REVIEW ARTICLE

Promoting Neurological Recovery following A Traumatic Peripheral Nerve Injury

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If a peripheral nerve is crushed, or if the nerve is cut and the ends sutured together soon after the lesion (anastomosed), neurological recovery is good. When a length of a peripheral nerve is destroyed, and anastomosis is not possible, the standard surgical repair technique is to graft a length/s of sensory nerve from the patient, into the gap. For gaps <2 cm neurological recovery is moderate, for gaps 2-4 cm recovery is generally poor, and for gaps >4 cm recovery is limited to non-existent. The limited recovery is because sensory nerves act as passive scaffolds for axon regeneration and do not actively promote axon regeneration. However, such grafts remain the "gold standard" for nerve repairs. New techniques are required that induce improved neurological recovery. This paper reviews current clinical and basic research techniques for inducing neurological recovery following traumatic peripheral nerve injuries.

Key Words: Nerve gaps, Nerve lesion, Neurological recovery, Axon regeneration

Interventions to Repair Peripheral nerve Injuries

Nerve Crush. Within several days of crushing a peripheral nerve, the injured axons begin to regenerate through their distal pathway until they reach their original targets with which they restore neurological function. The larger the number of axons that regenerate through the distal nerve, the greater the extent of neurological recovery (31, 67, 85). The number of axons that regenerate is influenced by the physiological state of the nerve pathway (1, 4, 31, 44, 68).

The Schwann cells in the denervated distal nerve release neurotrophic factors that promote axon regeneration, but also release extracellular matrix components that promote and inhibit axon regeneration, (21, 25, 43, 66, 72, 86, 147, 148). Thus, regeneration through the distal nerve is a balance of the influences of factors that both promote and inhibit regeneration. If the Schwann cells are present, such as after a simple nerve crush, virtually 100% of the axons regenerate and will innervate all the denervated synaptic sites (67). If the Schwann cells within the distal nerve pathway are killed, leaving only the extracellular matrix intact, the number of axons that regenerates to their targets decreases by 94% (67). This is because the factors required to trigger the regenerating axons to branch at extracellular matrix branch points are missing (67). Thus, Schwann cells along the distal nerve pathway and the cocktail of Schwann cell-released factors are critical for successful axon regeneration (67).

Nerve Transection – Nerve Gaps. If a nerve is transected and its ends are immediately sutured together (anastomosed), neurological recovery is generally excellent (122). The better the alignment of the nerve stumps to their original orientations the better the recovery, (94, 123). However, even without alignment and when a short gap is present in the nerve (<3 mm), the axons find the distal nerve stump and innervate their original targets.

When an injury destroys a short length of the nerve pathway (i.e. causing a <3 mm long gap), neurological recovery may occur without surgical intervention. This is due to a cascade of events by which fibrinogen seeps from leaky blood vessels in the injury site where it combines with thrombin, causing fibrinogen polymerization and formation of a 3-dimensional fibrin matrix (scaffold) within the nerve gap.

Although a fibrin clot promotes axon regeneration, its influence is increased by the migration of Schwann cells into the fibrin from the cut nerve ends. The Schwann cells within the fibrin release a physiological cocktail of neurotrophic and wound healing factors that increases the number of axons and the distance they regenerate into the fibrin.

Additional promotion of axon regeneration into the fibrin and across the nerve gap comes from the Schwann cells in the distal nerve. These Schwann cells also release their

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physiological cocktail of neurotrophic and wound healing factors. The source of these factors increases as a point source at the cut end of the distal nerve stump. As the factors diffuse sway from the end of the stump, and across the nerve gap, they form a concentration gradient with the highest concentration at the end of the distal nerve stump, and the lowest concentration at the central nerve stump. The regeneration of axons growing out of the central nerve stump is directed up the concentration gradient of Schwann cell-released factors, across the gap, and to the distal nerve stump (67). The regeneration of axons that reach the distal nerve stump continues to be directed into the distal nerve by the concentration gradient of Schwann cell-released factors ahead of them within the denervated distal nerve.

Bridging long nerve gaps – sensory nerve grafts. With nerve gaps longer than 3 mm a fibrin scaffold does not forms because the fibrin does not polymerize. Schwann cells have no place to migrant, the axons have no scaffold on which to regenerate across the nerve gap, and there is no neurological recovery (68, 77, 78, 81-83, 132-135). To induce axons to regeneration across nerve gaps longer than 3-mm the ends of the nerve must be anastomosed, or a conduit must be placed across the gap in which the fibrin scaffold can form, and in which neurotrophic factors can be contained.

Clinically and in animal models, it has been shown that axons can regenerate across nerve gaps up to 20 cm that have been bridged by autologous vein (29) and arterial grafts (5). However, these grafts lead to minimal neurological recovery because few axons regenerate the entire distance across the grafts (5). The number of axons that regenerate can be increased by bridging the nerve gap with autologous nerve grafts harvested from the cutaneous saphenous or sural nerves, (16, 61, 81, 96). Autologous (allogeneic / homogenetic) nerve grafts have been studied extensively in animal models (47, 59, 142). However, such grafts induce only a limited number of axons to regenerate, and only across gaps of 2-cm in length, while for gaps >2-cm neurological recovery is extremely limited (124). Even though sensory nerve grafts induce limited neurological recovery they remain the "gold standard" for clinical peripheral nerve repair (11, 31, 101).

Sensory nerve grafts have significant limitations. First, sensory nerves promote limited numbers of axons to regenerate (83, 84). Second, removing a length of autologous nerve causes a permanent sensory deficit of the cut nerve, and the surgery to remove the nerve graft can lead to scarring, or even the formation of painful neuromas. Third, the small diameter of the sensory nerve compared to that of the mixed sensory /motor nerve being repaired, typically requires the use of multiple nerve grafts. Securing multiple grafts requires the use of large numbers of sutures to connect the grafts to the central and distal nerve stumps, and sutures cause inflammation and scarring, both of which restrict axon regeneration (80). Finally, the small diameter of the grafted nerves often causes them to become ischemic or fibrosed, which further prevents axon regeneration and creates additional complications for the patient (80).

Histological examinations of sural nerve bridges show that the regenerating axons do not grow through the sural nerve bridge in intimate association with the Schwann cells as they do when they regenerate through a motor nerve bridge (19-21, 85, 86). Rather, the axons grow in association with the Schwann cell extracellular matrix sheathes (67, 68). Thus, sural nerve grafts serve only as a passive scaffold across which the axons regenerate, not as a pathway that actively promotes axon regeneration.

Motor nerve grafts induce more axon regeneration than sensory nerves, but it is ethically unacceptable to sacrifice a motor nerve for use as a graft because it requires permanently sacrificing that motor nerve function. Thus, the pure sensory sural nerve is typically used because its sacrifice leads to the loss of sensitivity only on the top of the foot and this deficit is considered a less significant loss than loss of function of a mixed motor/sensory nerve.

A variety of alternative materials has been tested for their ability to induce axon regeneration across long peripheral nerve gaps. These include: grafts of CNS tissue (6), Gore-Tex (3), collagen guides (7), gradients of factors within a tube (8), allographs (10), antibodies (92), factors that induced inflammation (32), and biodegradable polymer tubes (54). Most of these techniques have been tested on nerve gap less than 2-cm in length because none promote axon regeneration across gaps longer than 2-cm (21, 22, 73, 123, 128, 136).

Non-biological conduits to bridge nerve gaps. Other techniques for bridging nerve gaps are using of tubes of silicon or other materials sutured between the central and distal nerve stumps (tubulization) (46, 76, 77, 79). Tubulization has the advantage over nerve grafts in that it does not induce the migration of fibroblasts into the injury site where they inhibit axon in-growth. In addition, tubularization significantly reduces excessive collagen and scar formation, and prevents axons from escaping into surrounding tissues. Finally, tubes allow Schwann cells to migrate into the nerve gap from the distal stump and together with the in-growing axons (2, 130, 134, 135).

Although tubes have not yet proved very successful for promoting axon regeneration across gaps longer than 2-cm they have been highly useful for investigating the sequence of cellular and molecular events during peripheral nerve regeneration (40, 41, 134, 143). The conduit captures the natural exudate of the nerve stumps (fibrin), which polymerizes into longitudinally oriented fibrin fibers that serves as a conductive scaffold along which Schwann cells migrate from both the central and distal nerve stumps (39, 130, 134, 135, 143). Thus, tubes promote more extensive axon growth through a nerve gap than takes place in the absence of a tube and are used clinically for nerve defects up to 2-cm long (76, 96).

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 (74-76), and neurotropic influences (107). During days 3-7 the fluid is replaced by an acellular fibronectin positive, laminin negative fibrous matrix, which is critical for Schwann cell proliferation and for Schwann cells to migrate into the tube (46, 70, 71, 134, 135). Fibroblasts and Schwann cells migrate from both nerve stumps within 2 weeks of implantation (48, 119, 138, 139, 144). These tubes promote the regeneration of axons across gaps only up to 1-cm long.

3-Dimensional matrix filled tubes. Pre-filling tubes grafted into nerve gaps with various materials improves axon growth across nerve gaps. Gelfoam, (Pharmacia & Upjohn), a collagen matrix (133) and artificial fibrin sponge (Gelaspon) (38-41) are suitable matrices that enhance the migration of Schwann cells (40) and subsequent axon in-growth (45). However, in spite of these approaches axons do not regenerate through tubes longer than 2-cm.

Introduction of cells into the bridging tube. Another approach has been the placement of a series of short lengths of nerve placed, several millimeters from one another across a nerve gap, referred to as "stepping stones" (68, 87). This technique induces axon regeneration across a nerve gap, but the lengths of nerve are not stable within the long tube due to the cells becoming ischemic, which creates a toxic environment within the tube (87).

An alternative approach is the addition of dissociated Schwann cells to the matrix within a tube bridging a nerve gap (48). These Schwann cells secrete their neurotrophic factors which enhance axon regeneration through the tube (18, 21, 74, 76). One limitation with this approach is that Schwann cells have a limited distance they will migrate, and a limited number of times they proliferate (33, 34, 40). However, Schwann cell proliferation and migration is increased by the adding insulin and insulin-like growth factor to the matrix within the nerve gap. The presence of these factors induces axons to regenerate across nerve gaps up to 2-cm in length (40, 41, 143).

Addition of neurotrophic factors, cytokines, and other factors to the bridging tube

As indicated, insulin stimulates the regeneration of peripheral nerves (42) and when infused into a tube bridging a nerve gap enhances axon in-growth (105). Insulin (40, 41), and insulin-like growth factor-1 (42, 51-53, 63, 105, 125, 126), within a bridging tube significantly increase the number of Schwann cells that migrate into the tube. Additional factors that induce Schwann cell proliferation are platelet-derived growth factor-B (PDGF-B), acidic and basic fibroblast growth factors (b-FGF and a-FGF) (112), transforming growth factor (TGF-â) (114, 120) and neuregulins (24, 63, 90). Axolemmal membrane also stimulates proliferation of cultured Schwann cells (97, 98, 110, 111, 117), while NGF added to a tube enhances axon ingrowth (9, 58, 113). Multiple injections of a mixture of laminin, testosterone, ganglioside GM1 into the chamber also significantly increases the diameter and vascularization of nerve outgrowth (99). Fibronectin-laminin and fibronectin (9) added to tubes enhances axon regeneration through a 1.8-cm tube, predominantly by enhancing Schwann cell migration.

Axon regeneration could potentially be increased by the addition of other factors that promote nerve regeneration, such as the putative neurotrophic cytokines or neurokines (50). These factors derived from versatile fibroblast growth factor family, are made up of 7 members: FGF-1-7, the transforming growth factors beta (TGF- â), or the cholinergic differentiation factor (CDC)/ ciliary growth factor (CNTF)/ leukemia inhibitory factor (LIF) (131). While some (FGF-1, FGF-2 (acidic FGF), CNTF, and LIF) seem to act as postnatal survival factors involved in the maintenance of distinct central and peripheral neurons, others seem to act as neuropoietic and/or neural differentiation factors (CDF/LIF, TGF-â) with defined spatiotemporal expression during early postnatal development (140) and could also play significant roles in promoting axon regeneration.

The influence of the time between a nerve lesion and repair on neurological recovery. Immediate anastomosis of a lesioned radial nerve leads to almost perfect neurological recovery (65). However, anastomosis up to 14 days post injury leads to good recovery in only 49% of the patients, anastomosis 14 days to 6 months following the lesion leads to reasonable neurological recovery in only 28% of the patients, while anastomosis after 10 months (122) leads to no neurological recovery. The use of nerve grafts for a radial nerve with a gap lead to limited neurological recovery (23). The basis for these changes is unknown.

The influence of time a nerve graft has been denervated and the success of neurological recovery. The length of time between a nerve lesion and its repair significantly influences the extent of neurological recovery. Pre-degenerated nerve grafts provide more rapid initial axon in-growth than fresh nerve grafts (33, 64, 127), but do not influence the rate of regeneration (33, 64). The influence of pre-denervation is predominantly due to the proliferation of Schwann cells within the graft (116) and the neurotrophic factors they release (38, 56-58, 76, 119, 129, 133). This results from the proliferation of Schwann cells within the graft (115, 116). Another approach for improving axon outgrowth is to pre-denervate a nerve and leave it in situ for 5 days. A length of the denervated nerve is harvested and dissociated, and the dissociated Schwann cells are injected into the tube bridging a nerve gap (Kuffler, unpublished results). Although the presence of the Schwann cells improves the number of axons and distance they regenerate, there is no reliable protocol for this technique. However, for unknown reasons, axons do not tend to regenerate through old denervated allographs (142) and as stated above, no neurological recovery take place if the distal nerve is 10 or more months denervated (122). The basis for these changes is unknown.

Fibrin and platelet-rich fibrin glue for peripheral nerve repair. Fibrin glue is extensively used to repair lesioned peripheral nerves repair and sectioned central nervous system tissue (27, 28, 35, 49, 60, 95, 118). It is also extensively used to anastomose lesioned peripheral nerves (11-15, 55, 88, 89, 93, 94, 102-104, 109, 146). In fact, fibrin glue is a better for anastomosing peripheral nerves than sutures (14, 30, 62, 88, 100, 102, 103, 108). 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 (14, 30, 62, 88, 100, 102, 103, 108).

Fibrin has been tested as a scaffold within nerve gaps, but it use has not lead to a reliable mechanism for promoting axon regeneration across long nerve gaps. This is probably because for fibrin to be effective in promoting axon regeneration requires to interact 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, physiological fibrin within a nerve gap is not pure fibrin but platelet-rich fibrin (31, 35, 37, 100). The platelets are rich in factors that promote nerve regeneration and wound healing and they are released over about 4 days following platelet activation by injury. Thus, the platelets enrich the fibrin with axon regeneration-promoting factors and autologous platelet-rich fibrin promotes excellent axon regeneration (13, 28, 31, 55, 108).

Platelet-rich fibrin can be separated from a patient's or animal's own whole blood in the operating room by differential centrifugation of whole blood. This separation is a routinely used in many operating rooms, but mostly for the repair of damaged brain tissue, or for use in orthopedic surgery where fibrin is used as a glue to hold bone chips in place (26, 27). However, platelet-rich fibrin must be tested for its influence in inducing axon regeneration across long peripheral nerve gaps.

Inhibition of axon regeneration into the distal nerve. As stated, following denervation, the Schwann cells in the distal nerve up-regulate the synthesis and release of a collection of neurotrophic and extracellular matrix factors. Among the extracellular matrix factors are laminin and chondroitin sulphate proteoglycans (CSPGs) (17, 147). While laminin and neurotrophic factors promote axon regeneration, CSPGs inhibits axon regeneration (147). Although the overall balance of axon regeneration-promoting and -inhibiting favors axon regeneration, if CSPG is eliminated axon regeneration is faster and more extensive (91, 121, 141, 148). Therefore, to enhance neurological recovery, the lesioned axons must first be induced axons to regenerate across a nerve gap, and then down the distal nerve, which requires eliminating the factors that inhibit axon regeneration. CSPGs can be eliminated by the application of the enzyme C-ABC that digests CSPG, or by blocking CSPG synthesis via intramuscular injections of â-xyloside (91, 121). â-xyloside acts by preventing the glycosylation of the proteoglycan side chains, which are required for inhibition of axon regeneration (147).

Virtually none of the techniques developed in animal models has been applied clinically because almost all require the use of materials, such as antibodies, enzymes, recombinant neurotrophic factors, materials for the tubes, and materials placed in the nerve tubes, which are not FDA approved. Obtaining FDA approval requires years and is extremely expensive for each material or factor to be used. Finally, each factor must be tested separately and subsequently in various combinations prior to being tested clinically. Therefore, economical reasons prevent some of these techniques with great potential from being tested clinically.

Bridging a 4-cm long peripheral nerve gap. Working with adult rats, we tested various methods for inducing axon regenerating across 4-cm long peripheral nerve gaps. A length of sciatic nerve was removed and bridged with a polyethylene tube that was then filed with a 3-dimensional matrix, with or without the addition of a number of different factors.

3-Dimensional scaffolds. When the nerve gap was filled with a 3-dimensional matrix of extracellular matrix factors (Matrigel, Sigma Chemical) a few axons regenerated entirely across gaps (unpublished results). However, Matrigel begins losing its 3-dimensional structure within 1 week, which limits its effectiveness in inducing axon regeneration. Gelaspon (Ankerpharm, Germany), a bioresorbable fibrin matrix, maintains its 3-dimensional integrity for more than 4 weeks and induces a larger number of axons to regenerate entirely across gaps 4-mm gap, although 60% regenerate only 2.5-cm into a gap (N = 4) (unpublished results).

Concentration gradients of factors. This laboratory showed that the uniform distribution of Schwann cell released neurotrophic factors (peripheral nerve conditioned medium, CM) around neurons in culture medium induces both adult sensory and motor neurons to extend axons 10-fold longer than in the absence of these factors (69, 137). However, when the factors were presented as a concentration gradient of CM across nerve gaps, or was applied directly to the central stump of a nerve, the number of axons that regenerated increased significantly, even up concentration gradients 4-cm in length (36, 57, 106, 145).

Mini osmotic pumps (Alzet Pump, Durect Corp) were loaded with CM and a catheter attached to the pump. The open end of the catheter was positioned at the distal end of the nerve gap. The pumps (Alzet 2004, Durect Corp.) infuse the matrix within the gap at a constant rate of 0.5 µl per hour for 4 weeks. Diffusion of the factors in the CM away from the end of the catheter and into the nerve gap creates a concentration gradient of the factors, with its highest concentration at the tip of the catheter, and it's lowest at the central nerve stump. Such concentration gradients of neurotrophic factors induce axons to regenerate up the gradient and towards the distal nerve stump. This technique increased the number of axons that regenerated across the 4-cm long gaps by 50% compared to control preparations without CM infusion (N = 6) (unpublished results).

CM is obtained by placing a 2-cm length of sciatic nerve in 3 ml of culture medium for 5 days. During this time, the Schwann cells synthesized and released various neurotrophic as they do physiologically in situ. The CM is then harvested, filtered to remove cellular debris and maintains it biologically activity when kept at 37°C for more than 3 months, or for several years when kept at -85°C.

Dissociated Schwann cells within the fibrin matrix. As stated, Schwann cells of the denervated peripheral nerve release neurotrophic factors that induce axons to regenerate along the denervated distal nerve to their targets. We tested whether seeding the pure fibrin within a nerve gap with dissociated Schwann cells would influence axon regeneration into nerve gaps. The piece of peripheral nerve that was removed to make the nerve gaps was dissociated in the enzymes (collagenase-P, dispase, and DNase), and 10% of the dissociated Schwann cells were mixed with the fibrin matrix and used to fill the nerve gap. In the presence of the Schwann cells, the number of axons that regenerated across the nerve gap increased 25% compared to preparations without Schwann cells (unpublished results). Thus, both dissociated Schwann cells and the factors they secrete are good candidates for seeding the nerve gap to increase the number and distance axons regenerate.

Conclusions

A variety of techniques increase the number of axons and the distance that the axons regenerate across a nerve gap and into the distal nerve. The best techniques include a platelet-rich fibrin scaffold, seeding a nerve gap with Schwann cells, creation of concentration gradients of Schwann cell-released factors (CM), enhancing the rate of axon regeneration with FK-506 and eliminating regeneration inhibiting factors (CSPG). However, additional techniques are effective, such as elevating c-AMP in neurons, providing neurotrophic factors, and gene manipulations that enhance axon regeneration. Because each acts via a different mechanism, it is reasonable to assume that several techniques could be used simultaneously to maximize axon regeneration and neurological recovery. Some of the materials to be used in these combinations must now be tested in an animal larger than and with greater clinical relevance than the rat. Simultaneously, it is also time to start clinical testing of those materials that are FDA-approved and have been demonstrated to be effective in inducing axons regeneration in the animal models. Furthermore, non-FDA-approved, which are effective in inducing axon regeneration and neurological recovery in the animal models must receive FDA approval so they can be tested clinically. The results from our animal model studies, and preliminary results from our clinical trial, indicate that soon it will be possible to induce axon regeneration and complete neurological recovery from peripheral nerves that suffered traumatic injuries that resulted in gaps up to 8-cm in length.

Resumen

Si un nervio periferal es triturado, o si se corta el nervio y se suturan sus extremidades no mucho tiempo después de la lesión, hay una buena recuperación neurológica. Cuando un pedazo de nervio periferal es destruido y no es posible realizar una **anastomosis**, la técnica estándar para reparar el nervio es injertar un pedazo/s de nervio sensorial del paciente en el espacio. Para espacios de menos de 2 cm la recuperación neurológica es moderada, para espacios de 2-4 cm hay una pobre recuperación, y para espacios.4 cm la recuperación es bien limitada o inexistente. La recuperación limitada se debe a que los nervios sensoriales actúan como un armazón pasivo para la regeneración de

los axones y no promueven una regeneración activa de los axones. A pesar de esto, esta técnica permanece siendo el "estándar predilecto" para la reparación de nervios. Se requiere de nuevas técnicas que induzcan una mejor recuperación neurológica. Este artículo revisa técnicas clínicas y de investigación que promuevan recuperación neurológica después de una lesión traumática del nervio peripheral.

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