

Translational Strategies for Enhancing Motor and Sensory Recovery after Nerve Injury or Reconstruction

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Abstract

Thousands of patients suffer peripheral nerve injuries annually that lead to motor disability, dysesthesias, neuropathic pain, and lost economic productivity. The slow rate of nerve regeneration in humans of approximately 1 mm/day is associated with unpredictable and often incomplete end organ reinnervation. This brief review summarizes important research directions to improve outcomes of peripheral nerve injury and repair.

Abbreviations: ES: Electrical Stimulation; MUNE: Motor Unit Number Estimation; PNA: Processed (Decellularized) Nerve Allografts; cAMP: Cyclic Adenosine Monophosphate; BDNF: Brain-Derived Neurotrophic Factor; FDA: Food and Drug Administration.

Introduction

An ongoing challenge of many plastic surgery procedures is that of enhancing nerve regeneration to maximize motor and sensory recovery. Despite advancements in plastic surgery with vascularized composite allotransplantation, smart prosthetics, tissue engineering, robotics, and novel implant biomaterials, whenever peripheral nerves are injured or repaired, a major rate limiting step is the innate capacity of individual axons in the proximal nerve stump to sprout and regenerate to achieve end organ reinnervation. At the cellular level, multiple factors may affect the success of axon regrowth: neurotrophic factors, neurotropism (growth of axons down correct pathways), preferential motor reinnervation, revascularization, and fibrosis. In

particular, nerve regrowth in settings of delayed repair or across long distances are significant challenges as individual neurons undergo chronic axotomy (a neuron cell body not in contact with its peripheral end organ, leading to loss of regenerative capacity) and chronic denervation (Schwann cells in the distal nerve stump not in contact with the neuron cell body, leading to loss of progressive atrophy, loss of proliferative and migratory ability, and an overall inability to support axon regrowth from the proximal stump) [1]. Incomplete or inappropriate nerve regeneration can lead to a host of morbid consequences, including neuropathic pain from neuroma formation, altered sensation following breast reconstruction, incomplete motor reinnervation in hand transplantation or synkinesis from misdirected axonal growth [2]. A theme present in many plastic surgery procedures is the restoration of function and quality of life, and thus the need to improve outcomes after peripheral nerve injury or repair remains a vigorous area of research.

Brief electrical stimulation (ES) for 1 hour at 20 Hz has been shown to accelerate recovery after nerve injury in various animal models, including facial nerve, sciatic nerve, common peroneal nerve, and femoral nerve [3-6]. The effects of ES appear to accelerate the rate of axon crossing of suture sites, as opposed to increasing the innate rate of regeneration of 1-3 mm/day in rodents [7]. The cellular effects of ES are exerted proximally in the cell body, by upregulating factors such as GAP-43, BDNF, and cAMP. Importantly, stimulation periods of 1 hour or greater are equally effective in motoneuron recovery, but sensory nerve recovery is optimal at 1 hour and no longer, due to downregulation of *trkB* expression [8]. Experience of brief ES in human studies, while limited, has been logistically feasible and with very promising outcomes. One hour of 20 Hz ES immediately following carpal tunnel release in patients with electrophysiologic evidence of chronic median nerve compression neuropathy led to significant improvements in motor unit number estimation (MUNE), terminal motor latency, and sensory nerve conduction values [9]. Dramatic improvement in sensory modalities was noted with brief ES following digital nerve repair, while brief ES following cubital tunnel release resulted in increased MUNE, grip strength and key pinch strength [10,11]. Brief ES is currently being investigated for restoration of sensation after alloplastic breast reconstruction [12]. In a different paradigm, selective ES of peripheral nerves has also shown effectiveness in spinal cord injury patients to restore mobility, as well as respiratory, bladder, and bowel functions [13].

Nerve substitutes are an important resource for reconstruction of gap defects when autograft is limited or not available. Fresh nerve allotransplantation was and remains an area of great interest. Early experimental studies in rodents showed promising results, with histomorphometric measures of nerve regeneration and functional measures of target reinnervation comparable to that of autologous nerve grafts [14-19]. Reports of human studies of gaps as long as 37 cm similarly produced excellent outcomes. The main barrier to greater application has been the need for systemic immunosuppression to prevent allograft rejection. The use of cyclosporin A or tacrolimus (FK506) was necessary to prevent immune activation and fibrotic degeneration of the allograft. Interestingly, unlike other forms of tissue allotransplantation, immunosuppression for nerve allotransplants is transient and may be discontinued after regenerating host axons have traversed the graft without loss of function [20]. Nevertheless, the months to years' long course of "temporary" immunosuppression has been a barrier to greater acceptance, for fear of eliciting

systemic toxicity upon the patient. Fortunately, there have been important advances in nerve substitutes such as biosynthetic conduits and processed (decellularized) nerve allografts (PNA), which are readily available "off the shelf." Since the FDA approval in 2007 of AxoGen's Avance PNA, over 15,000 have been implanted in humans. Excellent clinical outcomes have been reported for small-calibre nerve gap defects up to 30-40 mm in length [21-23]. Reports for larger-calibre and longer nerve gaps have had variable results [24-26]. Promising future strategies include supplementation of PNAs with neurotrophic factors, Schwann cells, or stem cells to restore a more biologic environment for regenerating axon growth cones [27-29].

Finally, novel methods of local drug delivery have potential for improving nerve regeneration [30-32]. In the case of hand transplants, tacrolimus given as part of the immunosuppression protocol resulted in unexpectedly rapid nerve regeneration and target reinnervation [33]. In order for tacrolimus to be used more widely, its neuroenhancing effects must be isolated from its immunosuppressive effects. Hydrogel delivery systems with encapsulation of a drug in microspheres with predictable release kinetics offer a promising avenue for targeted and sustained neurotrophic drug delivery [34].

Advancements in strategies to enhance nerve regeneration such as electrical stimulation, nerve substitutes, and local drug delivery will play an important role in optimizing outcomes after progressively more advanced transplantation procedures, brain-machine interfaces, biomaterials, and fundamental plastic surgeries such as compression neuropathy and breast reconstruction.

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