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Review Article

Putative roles of soluble trophic factors in facial nerve regeneration, target reinnervation, and recovery of vibrissal whisking

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ABSTRACT

It is well-known that, after nerve transection and surgical repair, misdirected regrowth of regenerating motor axons may occur in three ways. *The first way* is that the axons enter into endoneurial tubes that they did not previously occupy, regenerate through incorrect fascicles and reinnervate muscles that they did not formerly supply. Consequently the activation of these muscles results in inappropriate movements. *The second way* is that, in contrast with the precise target-directed pathfinding by elongating motor nerves during embryonic development, several axons rather than a single axon grow out from each transected nerve fiber. *The third way* of misdirection occurs by the intramuscular terminal branching (sprouting) of each regenerating axon to culminate in some polyinnervation of neuromuscular junctions, i.e. reinnervation of junctions by more than a single axon. Presently, "fascicular" or "topographic specificity" cannot be achieved and hence target-directed nerve regeneration is, as yet, unattainable. Nonetheless, motor and sensory reinnervation of appropriate endoneurial tubes does occur and can be promoted by brief nerve electrical stimulation.

This review considers the expression of neurotrophic factors in the neuromuscular system and how this expression can promote functional recovery, with emphasis on the whisking of vibrissae on the rat face in relationship to the expression of the factors. Evidence is reviewed for a role of neurotrophic factors as short-range diffusible sprouting stimuli in promoting complete functional recovery of vibrissal whisking in blind Sprague Dawley (SD)/RCS rats but not in SD rats with normal vision, after facial nerve transection and surgical repair. Briefly, a complicated time course of growth factor expression in the nerves and denervated muscles include (1) an early increase in FGF2 and IGF2, (2) reduced NGF between 2 and 14 days after nerve transection and surgical repair, (3) a late rise in BDNF and (4) reduced IGF1 protein in the denervated muscles at 28 days. These findings suggest that recovery of motor function after peripheral nerve injury is due, at least in part, to a complex regulation of nerve injury-associated neurotrophic factors and cytokines at the neuromuscular junctions of denervated muscles. In particular, the increase of FGF2 and concomittant decrease of NGF during the first week after facial nerve-nerve anastomosis in SD/RCS blind rats may prevent intramuscular axon sprouting and, in turn, reduce poly-innervation of the neuromuscular junction.

1. Clinical relevance of nerve regrowth and patho-physiological background

Following peripheral nerve injury, the "post-paralytic syndrome", including mass movements (synkinesia) and altered reflexes (Bento and Miniti, 1993; Kerrebijn and Freeman, 1998; Kimura et al., 1975), has been attributed to (i) "misdirected" reinnervation (Montserrat and Benito, 1988; Sumner, 1990): (ii) trans-axonal exchange of abnormally intensive nerve impulses between axons from adjacent fascicles (Sadjadpour, 1975), and (iii) alterations in synaptic input to lesioned

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perikarya (cell bodies) (Bratzlavsky and vander Eecken, 1977; Graeber et al., 1993; Moran and Neely, 1996).

Misdirected or "aberrant" reinnervation has been recognized as the major reason for the post-paralytic syndrome. At the site of a nerve transection injury and surgical repair, it has two components: (i) regenerating axons are misrouted and fail to enter into their original endoneurial tubes as well as their original nerve fascicles (Aldskogius and Thomander, 1986; Anonsen et al., 1986; Baker et al., 1994; Brushart, 1993). (ii) Up to 25 axons with an average of five, grow out from each nerve fiber proximal to the injury site and into the denervated distal nerve stump (Aitken et al., 1947; Dyck and Hopkins, 1972; Morris et al., 1972; Shawe, 1955); this excessive branching may lead to re-innervation of different muscles (Ito and Kudo, 1994; Ribchester, 1988).

A third component of misdirected reinnervation after peripheral nerve transection and surgical repair is the terminal sprouting of regenerating axons. Upon reaching a denervated muscle target, each regenerating axon undergoes intramuscular branching (sprouting) to reinnervate many muscle fibers that compensate for limited axon regeneration; the limit of the motor unit enlargement is ~3–5-fold that is the same as the limit of axon sprouting from intact nerves after partial denervation (Fu and Gordon, 1995a; Rafuse et al., 1992; Rafuse and Gordon, 1996a, 1996b; Son et al., 1996). Sprouting has been regarded as an adaptive mechanism to compensate for reduced numbers of motoneurons that regenerate their axons (Gordon et al., 2004). However, the functional capacity of the smaller numbers of motor units, whose force output is increased by the inclusion of more muscle fibers, is obviously compromised by their reduced numbers and consequent larger force increments during their progressive recruitment (Gordon et al., 2004). Extensiive intramuscular sprouting leads to transient polyneuronal innervation of hindlimb muscles (Fu and Gordon, 1997; Gorio et al., 1983; Rich and Lichtman, 1989) but polyneuronal reinnervation may remain in other muscles, including reinnervated vibrissae after facial nerve injuries (Grosheva et al., 2017).

2. Effects of trophic factors on collateral axonal branching at the lesion site

2.1. Postlesional neurite regrowth consists of elongation and branching

Peripheral nerve transection is followed by attempted regeneration of the transected axons (Wilson and Perry, 1990). In the everyday clinical practice, however, functional recovery after peripheral nerve injury is the exception rather than the rule (Hall, 1989; Kline and Hudson, 1995; Lisney, 1989; Thomas, 1989). Many of the numerous regenerating axons that are emitted by each nerve fiber in the proximal nerve stump are misrouted through the endoneural tubes of fascicles that the axons did not populate prior to the injury. In turn, these axons are misdirected towards denervated targets hat they did not previously innervate (Ito and Kudo, 1994; Trachtenberg and Thompson, 1996), Indeed, regenerating motor axons randomly reinnervate denervated target muscles (Gillespie et al., 1986, 1987).

2.1.1. Collateral axonal branching at the site of lesion

Injury to the peripheral nerve sets initiates a complex series of changes distal to the site of injury, known collectively as Wallerian degeneration. Within 24 h after the lesion, the axonal content begins to necrotize and axonal debris is phagocytosed by blood-borne macrophages and proliferating Schwann cells (Hirata and Kawabuchi, 2002; McPhail et al., 2004; Perry and Brown, 1992). When resorption is complete, the Schwann cells form long chains of cells (bands of Büngner), which bridge the interfragmentary gap and form guiding channels for the regenerating branches on their way to the denervated target(s) (Büngner, 1891). The architectural pattern of the Büngner's bands of the peripheral stump remains unchanged for three months, after which progressive distortion by proliferating connective tissue occurs (Bisby, 1995). The process of Wallerian degeneration creates an environment that is supportive for axonal growth. The preference for axonal growth into a degenerating nerve ensures that the vast majority of axons will regrow into the distal stump if it remains in continuity with the proximal stump, a crush injury (Bisby, 1995) and, indeed, after microsurgical repair of a transected nerve, all motoneurons regenerate their axons into the distal nerve stump (Al-Majed et al., 2000).

Regenerating axons do not merely elongate towards the distal stump. Rather, they respond with *collateral axonal branching*, a lateral budding that occurs primarily at the nodes of Ranvier, up to 6 mm proximal to the nerve injury site (Bray and Aguayo, 1974) within hours after the injury (Sjoberg and Kanje, 1990). As axon regeneration proceeds, some of these supernumerary branches are pruned off over a period of up to 12 months (Bray and Aguayo, 1974) but the significantly higher numbers of myelinated and unmyelinated axons persist for even longer periods in the distal nerve stumps (Mackinnon et al., 1991).

The guidance of these growing axons to their final destination can be considered as a series of short-range projections to intermediate targets of Schwann cells under the influence of local guidance cues (see below). Neurons respond to these cues by formation of *growth cones* that generally emerge from the nodes of Ranvier, proximal to the injury site (Borgens, 1988; Ziv and Spira, 1997). The initial formation of growth cones occurs before the necessary and newly synthesized proteins are transported from the neuronal cell body to the site of axon injury, i.e. too rapidly to be dependent on the change in gene expression within the cell body (Smith and Skene, 1997). Thus, growth cones function with a large degree of autonomy from the cell soma, as they transduce contacted soluble and substratum- bound ligands into signals that coordinate cytoskeletal synthesis in a way that regulates the rate and direction of axon outgrowth (Catlett and Gomez, 2016; Lowery and Van Vactor, 2009).

The navigation of growth cones involves the detection and integration of extracellular signals, followed by a response that may include forward migration, retraction, branching and turning. Detection of guidance cues is facilitated by protrusion and retraction of filopodia and lamellipodia from the peripheral region (P-domain) of the growth cone, which contains bundles and networks of actin filaments (Letourneau and Ressler, 1984). In response to extrinsic cues, a growth cone exhibits changes in elongation rate and direction en route to its final destination (Buck and Zheng, 2002; Dent et al., 2011; Jung et al., 2013; Vitriol and Zheng, 2012).

Extrinsic cues control growth cone motility through an array of signaling cascades that control actin and microtubule dynamics to regulate growth cone advance and steering (Dent et al., 1999; Kornack and Giger, 2005; Lowery and Van Vactor, 2009; Schaefer et al., 2002, 2008; Vitriol and Zheng, 2012; Williamson et al., 1996). The regulation of actin polymerization/depolymerization is vital for axon growth and guidance (Wang et al., 2016).

2.2. Neurotrophic factors involved in axonal regrowth

The best characterized soluble neurotrophic agents are distributed into five different families:

1) The neurotrophins with nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and the neurotrophins (NT), NT-3 and NT-4/5.
2) The neuropoietin family with the neurocytokine ciliary neurotrophic factor (CNTF).
3) The TGF-β superfamily with the glial-cell-line derived neurotrophic factor (GDNF), neuturin (NTN), and parsephin.
4) The fibroblast growth factor family with the basic fibroblast growth factor (bFGF, FGF-2), the acidic fibroblast growth factor (aFGF), and FGF-5.
5) The somatomedin family with the insulin-like growth factor I (IGF-I)