Introduction: Functional motor recovery following peripheral nerve injuries is usually incomplete and often leads to irreversible muscle atrophy. Severity of muscle atrophy depends on the time the nerve takes to reach the end-organ. A cascade of phenomena characterizes the process that the muscle undergoes following the motor nerve injury. The decrease in the diameter (atrophy) begins in the center of the muscle fiber in the first weeks and progressively expands to the periphery. 

Electrophysiology: The fast twitch and maximum tetanic strength of the denervated muscle were improved when injected with IGF-1 and to a lesser extent with NGF (p=0.03 and 0.025) (Figures 1 and 2). Immunohistochemistry (Desmin, Vimentin, Acetylcholine receptor and DAPI). Paired t-test was used for statistical analysis.

Results: Electrophysiology: The fast twitch and maximum tetanic strength of the denervated muscle were improved when injected with IGF-1 and to a lesser extent with NGF (p=0.03 and 0.025) (Figures 1 and 2). Hematoxylin & Eosin: The diameter of myofibers was larger than the denervated control group and almost the same as normal muscles in the IGF-1 injected denervated muscles. Muscles injected with LIF sustained, to a lesser extent, the myofiber diameter following denervation (p=0.07) (Figure 3). The muscles injected with IGF-1 lost less weight than those injected with NGF, b-FGF and LIF (p<0.05) (Figure 4). Immunohistochemistry: Vimentin (fibrosis) and Desmin (regeneration) were negative in all the groups. DAPI staining showed an increase in the number of nuclei in the IGF-1 group (Figure 5). IGF-1 was also capable of sustaining the number of neuromuscular junctions (Figure 6).

Conclusion: Of all the growth factors that have demonstrated potential for regeneration in muscle injuries at 4 weeks, IGF-1 seems to be the most optimal protein to maintain the structure and function of the denervated muscle. The mechanism by which IGF-1 exerts its beneficial effect on the denervated muscle is still unclear, but its dual action as both a mitogen for muscle cells and neurotrophic activity to prevent nerve regeneration appears to be involved in the process.

Our future directions are to investigate the long-term effects of IGF-1 in denervated muscle and the possibility of using gene therapy for a sustained expression of IGF-1 within the denervated muscle. Indeed, the effects after direct administration of the growth factor are limited by a rapid clearance of the protein. The high doses required to produce an effect in a target organ may lead to toxicity due to the concentration necessary to maintain steady-state levels. For that reason we believed gene therapy is a feasible option to have a prolonged delivery of IGF-1 in adequate concentration in the target tissue with minimal systemic exposure.

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References: