Effects of activity-dependent strategies on regeneration and plasticity after peripheral nerve injuries

Esther Udina a, b, Stefano Cobianchi a, b, Ilari Allodi a, b, Xavier Navarro a, b, *

a Group of Neuroplasticity and Regeneration, Institute of Neurosciences and Department of Cell Biology, Physiology and Immunology, Universitat Autònoma de Barcelona, Bellaterra, Spain
b Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Spain

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SUMMARY

Peripheral nerve injuries result in loss of motor, sensory and autonomic functions of the denervated limb, but are also accompanied by positive symptoms, such as hyperreflexia, hyperalgesia and pain. Strategies to improve functional recovery after neural injuries have to address the enhancement of axonal regeneration and target reinnervation and also the modulation of the abnormal plasticity of neuronal circuits. By enhancing sensory inputs and/or motor outputs, activity-dependent therapies, like electrostimulation or exercise, have been shown to positively influence neuromuscular functional recovery and to modulate the plastic central changes after experimental nerve injuries. However, it is important to take into account that the type of treatment, the intensity and duration of the protocol, and the period during which it is applied after the injury are factors that determine beneficial or detrimental effects on functional recovery. The adequate maintenance of activity of neural circuits and denervated muscles results in increased trophic factor release to act on regenerating axons and on central plastic changes. Among the different neurotrophins, BDNF seems a key player in the beneficial effects of activity-dependent therapies after nerve injuries.

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1. Introduction

Peripheral nerve injuries result in loss of motor, sensory and autonomic functions in the denervated territory. Moreover, as a consequence of the nerve injury positive symptoms also appear, such as hyperreflexia, due to enhanced spinal motor responses, and hyperalgesia and pain, influenced by plastic changes of afferent projections in the spinal cord, in addition to the development of distorted central somatotopic maps of the reinnervated regions (Lundborg, 2003; Navarro et al., 2007). The functional loss can be recovered if injured axons grow into the distal stump and reestablish functional connections with appropriate peripheral target organs. The degree of reinnervation primarily depends on the severity of the injury, related to length of nerve disruption and misalignment of nerve stumps, and on the repair procedure applied (Valero-Cabré and Navarro, 2002). The ultimate goal of peripheral nerve repair is an effective functional recovery, which requires a sufficient amount of regenerated axons, but also appropriate target reinnervation, and restitution of adequate central connectivity in spinal circuits.

Various forms of exercise training are used in rehabilitation medicine to help maintaining muscle properties during denervation or paralysis and to promote functional recovery after neural injuries and in neurodegenerative diseases. During the regeneration-reinnervation period, enhanced sensory inputs and/or motor activity by means of electrostimulation or exercise have been shown to positively influence the neuromuscular functional outcome after experimental nerve injuries (Al-Majed et al., 2000; Asensio-Pinilla et al., 2009; Marquete et al., 2004; Vivo et al., 2008). Furthermore, activation of sensory afferents via electrical stimulation can result in modulation of spinal reflex circuits (Vivo et al., 2008) and amelioration of neuropathic pain (Nam et al., 2001; Sun et al., 2004). Intensive programs of sensory re-education after nerve injury can improve tactile discrimination and threshold perception, although this effect may wane after cessation of training (Shieh et al., 1998). Combined rehabilitation of motor and sensory functions by passive or active exercise programs may eventually lead to a better coordination of sensory-motor tasks and restoration of adequate circuitry at the spinal level. This review is focused on the effects of activity-dependent treatments, particularly exercise training, on peripheral nerve function.
Table 1

<table>
<thead>
<tr>
<th>Activity</th>
<th>Injury</th>
<th>Duration</th>
<th>Nerve regeneration</th>
<th>Collateral sprouting</th>
<th>Neuropathic pain</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swimming</td>
<td>SNC</td>
<td>3 d</td>
<td>↑ Axonal growth</td>
<td></td>
<td>↓ Allodynia 5–7 wk</td>
<td>Gutmann and Jakoubek (1963); Hutchinson et al. (2004)</td>
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<td></td>
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<td></td>
<td>Herbison et al. (1974)</td>
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<tr>
<td>Wheel running</td>
<td>Intact</td>
<td>2 h/d, 3–6 wk</td>
<td>↓ Reinnervation</td>
<td>↑ Reinnervation</td>
<td></td>
<td>Ghiani et al. (2007); Gomez-Pinilla et al. (2002)</td>
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<tr>
<td></td>
<td></td>
<td>1–2 h/d, 4–6 wk</td>
<td>↑ MAG, ↑PKA</td>
<td>↑ BDNF, GAP-43, CREB</td>
<td></td>
<td>Molteni et al. (2004); Ying et al. (2005)</td>
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<tr>
<td></td>
<td>SNF</td>
<td>3, 7 d</td>
<td>↑ Regeneration</td>
<td></td>
<td></td>
<td>Irintchev and Wernig (1987)</td>
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<tr>
<td></td>
<td></td>
<td>17/34 wk</td>
<td>↑ Regeneration in tibialis a. (2 wk), ↑ Regeneration in soleus muscle (8–12 wk)</td>
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<td></td>
<td>LGST</td>
<td>30 or 90 d</td>
<td>↑ Contraction</td>
<td></td>
<td>↑ MU enlargement</td>
<td>Tam et al. (2001)</td>
</tr>
<tr>
<td>Treadmill running</td>
<td>Intact</td>
<td>1 h/d, 4 wk</td>
<td>↑ BDNF, NT4, TrkB</td>
<td></td>
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<td>Skup et al. (2002); Wernig et al. (1991)</td>
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<td></td>
<td></td>
<td>9 h, 1–7 wk</td>
<td>↑ Sprouting ↑ Fiber type change</td>
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<td></td>
<td>PNTR</td>
<td>3 h/d, 10 wk</td>
<td>↑ CNAPs</td>
<td></td>
<td>↓ Allodynia; ↑ Allodynia</td>
<td>Marqueta et al. (2004); Cobianchi et al. (2010)</td>
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<td></td>
<td>CCI</td>
<td>1 h/d, 1 wk</td>
<td>↑ Regeneration</td>
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<td></td>
<td>1 h/d, 8 wk</td>
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<td></td>
<td>L4T</td>
<td>10 wk pre-injury</td>
<td>↑ Sprouting in plantaris, ↓ in soleus</td>
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<td>Gardiner et al. (1984)</td>
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<tr>
<td></td>
<td>L4T, LST</td>
<td>8 h/d, 3–28 d</td>
<td>↑ Sprouting and Schwann cells bridging</td>
<td></td>
<td></td>
<td>Tam and Gordon (2003); Herbst et al. (1980a,b); Seo et al. (2009)</td>
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<tr>
<td></td>
<td>SNF</td>
<td>1–2 h/d, 2–6 wk</td>
<td>↑ Type II fibers in plantaris muscle</td>
<td>↑ DRGs neurite growth, Schwann cells proliferation, ↑ GAP-43</td>
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<td></td>
<td></td>
<td>1 h/d, 14 d</td>
<td>↑ DRGs neurite growth, Schwann cells proliferation, ↑ GAP-43</td>
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<tr>
<td></td>
<td>SNTR</td>
<td>1 h/d, 4 wk</td>
<td>↑ Regeneration and reinnervation</td>
<td>↑ Sensory recovery</td>
<td></td>
<td>Asensio-Pinilla et al. (2009); Sabatier et al. (2008)</td>
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<tr>
<td></td>
<td></td>
<td>20 m/d, 2 wk</td>
<td>↑ Axon elongation and sprouting</td>
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<td></td>
<td></td>
<td>60 m/d, 2 wk</td>
<td>↑ Axon elongation but not sprouting</td>
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<td>Sabatier et al. (2008)</td>
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<tr>
<td></td>
<td></td>
<td>1 h/d, 4 wk</td>
<td>↑ Regeneration and reinnervation</td>
<td>↓ H-reflex excitability</td>
<td></td>
<td>Udina et al. (2011)</td>
</tr>
<tr>
<td>Bicycle training</td>
<td>PNC</td>
<td>2 h/d, 4 d</td>
<td>↑ Sprouts and reinnervation</td>
<td></td>
<td></td>
<td>Pachter and Eberstein, (1989)</td>
</tr>
<tr>
<td></td>
<td>SNTR</td>
<td>1 h/d, 4 wk</td>
<td>↑ Regenerated axons and reinnervation</td>
<td>↑ H-reflex excitability</td>
<td></td>
<td>Udina et al. (2011)</td>
</tr>
<tr>
<td>Mechanical stimulation</td>
<td>FeTR</td>
<td>Daily, 8 wk</td>
<td>↑ Reinnervation</td>
<td></td>
<td></td>
<td>Angelow et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>MTR</td>
<td>2 wk</td>
<td>No effect</td>
<td>↑ Sprouting nociceptive fibers</td>
<td>↑ Sensitivity</td>
<td>Sinis et al. (2008); Nixon et al. (1984)</td>
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<tr>
<td></td>
<td>DCNT</td>
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</table>

Injury: SNC: sciatic nerve crush; SNF: sciatic nerve freezing; L4T: spinal L4 root transection; LST: spinal L5 root transection; LGST: lateral gastrocnemius-soleus nerve transection; PNTR: peroneal nerve transection and repair;CCI: chronic constriction injury of sciatic nerve; SNTR: sciatic nerve transection and repair; PNC: peroneal nerve crush; FeTR: facial nerve transection and repair; MTR: median nerve transection and repair; DCNT: dorsal cutaneous nerve transection. Duration: m: minutes; h: hours; d: days; wk: weeks. Others: ↑: enhancement or increase; ↓: reduction or decrease; MU: motor units; CNAPS: compound nerve action potentials; DRGs: dorsal root ganglia.

and regeneration and on plastic changes in spinal circuits (see Table 1).

2. Effects of exercise training on neuromuscular function

Peripheral nerve lesion or spinal cord injuries induce inactivity and subsequent paralysis of affected skeletal muscles. Denervation or disuse leads to a progressive atrophy of skeletal muscles, with marked loss of muscle mass, decreased cross-sectional area of muscle fibers and changes in the mechanical and biochemical muscle characteristics (Boudriau et al., 1996; Gordon and Mao, 1994; Marqueta et al., 2006). These adaptations are most evident in muscles predominantly of slow-twitch, which show the highest rate of recruitment during normal activity. Amongst the fast-twitch muscles, the ones that are normally more active (e.g., extensors versus flexors in the hind limb) are also more affected by inactivity (Roy et al., 1999). In general, slow muscles become faster and fast muscles become slower following disruption of their nerve supply (Pette and Staron, 2001). Reinnervation of a previously denervated muscle partially restores its phenotype, indicating the importance of neural activity in the maintenance of muscle fiber types (Wang et al., 2002).

However, activity is not the only factor that influences the quality of the muscle. Alterations in the muscle are more marked after peripheral nerve injuries than after spinal cord lesions (Roy et al., 2002). The disruption of the neuromuscular unit after nerve lesion leads to the loss of both activity-dependent and -independent neural influences on the muscle.
Artificially maintaining muscle activity during denervation/paralysis may improve neuromuscular rehabilitation. Electrostimulation of denervated muscle, passive exercise and locomotion training have been shown to be effective strategies in retarding muscle atrophy and improving contractile response after reinnervation (Eberstein and Pachter, 1988; Henning and Lomo, 1987; Marqueste et al., 2004; Pachter and Eberstein, 1989; Soucy et al., 1996). In contrast to inactivity, increased neuromuscular activity or overloading (increased load to a muscle induced by surgical ablation of synergistic muscles) elicits fiber type transition from fast to slow (Pette, 2002). Muscle activity induced by stimulation may result in an autocrine release of trophic factors, thus avoiding the disuse effect following nerve or central lesions (Goldspink and Yang, 2001; McKoy et al., 1999). Muscle fibers are also capable of adjusting their phenotypic properties in response to muscle or nerve electrical stimulation (Marqueste et al., 2006; Pette and Vrbova, 1992), static stretching (Sakakima and Yoshida, 2003) and also to exercise (Booth and Thomason, 1991). To this respect, it was suggested that induced activity mimicking physiological motion would produce better preservation/recovery of muscle functional properties than conventional electrical stimulation (Marqueste et al., 2004, 2006). However, both forced exercise and electrical stimulation of the injured nerve had positive effects in promoting muscle reinnervation after nerve injury in rats (Asensio-Pinilla et al., 2009). Rather than the amount of electrical activity received, the effects seem to be mainly influenced by shortening or lengthening of the muscles (Gordon and Pattullo, 1993; Gordon et al., 2004).

3. Effects of exercise on peripheral nerve regeneration

An overview of the literature shows conflicting evidence on beneficial and deleterious effects of exercise on peripheral nerve regeneration and muscle reinnervation. Variations in the type of nerve injury, the exercise applied, time and intensity of training appear to be the main factors explaining the controversial results reported.

The amount and intensity of training play a key role in the positive effects of exercise after nerve injury. Hines (1942) reported beneficial results of daily running in a wheel only during the period of denervation, as trained rats showed a slightly but consistent increase in muscle mass and isometric muscle strength. Gutmann and Jakoubek (1963) found an early (3 days) increase in the axonal growth rate after bilateral sciatic nerve crush in rats forced to swim compared with that of sedentary controls. Nevertheless, long term hyperactivity induced by tenotony (tendon section) of synergist muscles (Herbison et al., 1973), intensive swimming (Gutmann and Jakoubek, 1963; Herbison et al., 1974), or treadmill running (Herbison et al., 1980a,b) for 2–6 weeks after crush lesion of the sciatic nerve in rodents tended to show deleterious effects on muscle function recovery. On the other hand, mice running voluntarily after their sciatic nerves were cut and re-sutured, initially demonstrated a delayed reinnervation, whereas at later stages postlesion nerve maturation was improved (Badke et al., 1989). Voluntary running produced a decreased weight and force in extensor digitorum longus muscles but an increased force and weight in soleus muscles (Irntchev et al., 1990, 1991). These changes are typical of endurance training and could be interpreted as beneficial. Consistent with these observations, van Meeteren et al. (1997a) reported beneficial effects of exercise training, in the form of voluntary static standing on both hindpaws, on the recovery of motor and sensory functions during the early phase of reinnervation after sciatic nerve crush. After 10 weeks of standing exercise (van Meeteren et al., 1997a) or treadmill training (Marqueste et al., 2004) fast nerve fibers increased in proportion and improved their conduction velocity. In mice, continuous moderate or intermittent high-intensity training promote axonal elongation after autograft repair (Sabatier et al., 2008). Besides, low but not high intensity treadmill training potentiates Schwann cell proliferation in the regenerating sciatic nerve in rats (See et al., 2009).

It can be hypothesized that, when initiated in the denervation phase, moderate exercise results in accelerated functional sensorimotor recovery, because exercise might be beneficial for axonal outgrowth, nerve maturation, and recovery of muscle contractile properties, whereas forced intense exercise tends to have a detrimental effect, especially on muscle function, and overwork may even damage partially denervated muscles (Herbison et al., 1973; Irntchev et al., 1991; van Meeteren et al., 1997a). It is important to note that, in most of the studies on laboratory rodents, these were submitted to exercise from 3 to 5 days after nerve lesion, to avoid possible damage to the sutured nerve, and also due to the lack of clear evidence that exercise is beneficial at very early stages of regeneration.

Little is known about the possible differential effects of passive, voluntary or forced exercise paradigms, differences that might affect the interpretation of results. Swimming and treadmill running increase physical activity, but may not merely represent physical overload, and, stress-related changes influence the results of training experiments (van Meeteren et al., 1997b). Some studies have shown that passive exercise of the denervated muscle before their reinnervation preserves the structure of the end-plates and enhance reinnervation (Pachter and Eberstein, 1989). In contrast, continuous passive motion of the hindlimb after tibial nerve section did not influence nerve regeneration, when this treatment was performed only during the first 14 days after injury (Kim et al., 1998). Recently, it has been demonstrated that daily brief manual stimulation (5 min/day for 2 months) of whisker pad muscles following section and repair of the pure motor facial nerve resulted in improved restoration of facial movements (whisking) and a reduction in motor endplate poly-innervation (Angelov et al., 2007; Guntinas-Lichius et al., 2007), indicating that activation of the intact sensory afferents could enhance motor regeneration. However, the same procedure did not influence the recovery, the degree of axonal sprouting or the extent of polynervation of motor endplates when applied to the mixed median nerve injured in the forelimb (Sinis et al., 2008).

In a recent study, both passive and active exercise produced similar slight improvement in regeneration of the rat sciatic nerve, as indicated by increased recovery of compound muscle action potentials (CMAPs) a higher number of regenerated axons in the distal nerve, and a reduction in the increased excitability of spinal reflexes after nerve injury (Udina et al., 2011). Interestingly, there were differences in the recovery of flexor (gastrocnemius) and extensor (tibialis anterior) muscles depending on the type of exercise. Treadmill walking prevented hyperreflexia in both muscles, whereas, with passive cycling, it was only observed in the gastrocnemius muscle (Fig. 1). Cycling mainly acts by alternating lengthening and shortening of the triceps surae (Houle et al., 1999), whereas in active running, both extension and flexion of the ankle are alternated by the animal. The differential effects of exercise training on different muscle responses have been also reported in spinalized animals (Roy et al., 1998, 2005). On the other hand, cycling exercise is able to prevent muscle atrophy after spinal cord lesion but not the transition of soleus myofibers from slow to fast (Houle et al., 1999), whereas treadmill training prevents both atrophy and conversion of myofiber type (Roy et al., 1999).

Regarding the mechanisms of action, Molteni et al. (2004) found that dorsal root ganglia (DRG) neurons exhibited increased neurite outgrowth when cultured from animals that had undergone 3 or 7 days of exercise compared with sedentary animals; neurite length in culture directly correlated with the distance that animals
Ran, DRGs from exercised animals had higher levels of BDNF, NT3, and GAP43 mRNAs than DRGs from sedentary animals. Inhibition of Trk neurotrophin receptor activity before exercise attenuated the exercise-dependent increase in neurite growth, indicating that activation of neurotrophin signaling pathways during exercise plays a critical role in promoting plasticity and growth of neurons. Moreover, exercise significantly decreased the levels of myelin-associated glycoprotein (MAG), a potent axonal growth inhibitor, suggesting that downregulation of MAG is part of the mechanism through which exercise reduces growth inhibition (Ghiani et al., 2007). This effect was suppressed by blocking the action of BDNF during exercise, suggesting a potential role of BDNF in mediating the effects of exercise on axonal growth (Chytrova et al., 2008).

4. Effects of exercise on motoneurons and reflex motor responses

Spinal motoneurons are sensitive to increased chronic activity and respond with phenotypic changes, which influence the manner in which these cells behave during voluntary recruitment (Gardiner et al., 2006). Motoneurons can adapt several functional relevant properties without losing the phenotype that designate them as fast or slow motoneurons. Some adaptations seem designed to have functional consequences during endurance exercise (increased capacity for axonal transport and for neurotransmitter release). Intense or mild endurance training in rats cause biophysical changes, such as hyperpolarized resting membrane potential and voltage threshold, and increase amplitude of afterhyperpolarization (Beaumont and Gardiner, 2003). This hyperpolarization may reduce the level of excitability for prolonged inputs. It is thus possible that exercise adapts motoneurons to a lower state of excitability. Although reflex responses evoked during voluntary contractions are potentiated following strength training, the corresponding H reflexes (i.e., the reflex response evoked by electrical stimulation of sensory afferents) and the F responses (late response induced by antidromic electrical stimulation of motor axons) at rest are not, suggesting that changes in intrinsic motoneuronal excitability are not involved in these responses (Sale et al., 1983).

Changes in spinal reflexes persist after nerve injury and reinnervation, and may impair motor unit activation and control of movement, accounting in part for the poor clinical outcome achieved after severe nerve injuries (Valero-Cabré and Navarro, 2001). Forcing the activity of the injured neurons, by either passive or active exercise, decreases the hyperreflexia observed after peripheral nerve lesions (Fig. 1) (Asensio-Pinilla et al., 2009; Udina et al., 2011). This attenuation of hyperreflexia can be due to regulatory actions from the increased expression of neurotrophic factors in the spinal cord (Vaynman and Gomez-Pinilla, 2005) or to the beneficial effects of exercise on the muscles. Altered neuronal excitability of injured motoneurons is recovered after reinnervation (Foehring et al., 1986), suggesting that functional contact with muscle is required for the full expression of the normal neuronal electrical properties. Exercise, by maintaining the trophism and normal properties of the muscle can facilitate the expression of still unknown muscular signals to the innervating axons and attenuate the post-injury hyperreflexia. Even during the denervation period, exercise of the limbs stimulates muscle afferents from proximal innervated muscles, which may influence the axotomized motoneurons by spinal synaptic connections normally silent (Koerber et al., 2006). The effects observed with exercise training on the spinal H reflex are not likely caused by actions on motoneuronal excitability during the reinnervation phase. Probably, alterations in segmental inhibition, mainly involving modulation of la presynaptic inhibition, may serve as a mechanism responsible for chronic training-induced adaptations in the H reflex (Zehr, 2006).

The effects of activity-dependent treatments on adaptive plasticity of spinal motor reflexes have been studied mostly after spinal cord injury, which usually leads to hyperreflexia and spasticity. Using an acute and chronic pattern of treadmill locomotor training, the enlarged H/M ratio (ratio between the amplitude of the H reflex wave and the amplitude of the direct M wave after electrical nerve stimulation) could be significantly suppressed in patients with spinal cord injury (Trimble et al., 2001). Passive bicycle exercise can also restore the frequency-dependent depression of spinal H reflex in a time-dependent manner following complete spinal transection in rats (Liu et al., 2010; Reese et al., 2006). Cycle training can likely be considered functionally equivalent to walking training in this context.

Recent research on the effects of activity on functional recovery after neural injuries is focused on the importance of afferent information from the periphery as a source of control of posture or locomotor tasks, in conjunction with the spinal circuitry to which central pattern generation is routinely attributed (Edgerton et al., 2008). Expression of brain-derived neurotrophic factor (BDNF), neurotrophin-4 (NT4), their receptor tyrosine kinase B (trkB), and growth-associated protein-43 (GAP-43) are all increased in lumbar spinal cord and DRG neurons by voluntary exercise and decreased in muscle paralysis (Gomez-Pinilla et al., 2002; Skup et al., 2002). Then, it can be hypothesized that maintenance of denervated muscle activity increases the release of trophic factor that will benefit

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**Fig. 1.** Plots of the recovery of compound muscle action potential (M wave) amplitude (top), and of the H/M ratio (ratio between the amplitude of the H reflex wave and the amplitude of the direct M wave after electrical nerve stimulation) (bottom) of the tibialis anterior muscle after sciatic nerve transaction and suture repair in the rat. One group received treadmill training at 5 m/min and another group received cycling exercise at 45 rpm, matching the number of step cycles in both activities. Note the increased levels of reinnervation in the late phase and the reduction of hyperreflexia during early phase of reinnervation (modified from Udina et al., 2011).
axonal regeneration and induce plastic changes in central synaptic connections.

5. Effects of exercise on collateral sprouting

After a peripheral nerve injury, neighboring intact nerve fibers are able to extend collateral branches into regions previously occupied by nerve fibers that have undergone degeneration. This phenomenon allows reinnervation of denervated targets as an adaptive mechanism to functionally rescue muscle and sensory targets.

Within partially denervated muscles, collateral sprouts emerge from the nodes of uninjured myelinated motor fibers above the motor nerve terminal to reinnervate nearby denervated muscles (Griffin and Thompson, 2008; Son and Thompson, 1995). The effects of neuromuscular activity on axonal sprouting and motor units enlargement have been controversial due to the conflicting findings of previous studies, which used different activity regimes and different muscles. Prolonged treadmill exercise was shown to have a preferential effect on promoting enlargement of fast-fatigable and fast-intermediate motor units in the partially denervated gastrocnemius (Einsiedel and Luff, 1994) and plantaris muscles (Gardiner et al., 1984). Since there was no evidence of muscle hypertrophy, the increased muscle force was attributed to changes in the extent of axonal sprouting. In contrast, other studies have reported that activity (wheeling exercise or functional overload) had no effects on motor unit enlargement by axonal sprouting in the plantaris muscle (Gardiner and Faltus, 1986; Michel and Gardiner, 1989).

A thorough evaluation of active and passive neuromuscular activity on muscles subjected to different extent of partial denervation (Tam et al., 2002; Tam and Gordon, 2003) showed that daily protocols of high activity (8 h daily running exercise or functional electrical stimulation of the nerve) constrained axonal sprouting and consequent motor unit enlargement in extensively denervated muscles. The same detrimental effect was not evident in moderately denervated muscles, where motorunit size increased normally following partial denervation. They further demonstrated that the inhibitory effect of increased neuromuscular activity takes place at the early onset of axonal sprouting in extensively denervated muscles (Tam and Gordon, 2003). Following denervation, terminal Schwann cells elaborate a network of long processes that grow from the vacant end plate, forming “bridges” to nearby innervated end plates. Activity seems to alter at least two responses triggered by denervation in muscles: the ability of the processes of terminal Schwann cells to form bridges with innervated synaptic sites (Love et al., 2003; Tam and Gordon, 2003), and the growth of axons along these processes (Love et al., 2003). Therefore, increased activity during the early phase of denervation after nerve injury can be detrimental for axonal sprouting and collateral reinnervation of denervated muscles. On the other hand, neuromuscular inactivity also reduces the degree of motor axon sprouting (Tam et al., 2002). Thus, present evidence is that too much or lack of neuromuscular activity is counterproductive for effective collateral reinnervation in partially denervated muscles.

Regarding collateral sprouting of sensory axons, unmyelinated and thin myelinated fibers show a strong capacity to sprout and enlarge their innervation territory (Diamond and Foerster, 1992; Nixon et al., 1984), whereas large myelinated fibers fail to produce functionally effective collateral reinnervation of adjacent denervated skin (Jackson and Diamond, 1984). Diamond and coworkers reported that collateral reinnervation of dorsal cutaneous “islands” of the rat skin was accelerated by repeated mechanical stimulation of the skin within the innervated regions, as well as by electrical stimulation of the uninjured nerves (Doucette and Diamond, 1987; Nixon et al., 1984). Activity-induced neurotrophic factor release promotes neuronal growth and plasticity, and may partially antagonize the restrictions for axonal sprouting by changing the intrinsic growth state of neurons. Indeed, administration of NGF and other neurotrophins in vivo potentiates collateral sprouting in the denervated skin (Diamond et al., 1992). In sciatic nerve injury models, collateral reinnervation of denervated skin territories by nociceptors may be related to the underlying hyperalgesia (Casals-Diaz et al., 2009). Thus, inhibition or modulation of collateral sprouting may be of interest for antinociceptive effects.

6. Effects of exercise on neuropathic pain

Peripheral nerve injuries often result in development of neuropathic pain symptoms, including spontaneous pain sensation, hyperalgesia and allodynia (painful perception caused by a normally non-painful stimulus). Neuropathic pain symptoms are also related to axonal regeneration mechanisms and functional recovery. After injury, mechanical allodynia affects the use of the injured paw and compromises successful rehabilitation (Vogelaar et al., 2004). However, only a few studies have investigated the effects of activity treatments on neuropathic pain after nerve injuries.

Cobianchi et al. (2010) found that, after chronic constriction of the sciatic nerve in mice, early short-lasting treadmill running was able to reduce mechanical allodynia and to normalize the walking pattern of the injured hindpaw. Interestingly, the reduction of allodynia was maintained for 2 months, even when treadmill running was interrupted at day 7. Reduction of allodynia after early short-lasting exercise correlated with reduced microglia and astroglia reactivity in the dorsal horn, but astrogliosis was not prevented by long-lasting treadmill running. Other studies also suggest that microglia activation can be related to the hyperalgesia observed after peripheral nerve injuries, and astrocytes may be involved in its maintenance (Cao and Zhang, 2008). These findings suggest that the effectiveness of activity-dependent treatments on neuropathic lesions are related to specific time windows after nerve injury when increased activity may stimulate or inhibit regeneration of injured axons. In line with this view, acute brief electrical stimulation for 1 or 4 h after lesion to the injured nerve enhanced axonal regeneration and muscle reinnervation, whereas chronic daily electrical stimulation was detrimental for nerve regeneration (Asensio-Pinilla et al., 2009). Activity treatments can enhance the plasticity of intact axonal projections to compensate the loss of sensibility provoked by the disruption of neighboring axons. Since synaptic plasticity and sprouting of sensory fibers enhance pain perception during the denervation and reinnervation phases, different activity protocols could differently act on neuropathic pain compared to effects on recovery of motor function.

The effects of treadmill running on pain symptoms may be attributable to its modulation on central and/or peripheral neurotrophin release like in nerve regeneration. Neurotrophins, such as BDNF, are up-regulated in several models of inflammatory and neuropathic pain (Ha et al., 2001; Pezet et al., 2002), and physical exercise is an important modulator of neurotrophin release in regenerating neurons (Molteni et al., 2004; Ying et al., 2005). There is evidence that BDNF may serve both pro- and antinociceptive roles in different contexts (Pezet and McMahon, 2006). After exercise, peripheral and/or central expression and delivery of BDNF depend on the site and model of injury (Vanelderen et al., 2010). BDNF redistribution between DRG neurons has been related to neuropathic pain; after nerve injury, BDNF is upregulated in small- and medium-sized neurons in rats with signs of neuropathic pain, whereas its expression was increased in large sensory neurons in rats without pain (Tender et al., 2010). The antinociceptive effects of central BDNF are thought to arise from its ability to increase the synthesis and release of serotonin in descending pathways.
or by rescuing GABAergic neurons and stimulating GABA release, both providing inhibitory modulation at the dorsal horn (Pezet et al., 2002; Vanelderen et al., 2010). Interestingly, treadmill exercise increases serotoninergic immunoreactivity in medullary raphe nuclei and spinal cord of rats submitted to sciatic nerve section. The increased serotoninergic nerve activity is parallel to the improvement in nociceptive responses and functional recovery. An alternative mechanism of action to explain the hypoalgesia induced by exercise could be the activation of endogenous opioids, specifically β-endorphins (Goldfarb and Jamartas, 1997; Koltyn, 2000). Otherwise, resistance exercise induced an antinociceptive effect mediated by β-endorphin immediately after training, although it lasted only a few minutes (Galdino et al., 2010).

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