans et al., 2001), the current experimental treatments of chronic spinal cord injury have not produced lengthy regeneration of adult CNS axons into host spinal cord when treatment has been delayed for 4 weeks or longer. Even then, regeneration depended upon a treatment paradigm that included supraphysiological exogenous neurotrophic factor support. Supraphysiological quantities of BDNF have also allowed bulbospinal neurons to regenerate into delayed grafts of peripheral nerve (Kwon et al., 2002a; Jin et al., 2000) and transplanted adult DRG neurons have regenerated for long distances through chronically degenerated host spinal cord (Davies et al., 1999). However, the combined impediments posed by the diminished regenerative capacity of chronically injured CNS neurons and the unfavorable environment of the chronically injured adult CNS have so far been insuperable. Promising interventions that have enhanced axon growth after acute injuries remain to be tested in chronic injuries. These include the administration of inosine (Benowitz et al., 1999) and the intracellular injection of cyclic AMP (Neumann et al., 2002; Qiu et al., 2002), new treatments that target the neuron’s intracellular metabolic response. Other novel treatments have targeted the extraneuronal milieu. The infusion of chondroitinase ABC at the time of cervical dorsal column section degrades chondroitin sulfate proteoglycans at the lesion site and promotes axon regeneration and recovery of fore limb locomotor performance (Bradbury et al., 2002). However, the collective evidence from studies of chronic injuries reinforces the idea that strategies that are successful after acute injuries are not sufficient for chronic injuries and further adjustments or modifications are necessary. The most promising treatments will therefore be those that combine efforts to enhance regeneration with strategies that promote recovery through other mechanisms, including rehabilitative training and pharmacological modulation of neurotransmitters. The currently available treatments, particularly those designed to enhance regeneration, are more likely to be successfully applied to patients with fresh injuries. The challenge for basic scientists is to identify features of successful acute interventions that can transcend the blockades imposed by a long-term injury situation. To facilitate implementation of these therapies it is the task of clinicians to identify those patients with no hope of useful recovery in the early days after injury so that treatments can begin as soon as possible.
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