Controlled Delivery of Nerve Growth Factor Enhances Sieve Electrode Interface with Peripheral Nerve Tissue

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Introduction: Development of advanced neuroprosthetic systems depends on the creation of a microelectrode device capable of selectively interfacing peripheral nerve tissue. One device capable of achieving such an interface is the regenerative sieve microelectrode. Sieve electrodes are thin-film devices containing a number of holes, some of which are circumscribed by metal ring electrodes. Upon implantation into a transected nerve, regenerating axons extend through the holes providing a chronic, high-specificity interface between ring electrodes and small groups of axons. Unfortunately, this superior electrical interface is dependent upon robust, successful nerve regeneration through the device, which has previously been demonstrated to inhibit nerve regeneration.[1] In contrast, fibrin-based delivery systems loaded with nerve growth factor (NGF) have been demonstrated to enhance peripheral nerve regeneration.[2] Therefore, we hypothesize that the addition of NGF-loaded delivery system to sieve electrode assemblies will enhance nerve regeneration through the electrode and provide superior nerve/electrode interface capabilities *in vivo*.

Methods: Custom-designed sieve electrodes were fabricated out of polyimide and gold using sacrificial photolithography. Following fabrication, 5 mm segments of silicone conduit were fixed to both sides of the electrode around the porous region. Prior to implantation in the sciatic nerve of male Lewis rats, silicone conduits attached to the electrodes were filled with either fibrin-based delivery system loaded with 50 ng/ml β-NGF (n=6) or saline (n=6). Silicone conduits 12 mm in length containing either NGF-loaded delivery system (n=3) or saline (n=3) and no sieve electrode were similarly implanted as controls. Nine months post-operatively, functional nerve regeneration through implanted devices was assessed *in situ* via nerve conduction studies, and measurement of maximal isometric force production resulting from sciatic nerve stimulation. Measurements were compared to similar analyses of uninjured sciatic nerves (n=6). Nerve interface capabilities were assessed *in situ* by stimulating regenerated nerve tissue via implanted sieve electrodes while simultaneously recording force production in multiple muscle groups. Regenerated nerve segments were then explanted, fixed, and embedded in either OCT compound or Araldite 502 for morphological or histomorphometric evaluation, respectively.

Results: Histological analysis demonstrated that sieve electrode assemblies containing NGF-loaded fibrin delivery system supported greater numbers of nerve fibers, a greater percent nerve area, and greater numbers of myelinated nerve fibers than assemblies containing saline. (Fig. 1) Sieve electrode assemblies containing

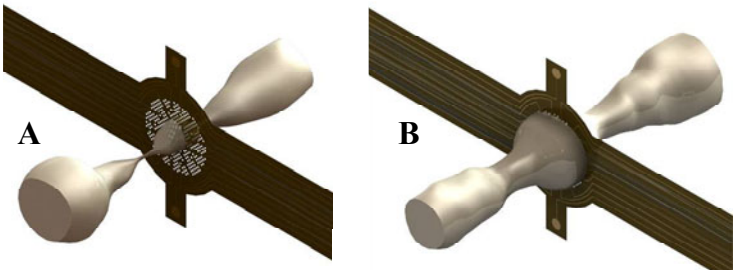

Figure 1. 3-D reconstruction of regenerated nerve extending through sieve electrode in the absence (A) and presence (B) of fibrin-based delivery system loaded with β-NGF.

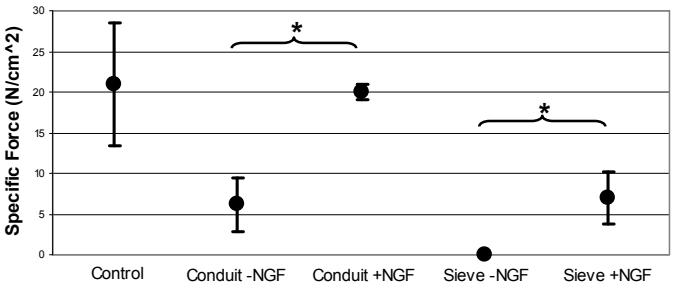

Figure 2. Comparison of specific force production in the extensor digitorum longus muscle across experimental groups. (* denotes $p<0.05$ across presence of delivery system + NGF)

delivery system and NGF also facilitated significant increases in muscle force recovery (Fig. 2) and increases in conducted compound neural action potential amplitude, compared to those containing saline. Despite inhibiting functional nerve regeneration to some extent, implanted sieve electrodes paired with NGF-loaded delivery system achieved stable interfaces with multiple groups of regenerated motor axons, allowing for graded recruitment of multiple muscles within the lower leg.

Conclusions: The present study demonstrates that controlled delivery of β-NGF enhances functional nerve regeneration through sieve electrodes, which subsequently facilitates superior nerve/electrode interface capabilities. These findings suggest that controlled delivery of NGF is equally useful in promoting nerve regeneration in the presence of both physiological and artificial barriers, and that controlled delivery of NGF may improve the clinical applicability of sieve electrodes. Furthermore, this study demonstrates that controlled delivery of trophic factors may modulate neural activity at the tissue/electrode interface, providing support for future investigations into devices capable of simultaneously interacting with tissue on both a bioelectric and biomolecular level.

References:

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