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

Esther Udina[a,b], Stefano Cobianchi[a,b], Ilary 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.

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; Marqueste 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

* Corresponding author at: Facultat de Medicina, Universitat Autònoma de Barcelona, E-08193 Bellaterra, Spain. Tel.: +34 935811966; fax: +34 935812986.
E-mail address: xavier.navarro@uab.cat (X. Navarro).

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Table 1
Summary of activity-induced effects in animal models of peripheral nerve injuries.

Activity	Injury	Duration	Nerve regeneration	Collateral sprouting	Neuropathic pain	Reference
Swimming	SNC	3 d	↑ Axonal growth			Gutmann and Jakoubek (1963)
		25 m/d, 7 wk			↓ Allodynia 5–7 wk	Hutchinson et al. (2004)
		2 h/d, 3–6 wk	↓ Reinnervation			Herbison et al. (1974)
		1–2 h/d, 4–6 wk	↑Reinnervation			
Wheel running	Intact	3, 7 or 28 d	↓MAG, ↑PKA ↑BDNF, GAP-43, CREB			Ghiani et al. (2007); Gomez-Pinilla et al. (2002)
	SNC	3, 7 d	↑Regeneration ↑BDNF, NT3, GAP-43			Molteni et al. (2004); Ying et al. (2005)
	SNF	17/34 wk	↑Degeneration in tibialis a. (2 wk), ↑Regeneration in soleus muscle (8–12 wk)			Irintchev and Wernig (1987)
	L4T, L5T	8 h/d, 4 wk		↓Sprouting in tibialis a. muscle		Tam et al. (2001)
	LGST	30 or 90 d	↑Contraction	↑ MU enlargement		Seburn and Gardiner (1996)
Treadmill running	Intact	1 h/d, 4 wk	↑BDNF, NT4, TrkB			Skup et al. (2002)
		9 h, 1–7 wk	↑Sprouting ↑ Fiber type change			Wernig et al. (1991)
	PNTR	3 h/d, 10 wk	↑ CNAPs			Marqueste et al. (2004)
	CCI	1 h/d, 1 wk	↑ Regeneration		↓ Allodynia; ↑Allodynia	Cobianchi et al. (2010)
		1 h/d, 8 wk				
	L4T	10 wk pre-injury		↑Sprouting in plantaris, ↓in solueus		Gardiner et al. (1984)
	L4T, L5T	8 h/d, 3–28 d		↓ Sprouting and Schwann cells bridging		Tam and Gordon (2003)
	SNC	1–2 h/d, 2–6 wk	↑Type II fibers in plantaris muscle			Herbison et al. (1980a,b)
		1 h/d, 14 d	↑ DRGs neurite growth, Schwann cells proliferation, ↑GAP-43			Seo et al. (2009)
	SNTR	1 h/d, 4 wk	↑ Regeneration and reinnervation		↑Sensory recovery	Asensio-Pinilla et al. (2009)
		20 m/d, 2 wk	↑Axonal elongation and sprouting			Sabatier et al. (2008)
		60 m/d, 2 wk	↑Axon elongation but not sprouting			Sabatier et al. (2008)
		1 h/d, 4 wk	↑Regeneration and reinnervation		↓H-reflex excitability	Udina et al. (2011)
Bicycle training	PNC	2 h/d, 4 d	↑ Sprouts and reinnervation			Pachter and Eberstein, (1989)
	SNTR	1 h/d, 4 wk	↑Regenerated axons and reinnervation		↓H-reflex excitability	Udina et al. (2011)
Mechanical stimulation	FcTR	Daily, 8 wk	↑ Reinnervation			Angelov et al. (2007)
	MTR		No effect			Sinis et al. (2008)
	DCNT	2 wk		↑Sprouting nociceptive fibers	↑Sensitivity	Nixon et al. (1984)

Injury: SNC: sciatic nerve crush; SNF: sciatic nerve freezing; L4T: spinal L4 root transection; L5T: 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; FcTR: 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 inactivation 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; Marqueste 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.