Annals of Anatomy 193 (2011) 354–361

Contents lists available at ScienceDirect

Annals of Anatomy

journal homepage: www.elsevier.de/aanat

Enhancing recovery from peripheral nerve injury using treadmill training

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ARTICLE INFO

Article history:
Received 28 December 2010
Received in revised form 3 February 2011
Accepted 22 February 2011

Keywords:
Axon regeneration
Exercise
Neurotrophins
Synaptic stripping
Peripheral nerve

SUMMARY

Full functional recovery after traumatic peripheral nerve injury is rare. We postulate three reasons for the poor functional outcome measures observed. Axon regeneration is slow and not all axons participate. Significant misdirection of regenerating axons to reinnervate inappropriate targets occurs. Seemingly permanent changes in neural circuitry in the central nervous system are found to accompany axotomy of peripheral axons. Exercise in the form of modest daily treadmill training impacts all three of these areas. Compared to untrained controls, regenerating axons elongate considerably farther in treadmill trained animals and do so via an autocrine/paracrine neurotrophin signaling pathway. This enhancement of axon regeneration takes place without an increase in the amount of misdirection of regenerating axons found without training. The enhancement also occurs in a sex-dependent manner. Slow continuous training is effective only in males, while more intense interval training is effective only in females. In treadmill trained, but not untrained mice the extent of coverage of axotomized motoneurons is maintained, thus preserving important elements of the spinal circuitry.

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1. Introduction

Injured axons in peripheral nerves regenerate better than those in the central nervous system, but the functional outcomes observed clinically after peripheral nerves are injured are often so poor that some form of long term disability results (Brushart, 1998; Frostick et al., 1998). The three reasons most often given for these poor outcomes are: (1) that the regeneration of axons in injured peripheral nerves is slow and not all axons participate, leading to a functionally inadequate reinnervation of muscles (Fu and Gordon, 1995, 1997; Gordon, 2009); (2) that regenerating motor axons are misdirected and reinnervate functionally inappropriate targets (Evans et al., 1991; de Ruiter et al., 2008); and (3) that plastic changes in the central nervous system (CNS) that accompany peripheral axotomy alter the relationship of circuitry in the CNS and the reinnervated muscles (Alvarez et al., 2010). Currently, there is no accepted medical treatment for traumatic peripheral nerve injuries that addresses these concerns. The standard of care is to provide a tension free repair of cut nerves and allow the process of regeneration to proceed.

Exercise as a means of improving brain health and function has received considerable recent attention (Adlard and Cotman, 2004; Adlard et al., 2004) at least in part because it has been shown to induce the synthesis of both brain derived neurotrophic factor (BDNF) and its receptor, trkB, in rats and to promote recovery after CNS injury (Gomez-Pinilla et al., 2001; Hutchinson et al., 2004; Molteni et al., 2004; Ploughman et al., 2005). Therapeutic exercise thus could form a useful means of stimulation to the growth of regenerating peripheral axons that would require very little clinical intervention. Because it activates motor and primary afferent neurons naturally, via their own neural circuits, one might expect that exercise could produce enhanced axon regeneration without increasing the misdirection of those axons to inappropriate targets. Additionally, this natural activation might have effects on the CNS consequences of peripheral nerve injury. Indeed, we have found that exercise in the form of treadmill training has beneficial effects on all three of the critical aspects of recovery from peripheral nerve injury listed above. In the review that follows, we will delineate these effects and discuss the need for and direction of future studies.

2. Treadmill training enhances axon regeneration in cut peripheral nerves

Physical activity during the recovery period has been shown to improve motor function after spinal cord injury, both clinically and in experimental animals (Skinner et al., 1996; Edgerton et al., 1997; Hutchinson et al., 2004). Improvements in both sensory and motor functions have been described. Along with the successful effects of treadmill training in spinal cord injured cats by Rossignol and colleagues (Chau et al., 1998), Edgerton and colleagues have advocated treadmill exercise as a treatment for patients with spinal cord injury. They showed that both voluntary exercise (Gomez-Pinilla

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doi:10.1016/j.aanat.2011.02.013

et al., 2002; Engesser-Cesar et al., 2005) and treadmill training (Ying et al., 2005; Heng and de Leon, 2009) resulted in substantial increases in the expression of BDNF and neurotrophin-3 (NT-3) in the spinal cord, and that this was a likely source of support of the local neuronal circuitry caudal to the injury site (Courtine et al., 2009). Both the Edgerton group (Edgerton et al., 2004) and Basso and colleagues (Hutchinson et al., 2004) provided strong evidence for improvement in functional recovery in animals with spinal cord injuries. Although limitations to this approach have been recognized (Barbeau et al., 2006), a number of studies have been published establishing the potential value of treadmill training in spinal cord injury (reviewed by Wessels et al., 2010). Treadmill training for spinal cord injured patients is now a part of many rehabilitation therapy clinics worldwide.

Until recently, the effects of applied exercise during the recovery period following peripheral nerve injury had been less extensively studied. Application of exercise *prior to* peripheral nerve injury is thought to have a protective effect and is said to "prime" adult dorsal root ganglion neurons for increased axon regeneration (Molteni et al., 2004). Marqueste et al. (2004) showed that treadmill exercise following transection of the common fibular nerve induced better functional recovery of muscle sensory axons. The effects of exercise on motor function after peripheral nerve injury were equivocal. Some had concluded that exercise has beneficial effects (van Meeteren et al., 1997, 1998) but others have argued that it does not (Soucy et al., 1996).

Because treadmill exercise was known to increase the expression of neurotrophins and their receptors in spinal motoneurons (Funakoshi et al., 1995; Gomez-Pinilla et al., 2002; Hutchinson et al., 2004; Molteni et al., 2004), we evaluated the effects of modest daily treadmill training on axon regeneration following peripheral nerve injury. We have used mice in which a subset of the sensory and motor axons in peripheral nerves are marked completely by yellow fluorescent protein (YFP) (Feng et al., 2000) to study the elongation of fluorescent regenerating axon profiles into segments of the same nerves harvested from strain-matched mice without fluorescence. Repairing the nerves with these grafts enabled easy visualization of YFP+ axons without interference of fluorescent products of degenerating axons. It also enabled us to use mouse genetics to manipulate the regenerating axons and the environment through which they elongate separately. Using a simple treadmill training program similar to one of those used successfully by Basso and her colleagues (Hutchinson et al., 2004), we showed that 1 h of daily continuous slow walking begun on the third day following transection and surgical repair of different peripheral nerves in wild type mice resulted in a striking increase in the length of regenerating axons through grafts from wild type littermates (Fig. 1). These enhancing effects of regular training were observed as early as 1 week after nerve transection and persisted for at least 2 weeks following the cessation of daily training. Similar enhancement was found in mice where cut nerves were repaired using simple end-to-end anastomosis of the cut stumps using retrograde labeling of motoneurons as an assay of regeneration (English et al., 2009) and in rats with similar transection and repair, restoration of evoked compound muscle action potentials (M responses) occurred at earlier post-transection times than in untrained controls (Boeltz et al., 2010). Treadmill training thus results in enhancement of axon regeneration in cut peripheral nerves.

We chose to impose treadmill exercise on our animals rather than allow them to exercise voluntarily, because we wanted to be able to control the intensity, duration, and pattern of training. However, when compared to the patterns of training used by mice voluntarily (De Bono et al., 2006), our slow continuous training paradigm was quite different. During voluntary exercise, mice run at much greater speeds, up to 80% of their maximum running speed, and they do so for relatively short durations. The durations of these

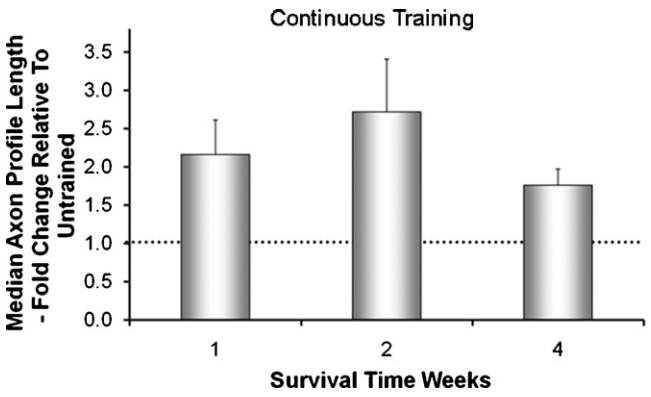

Fig. 1. The effects of continuous treadmill training on axon regeneration in peripheral nerves. Cut common fibular nerves in *thy-1-YFP-H* mice were repaired with a short length of nerve harvested from a non-fluorescent littermate. Animals were trained continuously for 1 h per day at a slow treadmill speed (10 m/min), 5 days per week for no more than 2 weeks. Using images of optical sections made through these grafts, the lengths of YFP+ regenerating axon profiles were measured at different survival times. Average median axon profile lengths, expressed as a percentage of untrained controls (±SEM, $N = 4$ for each), are shown. The horizontal dashed line at 1.0 indicates the length of regenerating axons in untrained controls.
Data are from Sabatier et al. (2008).

intervals is approximately 2 min and bouts of running are separated by rest periods of 5 min (De Bono et al., 2006). Mice repeat this interval training many times each night, and females run approximately twice as many intervals as males (De Bono et al., 2006). Based on these observations, we treated mice with cut and graft-repaired nerves using an interval training paradigm. Animals covered the same distance (600 m), but at a faster speed (20 m/min), and in 2 min intervals separated by 5 min of rest. This interval training for 2 weeks resulted in regenerating axons that were approximately twice as long as untrained controls, the same enhancement of axon regeneration found with slow continuous walking (Sabatier et al., 2008). Reducing the number of training intervals to as few as two had no significant effect on the amount of enhancement of axon regeneration (Fig. 2). Running for a single 2-min interval or more extensive interval training at slow treadmill speeds were both ineffective in enhancing axon regeneration. Thus, both slow continuous walking and faster running at intervals are paradigms that enhance axon regeneration in cut peripheral nerves.

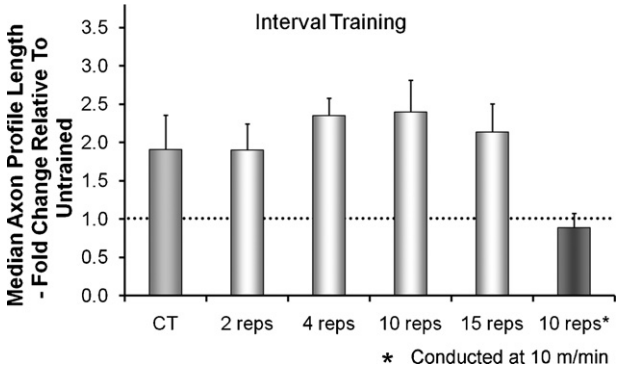

Fig. 2. The effects of interval treadmill training on axon regeneration in peripheral nerves. The paradigm used was similar to that described for Fig. 1 except for the pattern of treadmill training. Animals were trained at a faster treadmill speed (20 m/min), for 2 min and then rested for 5 min. This interval was repeated different numbers of times. Training was conducted 5 days/week for 2 weeks. Average median axon profile lengths, expressed as a percentage of untrained controls (±SEM, $N = 4$ for each), are shown. The horizontal dashed line at 1.0 indicates the length of regenerating axons in untrained controls.
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