

Mechanisms of Disease: what factors limit the success of peripheral nerve regeneration in humans?

Ahmet Höke

SUMMARY

Functional recovery after repair of peripheral nerve injury in humans is often suboptimal. Over the past quarter of a century, there have been significant advances in human nerve repair, but most of the developments have been in the optimization of surgical techniques. Despite extensive research, there are no current therapies directed at the molecular mechanisms of nerve regeneration. Multiple interventions have been shown to improve nerve regeneration in small animal models, but have not yet translated into clinical therapies for human nerve injuries. In many rodent models, regeneration occurs over relatively short distances, so the duration of denervation is short. By contrast, in humans, nerves often have to regrow over long distances, and the distal portion of the nerve progressively loses its ability to support regeneration during this process. This can be largely attributed to atrophy of Schwann cells and loss of a Schwann cell basal lamina tube, which results in an extracellular environment that is inhibitory to nerve regeneration. To develop successful molecular therapies for nerve regeneration, we need to generate animal models that can be used to address the following issues: improving the intrinsic ability of neurons to regenerate to increase the speed of axonal outgrowth; preventing loss of basal lamina and chronic denervation changes in the denervated Schwann cells; and overcoming inhibitory cues in the extracellular matrix.

KEYWORDS axotomy, chronic denervation, nerve regeneration, Schwann cells

REVIEW CRITERIA

PubMed was searched using Entrez for articles published up to 31 December 2006, including electronic early release publications. Search terms included "peripheral nerve regeneration", "chronic denervation", "bands of Büngner", "chondroitin sulphate proteoglycan" and "nerve repair". The abstracts of retrieved citations were reviewed and prioritized by relative content. Full articles were obtained and references were checked for additional material when appropriate.

A Höke is an associate professor of neurology and neuroscience and the Director of the Neuromuscular Division in the Department of Neurology at Johns Hopkins Hospital, Baltimore, MD, USA.

Correspondence

Johns Hopkins Hospital, Department of Neurology, Pathology 509, 600 N Wolfe Street, Baltimore, MD 21287, USA
ahoke@jhmi.edu

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INTRODUCTION

Over the past century, two dogmas have dominated the nerve regeneration field: first, that CNS neurons cannot regenerate in adult mammals; and second, that adult mammalian peripheral nervous system (PNS) neurons can regenerate easily and completely. The first of these dogmas was disproved by Albert Aguayo and colleagues through a series of elegant experiments, in which they showed that, when placed in a PNS environment, adult mammalian CNS axons can regenerate. This finding indicated that CNS neurons do not have an innate inability to regenerate.^{1–3} The second dogma, on the other hand, has been more difficult to challenge; when injured, adult mammalian peripheral axons can and do regenerate. As explained in this Review, however, this regeneration does not always translate into successful functional outcomes following repair of human nerve injuries.

Relatively limited data are available regarding the exact incidence and prevalence of peripheral nerve injuries in trauma patients. A large study of all trauma patients evaluated at a single institution showed that 2.8 percent of trauma patients had peripheral nerve injuries that required surgical intervention.⁴ Most peripheral nerve repairs result in a degree of functional recovery, but in most cases the results are suboptimal. An extensive set of experiences is documented in four excellent books by Kline and Hudson, Mackinnon and Dellon, Sunderland, and Woodhall and Beebe.^{5–8}

Many factors determine the success of surgical repair after nerve injury, including the type and timing of repair (primary versus secondary repairs), the surgical technique used in the repair (fascicular versus epineurial repair), requirement for a graft and the type of nerve graft used (e.g. autologous nerve grafts, artificial nerve conduits or nerve allografts), the location of the lesion (i.e. how far it is from the target muscle or skin), and the age of the patient. Many of these factors are related to the intrinsic ability of the peripheral axons to regenerate, the distal nerve

segments to support that regeneration, and the target tissues to receive the regenerating axons. Unfortunately, despite many years of research in nerve regeneration, no significant therapeutic advances have been made in these areas. The only significant areas of improvement with regard to outcomes have been related to the surgical techniques used in nerve repairs; these advances have been reviewed elsewhere.^{9,10}

In contrast to the lack of novel therapeutic approaches in human nerve repairs, the literature is full of techniques, materials and therapies that work in animal models of peripheral nerve injury. In this Review, I will highlight the differences between these animal models and the human situation, outlining why the current animal models do not recapitulate the human condition and are consequently unlikely to yield useful therapeutic advances.

NEURONAL DETERMINANTS OF PERIPHERAL NERVE REGENERATION

Why is nerve regeneration poor in humans compared with animal models? One of the main limitations of most nerve injury and repair studies is that they are done in small rodents such as mice and rats, and the distance over which nerves are required to regenerate is extremely small compared with human nerve injuries. After primary repair of a sciatic nerve transection in the mid-thigh—the most commonly used peripheral nerve injury model—mice and rats will recover fully. The rate of regeneration of motor and sensory axons is 1–4 mm/day, similar to the rate of slow axonal transport.^{11,12} This relationship is not a coincidence—important components of the axonal cytoskeleton have to be synthesized in the cell body and transported down the axon to the regenerating growth cone. This intrinsic ability of the peripheral axons to regenerate can be enhanced by an experimental phenomenon known as a ‘conditioning lesion’. If a crush is made in the rodent sciatic nerve, the rate of regeneration after a more proximal second crush is enhanced.^{13,14} This increased rate of regeneration correlates with increased gene expression and protein synthesis in the neuronal cell body, and with an increased rate of slow axonal transport.^{11,15,16}

One of the peculiar aspects of the dorsal root ganglion (DRG) sensory neurons is that they have axonal branches both in the PNS and in the CNS. The central branches of DRG

sensory neurons can regenerate within the dorsal roots but fail to enter the spinal cord at the dorsal root entry zone. Similarly, the same central branches of DRG sensory neurons, when injured within the spinal cord, can regenerate if they are grafted into a peripheral nerve branch, but they do not normally regenerate once they re-enter the CNS.^{2,3} Studies in animal models have shown that a conditioning lesion in the peripheral branch can enhance regeneration of central branches of DRG sensory neurons within the spinal cord,¹⁷ an effect that can be mimicked by injection of db-cAMP (dibutyryl cyclic AMP) into the DRG.^{18,19} The latter observation, however, does not translate into enhanced regeneration in the PNS: a db-cAMP injection into the DRG does not enhance regeneration of peripheral axons of the sensory neurons after sciatic nerve transection, or of the central branches when a peripheral nerve graft is provided in the dorsal columns.²⁰ This important observation indicates that although db-cAMP might have a positive effect on regeneration through the inhibitory environment of the CNS, unlike a conditioning lesion it does not increase the intrinsic capacity of the peripheral axons to regenerate. Future experiments that compare gene expression changes in the DRG sensory neurons evoked by db-cAMP injections and conditioning lesions might be useful for identifying candidate genes that underlie the enhanced regenerative capacity associated with a conditioning lesion.

So, if peripheral axons have the ability to regenerate, and this regeneration can be enhanced experimentally, why do they fail to regenerate effectively in humans? Part of the answer lies in the distance to the target, and the time that the axon takes to reach that target in humans. One of the main shortcomings of the most commonly used experimental models of nerve regeneration is that they do not replicate this important aspect of human nerve regeneration. This issue is further complicated by the possibility that the rate of regeneration of peripheral axons is slower in humans than in rodents.^{21–23} Even if human nerves had the same rate of regeneration as the rodent peripheral axons, however, they have a much longer distance to their targets, and, during this prolonged regenerative attempt, the distal nerve segments remain without axonal contact; that is, they become ‘chronically denervated’. Similarly, the axons remain without a target tissue for

a prolonged time period, and the neuron is considered to be 'chronically axotomized'. A more appropriate rodent model of this situation would be a nerve repair after chronic nerve injury.

In a series of elegant experiments, Fu and Gordon investigated whether impaired recovery after delayed nerve repairs is attributable to chronic axotomy (the axons lose their ability to regenerate in the absence of target innervation), or to chronic denervation (Schwann cells in the distal nerve without axonal contact lose their ability to support regeneration in the absence of axonal contact).^{24,25} In one experiment, these authors axotomized the tibial nerve, and, at various time points during the 12 months that followed, they performed a repair whereby they sutured the chronically axotomized tibial nerve to freshly transected peroneal nerves. They asked whether the axons of the tibial nerve, which had not encountered a target tissue for many months, could regenerate through the peroneal nerve, which was considered to be an acutely denervated distal nerve segment.²⁵ Although there was some decline in the regenerative capacity of the axons after 3 months of chronic axotomy, this was relatively small, and was compensated for by collateral sprouting and formation of larger motor units; the muscle fiber size and the force generated were very similar to those observed with immediate surgical repairs.

By contrast, chronic denervation was found to be detrimental to the success of regeneration.²⁴ Fu and Gordon transected the peroneal nerve and left the distal peroneal nerve denervated for 12 months. Then, they transected the tibial nerve and sutured it to the chronically denervated peroneal nerve segment and asked whether freshly axotomized tibial axons, which normally regenerate very well in rats, could regenerate through the distal nerve segment that had been deprived of axonal contact for a prolonged period. Compared with immediate nerve repair, after 12 months of chronic denervation there was a dramatic decline in the number of tibial motor axons regenerating through the distal denervated peroneal nerve. In a more recent study, Gordon's group has shown that this decline in regenerative capacity in the chronically denervated nerves starts 8 weeks after injury, and that by 6 months of chronic denervation there is almost no regenerative support for axons.²⁶

NON-NEURONAL DETERMINANTS OF PERIPHERAL NERVE REGENERATION

Why do chronically denervated distal nerves lose their ability to support regeneration? The answer to this question lies in the changes that occur in Schwann cells and the basal lamina that these cells provide (Figure 1). In an intact adult peripheral nerve, the Schwann cells provide a basal lamina that is contiguous longitudinally throughout the nerve; this structure is called the Schwann tube.²⁷ In an acutely denervated distal nerve, the Schwann cells align longitudinally, forming arrays known as 'bands of Büngner',^{28,29} and the Schwann tube remains intact. If regeneration of axons into a distal nerve segment is prevented and the Schwann cells lose axonal contact for a prolonged period of time, the Schwann cells atrophy, the basal laminae are not maintained, and the bands of Büngner and Schwann tubes start to disappear.^{30,31} These observations, which were originally made in animal studies, were recently confirmed in human surgical specimens.³²

The presence of a basal lamina is one of the most important characteristics that differentiates the PNS from the CNS. Unlike in the PNS, the myelinating cells in the CNS lack a basal lamina, and the absence of this structure might be an important determinant of regenerative failure in the CNS. The Schwann cell basal lamina is rich in extracellular matrix molecules that promote axon growth, such as laminin and type IV collagen.³³⁻³⁵ This rich extracellular matrix might also serve as a reservoir of growth factors secreted by Schwann cells. If this is the case, when a peripheral axon is injured, the regenerative sprout, surrounded by the growth-promoting properties of the basal lamina, would have a very favorable environment in which to elongate. The growth factors secreted by denervated Schwann cells and their role in axonal regeneration are reviewed extensively elsewhere,³⁶⁻³⁹ and will not be discussed further here.

Promotion of axon growth is probably not the only function of the bands of Büngner and the Schwann cell tubes. An equally important role might be the shielding of the axon from endoneurial growth inhibitory molecules during nerve regeneration. In the CNS, there are two major groups of molecules that inhibit axonal regeneration: the myelin-associated molecules, and the proteoglycans that are present in the extracellular matrix.⁴⁰ After injury, chondroitin sulfate proteoglycans are upregulated by astrocytes and form an important component of the so-called

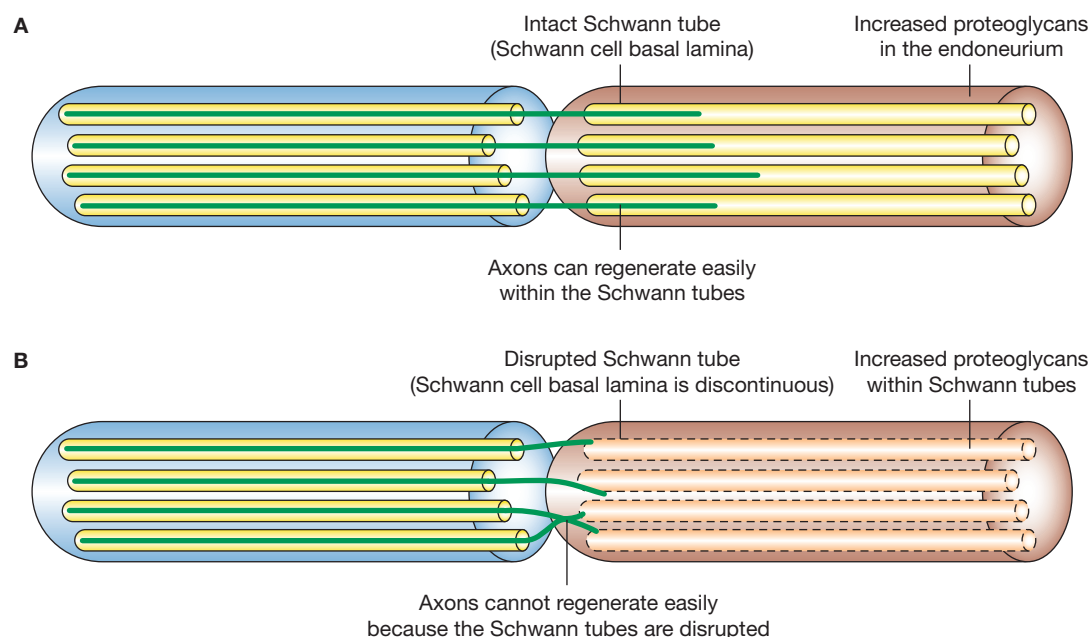


Figure 1 Challenges to nerve regeneration in acute denervation versus chronic denervation in the peripheral nervous system. The blue-shaded area is normal endoneurium, and the brown-shaded area is endoneurium in which the expression of chondroitin sulfate proteoglycans is increased. **(A)** Acute denervation and regeneration. In acute denervation, there is upregulation of proteoglycans in the endoneurium, but the Schwann tubes remain intact and allow regeneration to occur easily by providing a growth-promoting substrate and shielding the growth cone from the inhibitory extracellular matrix components (chondroitin sulfate proteoglycans). **(B)** Chronic denervation and regeneration. In chronic denervation, the integrity of the Schwann tubes is not maintained, and the regenerating axons have to navigate through a territory that does not support regeneration: with loss of the basal lamina, there is a reduction in growth-promoting molecules such as laminin, and the axons are exposed to the growth-inhibiting molecules in the extracellular matrix.

'glial scar'.^{41,42} As in the CNS, there is upregulation of chondroitin sulfate proteoglycans in the endoneurium of peripheral nerves after injury.⁴³ Upregulation of this growth inhibitory molecule is maintained in chronically denervated distal nerve segments.⁴⁴ When the glycosaminoglycan side chains of chondroitin sulfate proteoglycans are degraded by chondroitinase, regeneration of CNS axons improves.^{45,46} Similarly, when the peripheral nerves are treated with chondroitinase, regeneration is enhanced.^{47–49} The improvements in peripheral nerve regeneration noted in these studies, however, are relatively small, because acute injury paradigms with primary repair were used to study the rate of regeneration. In these models, peripheral axons regenerate relatively well even in the absence of any external treatment.

A more appropriate model by which to test this phenomenon would be delayed secondary repair after prolonged denervation, a model that mimics the human nerve repair situation

much better than primary repair models in rodents. One of the main shortcomings of the latter models is that the bands of Büngner and the Schwann cell tubes remain intact, so all the regenerating motor or sensory axons have to do is to cross the repair site and enter one of the Schwann cell basal lamina scaffoldings. Once the axons are inside the basal lamina scaffolding, they are provided with growth-promoting factors and cell adhesion molecules, and are shielded from the inhibitory environment of the endoneurium. With chronic denervation, on the other hand—both in humans even with primary repair and in rodent models after delayed secondary repair—without the growth-supporting properties of the Schwann cell basal lamina, the axon has to find its way around inhibitory molecules in the endoneurium to reach its target (Figure 1).

Regenerating peripheral axons can certainly traverse environments rich in growth-inhibiting proteoglycans; they do this at sites of repair. The

molecules that help axons navigate through a proteoglycan-rich extracellular matrix are not completely known, but matrix metalloproteases are probable candidates. Matrix metalloprotease-2, secreted by growing axon tips, can degrade chondroitin sulfate proteoglycans and aid in peripheral nerve regeneration.⁵⁰ The matrix metalloproteases can also be delivered to the chronically denervated nerve segments through other means, such as neural stem cells, and can improve regeneration even in a model of secondary repair after chronic denervation in rats.⁴⁴

FUTURE DIRECTIONS IN HUMAN PERIPHERAL NERVE REGENERATION

As discussed above, the main impediment to a successful outcome after nerve repairs in humans relates to the changes that occur distally in the nerve. This issue can be overcome by two approaches: either we have to speed up the intrinsic rate of regeneration of motor and sensory peripheral axons so that the distal nerve segments do not have time to undergo atrophy and loss of the bands of Büngner and Schwann tubes, or we have to find a way to prevent or reverse the changes in the distal nerve. As mentioned above, a comparison of changes in gene expression in the DRG neurons with a conditioning lesion and db-cAMP treatment might provide insights into mechanisms that allow regeneration of the central axons to occur in a growth-inhibiting environment with no basal lamina. The assumption would be that differentially upregulated genes could perhaps be developed as therapeutic targets to enhance regeneration of peripheral axons through chronically denervated nerve segments.

Similarly, examination of gene expression changes in the distal stumps of transected nerves could provide insight into why the Schwann cells atrophy and lose their basal laminae. We already know that certain growth-supporting molecules that are upregulated immediately after loss of axonal contact are not maintained when the denervation is prolonged. Some of these molecules are growth factors—such as glial cell-line derived neurotrophic factor⁵¹—and some are receptors for growth factors—such as erbB receptors for neuregulins,⁵² or the low-affinity nerve growth factor receptor p75.⁵³

The changes in neuregulin receptors are likely to be very important, pointing to loss of trophic support from axons. The trophic

support that exists in the nervous system is often bidirectional—the Schwann cells provide neurotrophins for the axons, and the axons provide neuregulins, which are the most potent mitogens for Schwann cells.⁵⁴ How do we maintain the ‘regeneration-supporting’ phenotype of an acutely denervated Schwann cell? Once chronically denervated, do Schwann cells lose their ability to become ‘reactivated’ and start providing regeneration support in the form of secretion of neurotrophic factors and maintenance of intact basal lamina scaffoldings? Our ability to develop truly ground-breaking therapies for human nerve regeneration will depend on the answers to questions such as these.

CONCLUSIONS

Advances in surgical techniques have brought significant improvements in the repair of human nerve injuries, but we are still awaiting the next therapeutic breakthroughs in human nerve regeneration. The real advances will come from understanding the molecular mechanisms that underlie axonal growth, the role of axonal transport in regeneration, and the molecular and cellular changes in the distal portions of the nerves that impede regeneration. The findings from these studies in peripheral nerve regeneration are likely to have a broader impact on neurodegenerative disease in general, because basic mechanisms of axonal growth and overcoming the impediments to growth are likely to be shared between the CNS and PNS neurons. We have already seen a flow of interest in chondroitin sulfate proteoglycans in the reverse direction, from the CNS regeneration literature into the peripheral nerve regeneration field.

Although the ultimate goal of all of these studies is to improve nerve regeneration in humans, it will be equally important to develop appropriate animal models in which to test candidate therapies. These models will need to take into consideration the fact that human nerve regeneration takes a long time because of the distances involved. Because these prolonged time periods lead to chronic denervation changes, the animal models need to recapitulate similar changes in the nerves and challenges to regeneration. In small rodents, the appropriate model would be secondary repair after chronic denervation. Alternatively, the nerve regeneration experiments could be done in larger animals, but the costs of such experiments, on a large scale, is likely to be prohibitive.

KEY POINTS

- Functional recovery after peripheral nerve repairs in humans is suboptimal
- Impaired nerve regeneration in humans is primarily attributable to chronic denervation changes in the distal nerve because of the limitations of speed of nerve regeneration and the distances involved
- Better therapies for nerve regeneration will need to address the following issues: improving the intrinsic ability of neurons to regenerate to increase the speed of axonal outgrowth; preventing loss of basal lamina and chronic denervation changes in the denervated Schwann cells; and overcoming inhibitory cues in the extracellular matrix
- Animal models that take these issues into consideration, such as secondary repair after chronic denervation in rats, are required to test new therapies that are relevant to human nerve regeneration

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Competing interests

The author declared he has no competing interests.

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