NEUROSCIENCES

Advances in Spinal Cord Repair Techniques

IVÁN SOSA, MD*; ONIX REYES, MD†; DAMIAN P. KUFFLER, PhD‡

Daily US accidents result annually in over 20,000 cases of traumatic spinal cord injury associated with complete and permanent paraplegias and quadriplegias frequently associated chronic pain. This amounts to new annual health care a costs of $3.2 billion, and a total annual cost for all such individuals in the US of $96 billion. Tens of thousands of additional people suffer lesser degrees of permanent debilitating lost spinal cord function. To help these people recover neurological functions, and simultaneously reduce the enormous suffering, and the associated medical expenses, requires developing techniques that induce the regeneration of lesioned adult human spinal cord axons. A number of techniques lead to varying degrees of axon regeneration and neurological recovery in the rat, but the recovery is invariably limited. While other approaches show potential, they have not led reliable neurological recovery. Most spinal cord repair techniques cannot be applied clinically because they require materials that are not FDA-approved. However, several FDA-approved materials are available that hold great promise for inducing axon regeneration, especially when used simultaneously. Here we review efforts to induce the regeneration of spinal cord axons, how what is known about promoting regeneration of axons across peripheral nerve gaps may be applied to repairing spinal cord lesions, and finally, how several readily available materials may induce axons to regenerate in the spinal cord and restore neurological function.

Each year in the United States, more than 20,000 individuals become quadriplegic or paraplegic. In addition, there are currently in the United States over 300,000 people suffering severe neurological deficits due to spinal cord injuries. Even minor neurological improvements would be of enormous benefit in those individuals. Although physical therapy and mechanical devices improve these individuals those life styles, no techniques induce any neurological recovery.

There appears to be a general-consensus that to induce neurological recovery following a spinal cord lesion requires changing the cellular environment of the injured spinal cord from one that is inhibitory to axon regeneration, to one that is permissive to, and promotes axon regeneration. The steps in this process are to eliminate or neutralize the various factors associated with activated astrocytes and oligodendrocytes that inhibit axon regeneration, eliminate scar tissue, provide neurotrophic and other factors that induce axons regeneration, and finally, make the axons receptive to the regeneration-inducing factors

Using several of these approaches in animal models, lesioned adult rat spinal cord axons regenerate across a lesion site and into the intact spinal cord where they bring about limited neurological recovery. However, none of these techniques has been applied to a large animal model, or can be used clinically. In addition to the methods just mentioned, we believe that neurological recovery can be achieved if one were to apply to the injured spinal cord the physiological mechanisms that are used by the adult human peripheral nervous system to repair itself.

We will first discuss the basis for the failure of spinal cord axons to regenerate, and the success of axon regeneration in the peripheral nervous system. Finally, we will discuss an approach that mimics the peripheral nerve repair mechanism that can be applied clinically to a spinal cord lesion.

*Section of Neurological Surgery, Medical Sciences Campus, University of Puerto Rico, San Juan, P R, †Doctor's Hospital, Manati, PR, ‡Institute of Neurobiology, Medical Sciences Campus, UPR, San Juan, PR\

Address correspondence to: Damien Kuffler, PhD, Institute of Neurobiology, 201 Blvd. Del Valle, San Juan, PR 00901,Tel/fax: 787-721-1235, e-mail: dkuffler@hotmail.com

Introduction

Why is there regeneration and neurological recovery in the PNS but not the CNS?. During development and regeneration of the adult nervous system, axons are promoted to regenerate and navigate to their specific targets through a complex molecular environment.

Gradients of target-derived factors both attract and repel regenerating axons (2, 31, 68, 82, 89, 116, 132, 156, 180). GTPases of the Ras family transduce extracellular signals into responses that lead to directed neurite outgrowth (59) mediated by trkA receptors (58). Sprouting of axon collateral branches is important for the establishment and refinement of neuronal connections, during both development and regeneration, and neurotrophins provide local cues to stimulate the formation of collateral axon branches (59). However, at birth, once all required synaptic connections have been established, the CNS changes so that it inhibits virtually all axon regeneration following injury. On the other hand, the PNS remains permissive to and promoting of axon regeneration.

Promoting PNS regeneration. Differential screening of cDNA libraries of crushed and non-injured rat sciatic nerve, consisting predominantly of Schwann cells, show that more than 60 genes and their products have a specific temporal pattern of up and down regulation following peripheral nerve lesion (14, 62, 182). Clearly some, but not all, of these genes are for factors important to promoting PNS axon regeneration (157).

CNS neurons are sensitive to, and respond to, the neurotrophic factors up-regulated following trauma to the PNS. However, following CNS trauma few neurotrophic factors are synthesized and released within the CNS (22, 46, 71, 79), or they are not in sufficient amounts to induce axon regeneration. But, CNS trauma also induces glial cells (analogous to PNS Schwann cells) to up-regulate factors that inhibit axon regeneration (63). Although axons within the CNS do not regenerate, the same axons regenerate extensively when provided a PNS environment (11, 34, 47, 140, 155, 166). Thus, it is the cellular environment of the CNS that inhibits axon regeneration, not the ability of the axons to regenerate (11, 23, 47).

Regeneration Inhibiting Molecules

Oligodendrocytes. Inhibition of motor axon regeneration after adult mammalian CNS injury is largely attributable to the Nogo protein associated with oligodendrocytes and their myelin (25-27, 52, 64, 138, 146-148). However, there are two other myelin-associated inhibitors of regeneration: myelin-associated glycoprotein (MAG) (112, 119), and oligodendrocyte myelin glycoprotein (OMgp) (165). MAG, OMgp and one Nogo domain, Nogo66, interact with the same receptor, the Nogo receptor (39, 56, 98, 165). In addition, there is the family of chondroitin sulphate proteoglycans (CSPGs) that inhibit axon regeneration into and within the spinal cord (152, 153).

Neutralizing the Nogo receptor in the injured spinal cord by means of the antibody Nogo-A leads to axons regeneration by eliminating the inhibitory influence of Nogo (73, 83, 94-96, 149-151). Recently it has been demonstrated that neutralizing Nogo with the antibody Nogo-A enhances axon regeneration by the up-regulation of NF-68, MAP-2 and MAP-5 in the lesioned spinal cord axons (Craveiro et al., 2004).

Astrocytes. Neurons grafted atraumatically into adult rat white matter tracts regenerate their axons, while neurons grafted into white matter post trauma do not regenerate (35, 36). Thus, astrocytes do not inhibit axon growth until trauma makes them reactive (35, 36).

The dorsal root entry zone (DREZ) forms the junction between the dorsal roots of the PNS and the spinal cord (CNS). Reactive astrocytes of the DREZ prevent lesioned primary sensory axons from elongating into the DREZ (35, 45, 54, 60, 99, 111, 133). This is due to the impenetrable membrane bound molecular barrier of chondroitin sulfate proteoglycan (CSPG) (5, 21, 39, 57), composed of cytotactin/tenascin (CT) and chondroitin 6 sulfate containing proteoglycans (C 6S PG) (133), which also inhibits Schwann cell invasion of the CNS (60).

Glial Scars Inhibit Axon Regeneration. CNS injury induces reactive astrocytes to form regeneration inhibitory astrocytic scars that form a mechanical barrier through and around the tissue in which axons cannot regenerate (35, 36, 61, 166). Further, the neurites that fail to grow become enclosed by CSPG (35, 133).

Mechanisms for Promoting Regeneration into and within the CNS. Mechanisms that induce axon regeneration into and within the adult rat CNS include: (1) antibodies that bind to and neutralize the inhibiting factors, (2) enzyme digestion of the factors that inhibit regeneration, (3) down-regulating the synthesis of the regeneration-inhibiting factors, (4) inducing axons to ignore the regeneration inhibiting signals, and (5) overwhelming the inhibition with regeneration-promoting factors.

1. The inhibition of axon regeneration of Nogo can be neutralized by the Nogo-A antibody that binds to its functional site (145). When Nogo is blocked by the Nogo-A antibody axons can grow over oligodendrocytes and regenerate through the lesioned cortico-spinal tract (4, 19, 26, 145, 160, 177)
2. The glycosaminoglycan (GAG), such as chondroitin sulfate proteoglycan (CSPG), associated with activated astrocytes inhibits axon regeneration. However, it can be eliminated by digestion with the enzyme chondroitinase (C-ABC) making astrocytes permissive to axon regeneration (35, 111, 133, 183). If a large bolus of C-ABC in infused into a rat spinal cord lesion site, the injured axons can regenerate across the lesion and into the injured spinal cord (16). Further, the

infusion of C-ABC into the CNS induces uninjured axons to extend collateral sprouts that innervated denervated regions of the CNS (161, 164). Metalloproteases (MMPs) are another method for eliminating GAG inhibition of axon regeneration. Neurons synthesize and transport MMPs to their growth cones, where they are released and inactivate CSPG (49, 91, 159, 176, 184, 185). This action exposes regeneration-promoting laminin that is otherwise masked by CSPG, thereby converting the substrate from one that inhibits to one that promotes axon regeneration. However, most growth cones of adult neurons lack sufficient amounts of MMPs to digest all the regeneration-inhibiting factors in the CNS, and thus their ability to regeneration remains blocked.

3. The synthesis and expression of CSPG is up-regulated by Schwann cells following peripheral nerve denervation (184). However, intramuscular injection of b-xyloside blocks all synthesis of CSPG, and within 5 days the existing on CSPG on the Schwann cell is turned over and internalized (Muir et al., 1998), causing the Schwann cells to become CSPG-free, leading to an enhanced rate of axon regeneration (184).
4. The elevation of the concentration of neuronal cAMP causes the axons of these neurons no longer to be inhibited by MAG or myelin (24, 156) and allows them to regenerate within the lesioned spinal cord (125, 137, 139).

   cAMP can be elevated in neurons by application of the membrane diffusible analog, dibutyryl-cAMP (db-cAMP) (1-5 mM) (24). However, the influence of cAMP to ignore the inhibitory factors is enhanced if the neurons are pretreated, "primed", with the neurotrophic factors BDNF, NGF, and GDNF (200 nM) (24).

   The Ras-extracellular signal-regulated kinase (Erk) pathway is activated by neurotrophins that play a role in survival and differentiation (81). In non-neuronal cells, activated Erk phosphorylates and inhibits a subfamily of the group of enzymes that degrade cAMP, phosphodiesterases 4 (PDE4s) (3, 69, 108). The PDE4 subfamily are cAMP specific represents the most abundant PDEs in neuronal tissue (70%) (77). Neurotrophins elevate cAMP by an Erk-dependent inhibition of PDE, and a threshold of cAMP-PKA activation is required for both BDNF and db-cAMP to overcome inhibition by MAG.
5. Receptors to BDNF, NT-3 and CNTF (22, 46, 71), and the neurotrophins BDNF and NT-3 (63) are present in the CNS. This suggests that an insufficient concentration of these factors limits CNS regeneration and that elevating their concentration would induce regeneration. NGF (50, 72, 128, 130), and NT-3 (185) each induce CNS axon regeneration. However, combinations of BDNF, NT-3, CNTF, and NT-4 (15, 17, 18, 70, 71, 75, 80, 129, 142, 144, 163, 173), induce more extensive CNS regeneration than any neurotrophic factor alone. But, axon regeneration still remains limited, possibly due to the lack of using the correct combination of factors, the lack of appropriate substrate bound factors, or the presence of additional regeneration-inhibiting factors.

Schwann cells release most of the necessary neurotrophic and substrate bound factors needed to permit, promote, and direct axon outgrowth (13, 38, 59, 132, 140, 171, 180). Therefore, Schwann cells have been proposed as the ideal candidates for implanting into the CNS to promote axon regeneration. Unfortunately, once implanted into the CNS, Schwann cells do not induce axon regeneration. This appears to results from the CNS environment influencing the Schwann cells so they no longer release neurotrophic factors (50, 84, 85, 97, 118, 131, 140). An alternative approach is to implant a graft, such as embryonic spinal cord tissue, into the spinal cord lesion site and infuse the graft with Schwann cell-released factors, such as the neurotrophins BDNF and NT-3. Such an infusion induces more extensive axon regeneration within the CNS lesion than is induces by the graft alone (20, 162, 174, 175).

Promoting axon outgrowth in vitro and in vivo. As indicated earlier, denervated Schwann cells up-regulate the synthesis and release of a host of factors. Among these are the extracellular matrix bound protein laminin and the proteoglycan CSPG that inhibits axon outgrowth, and diffusible neurotrophic factors that promote axon regeneration. Therefore, whether Schwann cells induce or inhibit axon regeneration depends on the balance between their axon regeneration promoting and inhibiting factors. The diffusible regeneration-promoting factors are predominantly diffusible (86, 88-90). This physiological cocktail of Schwann cell-released regeneration-promoting factors can be harvested by placing a lengths of teased peripheral nerve in culture medium and then collecting the medium (peripheral nerve conditioned medium, CM) after 5 days (38).

Adult frog, rat, and human dorsal root ganglion (DRG) neurons in vitro all respond to these factors by extending processes 10-fold longer than those of control neurons (38, 90, 158). The combination of factors also reduces the number of processes from 4 to 2, and causes the processes to be straight with little branching, compared to curvy with many branches as seen for control neurons (38, 90, 158).

When the factors in CM are presented as a

concentration gradient to growth cones of adult frog and rat sensory and motor neurons in vivo, the growth cones "read" the direction of the concentration gradient of factors. As a result the growth cones turn and they regenerate up concentration gradients even several cm's in length (90, 180).

Axon Regeneration across Peripheral Nerve Gaps. Axon cannot regenerate across a peripheral nerve gap longer than 3 mm because no scaffold forms in the gap. Without a scaffold the axons have nothing on which to regenerate across the nerve gap (87, 103-107, 167-170). To induce axon regeneration in the case of a peripheral nerve gaps longer than 3 mm, when the ends of the nerve can not be anastomosed, a conduit must be created across the gap to support axon regeneration.

Clinically, and in animal models, peripheral nerve gaps up to 8 cm can be bridged by autologous vein (30) and arterial grafts, but they lead to minimal neurological recovery (1). Greater numbers of axons regenerate across nerve gaps through autologous nerve grafts harvested from the cutaneous saphenous or sural nerves, (12, 76, 105, 117). Autologous (allogeneic / homogenetic) nerve grafts have been studied extensively in animal models (53, 74, 178). However, such grafts induce only limited numbers of axons to regenerate, and only across gaps of 1.5-2 cm in length, while for gaps greater than 2 cm neurological recovery is extremely limited (154). Although sensory nerve grafts remain the standard clinical repair technique they induce limited neurological recovery (6, 33, 121).

For the repair of the lesioned spinal cord, biodegradable conduits or artificial dura are critical to inducing axon regeneration and neurological recovery when the normal dura is damaged (126, 127).

Empty and filled tubes

Empty nerve tubes. Within hours of implanting an empty tube, it becomes filled with a fluid enriched with neurotrophic factors, extracellular matrix and other molecules which exert neurotrophic (100-102), and neurotropic influences (134). During day 3-7 the fluid is replaced by an acellular fibronectin positive, laminin negative fibrous matrix, which is critical to Schwann cells proliferation and migration into the tube (51, 92, 93, 169, 170). Fibroblasts and Schwann cells migrate from both nerve stumps within 2 weeks of implantation (65, 143, 172, 174, 179). These tubes promote the regeneration of axons across gaps only up to about 1-cm in length.

3-Dimensional matrix filled tubes. Pre-filling tubes grafted into nerve gaps with various materials improve the number of axons that grow across nerve gaps. Gelfoam, (Pharmacia & Upjohn), a collagen matrix (168), and artificial fibrin sponge (Gelaspon) (41-44) are also suitable matrices for enhancing the migration of Schwann cells (43) which promote the subsequent in-growth of axons (48). However, in spite of these approaches axons do not regenerate through tubes longer than 2 cm.

Recently a novel combination of materials has been shown to induce axons regeneration and neurological function following the lesion of the adult rat spinal cord. A semi-permeable polyacrylonitrile/polychloride copolymer guidance channel was used as a conduit to bridge a 4-mm gap in adult rat spinal cords. The channel was filled with a 3-dimensional Matrigel matrix, Schwann cells, olfactory-ensheathing glial grafts and the enzyme C-ABC. This combination induced axon regeneration entirely across the gap and into the intact spinal cord leading to functional walking of the animals (55).

Fibrin glue scaffold for peripheral nerve repair. Fibrin glue is extensively used to repair lesioned peripheral nerves repair and sectioned central nervous system tissue (28, 29, 37, 66, 75, 115, 141). Fibrin is also extensively used to anastomose lesioned peripheral nerves (6-10, 67, 109, 110, 113, 114, 122-124, 136, 181). In fact, fibrin glue is significantly better for anastomosing peripheral nerves than sutures (9, 32, 78, 109, 120, 122, 123, 135). Fibrin glue is both faster and easier to use than sutures, leads to more successful neurological recovery than sutures, and causes fewer complications, such as infections and inflammation (9, 32, 78, 109, 120, 122, 123, 135).

Fibrin as a scaffold within peripheral nerve gaps does not lead to the reliable promotion of axon regeneration across long gaps, probably because it requires interactions with additional factors. Although fibrin is part of the physiological mechanism by which the body attempts to promote axons to regenerate across a peripheral nerve gap, physiologically fibrin does not act alone. Rather, fibrin acts in combination with platelets, as platelet-rich fibrin (33, 37, 40, 120). The platelets, rich in factors that promote nerve regeneration and wound healing, release their factors slowly over about 4 day, which enriches the fibrin with axon regeneration-promoting factors. Thus autologous platelet-rich fibrin promotes excellent axon regeneration (8, 29, 33, 67, 135). Platelet-rich fibrin may be even more effective than pure fibrin in inducing axon regeneration across a spinal cord lesion.

Promoting axon regeneration across long peripheral nerve gaps. By replicating the physiological mechanism of nerve repair in vivo, we developed a technique that induces axons to regenerate across 4-cm long adult rat peripheral nerve gaps (unpublished data). For a nerve gap bridged with an empty silicon tube, 25% of the axons that regenerated out of the central nerve stump regenerated entirely across the gap. Filling the bridging tube with a

fibrin matrix increased the number of axons that regenerated entirely across the gaps by 50%. Creating a concentration gradient of Schwann cell CM cross the nerve gap caused a 2-fold increase in the number of axons that regenerated entirely across the nerve gap. If the gap was infused simultaneously with insulin-like growth factor and tumor growth factor, instead of CM, the number of regenerating axons was also increased. These results suggest that infusing additional combinations of factors would further increase the number of axons that regenerate out of the central nerve stump and across the nerve gap.

Techniques for inducing Clinical Neurological Recovery following Paraplegia. We hypothesized that application of the technique that induced the axon regeneration across a long peripheral nerve gap in our animal model will also induce axon regeneration into and across a spinal cord lesion. However, as indicated previously, many of the materials we applied to induce axon regeneration in the adult rat cannot be applied clinically. Therefore, we must start working with materials that are approved for clinical use, and that are as similar as possible to those we used in the animal model.

To test our hypothesis clinically we can only work with patients who are paraplegics and have suffered a complete anatomical spinal cord transection. If all the spinal cord tissue has been destroyed then any observed neurological recovery can only have developed by axon regeneration across the spinal cord lesion their developing synapses on their appropriate targets in the opposite end of the spinal cord. The development of sensory and motor will indicate that axons have regenerated in both directions across the spinal cord gap.

Clinical tests are presently underway to determine whether bridging a spinal cord gap with a bioresorbable tube filled with a 3-dimensional matrix rich with neurotrophic and wound healing factors induces neurological recovery following a complete anatomical spinal cord transection.

Resumen

Diariamente en EU ocurren accidentes de personas que resultan en 20,000 casos anuales de traumas en la espina dorsal causando completa y permanente paraplegía o cuadraplegía, condiciones asociadas a dolores crónicos. En EU el costo del cuidado médico de estos pacientes suma a un total de $3.2 billones por individuo y un costo total anual de $96 billones. Adicional a estos casos, miles de personas sufren en menor grado de otras degeneraciones en la espina dorsal que resultan en la debilitación permanente de sus funciones. Para ayudar a estas personas a recuperar sus funciones neurológicas, reducir el sufrimiento y los costos médicos asociados, se requiere del desarrollo de nuevas técnicas que induzcan regeneración de los axones en el área afectada de la médula espinal en adultos. Hay varias técnicas que han logrado en cierto grado inducir la regeneración de axones y una recuperación neurológica limitada en ratas. Otros métodos existentes muestran un buen potencial pero no han obtenido una recuperación neurológica confiable. La mayoría de las técnicas para reparar lesiones en la médula espinal no se pueden aplicar clínicamente porque requieren la utilización de materiales no aprobados por la FDA. A pesar de esto, hay materiales aprobados por la FDA que tienen el potencial de ser utilizados como agentes para inducir regeneración de axones, especialmente si se usan simultáneamente.

Nuestro objetivo es hacer una revisión de los diferentes métodos desarrollados para inducir regeneración de los axones en la espina dorsal; segundo cómo aplicar el conocimiento existente, sobre regeneración de los axones a través de lesiones en el sistema nervioso periferal, para reparar lesiones en la espina dorsal; y por último, analizar ciertos materiales disponibles para inducir la regeneración de axones en la médula espinal y restaurar las funciones neurológicas.

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