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Nerve regeneration in the peripheral nervous system versus the central nervous system and the relevance to speech and hearing after nerve injuries

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Abstract

Schwann cells normally form myelin sheaths around axons in the peripheral nervous system (PNS) and support nerve regeneration after nerve injury. In contrast, nerve regeneration in the central nervous system (CNS) is not supported by the myelinating cells known as oligodendrocytes. We have found that: 1) low frequency electrical stimulation can be used to elevate cAMP thereby promoting regeneration of CNS axons and 2) a conditioning lesion, created by a crush of the peripheral branch of the dorsal root ganglion sensory neurons along with a simultaneous cut of these axons in the CNS, promotes even greater neural outgrowth than electrical stimulation. The effectiveness of the lesion results from both an acceleration of axon outgrowth and an increase in the rate of axon growth. However, electrical stimulation remains a more viable treatment of nerve injuries to stimulate regeneration and has been successfully used to promote development of the auditory pathways in children with severe to profound deafness who use cochlear implants. Without nerve regeneration, there is only a random reinnervation of affected muscles. An example occurs when the laryngeal nerve attempts to reinnervate the vocal cords after injury, causing deficits in speech. Synkinesis occurs when reinnervation of antagonistic muscles effectively paralyze the vocal cords and, in turn, severely compromises speech. The misdirection of laryngeal nerve reinnervation can be alleviated surgically by strategies favoring inspiratory abduction.

Learning outcomes: Readers of this article will gain an understanding of (1) the potential for axon regeneration in the central nervous system and (2) problems and possible solutions for random reinnervation of laryngeal muscles for speech.

Abbreviations: AB, abductor muscle; AD, adductor muscle; CNS, central nervous system; CTB, cholerotoxin B; CL, conditioning lesion; DRG, dorsal root ganglion; ES, electrical stimulation; EABR, evoked auditory brain stem response; ECAP, evoked compound action potential; MAG, myelin associated glycoprotein; Omgp, oligodendrocyte myelin glycoprotein; PNS, peripheral nervous system; PDE, phosphodiestase; PKA, protein kinase A; RLN, recurrent laryngeal nerve.

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1. Introduction

1.1. The glial cells that myelinate axons in the peripheral and central nervous systems

Schwann cells that myelinate axons in the peripheral nervous system (PNS) are pivotal to the capacity of the injured motoneurons and sensory neurons to regenerate their lost peripheral axons. Each Schwann cell envelops a single axon and the action potentials are conducted from node to node between the myelin sheaths along the peripheral nerve fiber. In the case of the motoneurons whose cell bodies lie within the grey matter of the CNS, the motor nerve fibers are intermingled with those of the sensory and the autonomic nerve fibers within nerve bundles or fascicles of the peripheral nerves. The sensory neuronal cell bodies lie within dorsal root ganglia outside of and alongside the spinal cord. The sensory neurons are bipolar, having both a peripheral as well as a central axon, the latter which enters the spinal cord, or in the case of the cranial nerves, enters the midbrain through the pia mater. The peripheral axons of both the motor and sensory nerves are myelinated by the growth permissive Schwann cells of the PNS whilst the central axons of the sensory neurons enter the spinal cord where the axons travel to the brain via myelinated axons in the white matter of the spinal cord and are myelinated by oligodendrocytes.

1.2. Peripheral nerve injury and axon regrowth to restore movement and sensation

Peripheral nerve injury results in Wallerian degeneration of the axons that are separated from the cell bodies. The Schwann cells divide and initially phagocytose myelin and axonal debris on their own before they are joined by infiltrating macrophages via the disrupted nerve blood barrier to complete the destruction and phagocytosis of all debris (Fu & Gordon, 1997; Sulaiman & Gordon, 2003; Sulaiman, Midha, & Gordon, in press). The axons that remain attached to the cell body, proximal to the nerve injury, are sustained with intact myelin although their diameters decline. Regenerating axons sprout from the cut end and grow within the Schwann cell-lined endoneurial tubes that support nerve growth (regeneration). When the regenerating axons reach the target muscles and sense organs, they remake functional connections to restore movement and sensation (Gordon & Stein, 1982). As the axons regenerate, the Schwann cells progressively remyelinate the axons, the size of the nerves returning to normal after the nerves make functional connections with their target muscles (Gordon & Stein, 1982).

1.3. Myelin associated inhibitors of the oligodendrocytes prevent regeneration of injured nerves in the central nervous system

Oligodendrocytes, the glial cells of the CNS, myelinate several axons, the conduction of action potentials in central axons also being rapid from node to node between the myelin sheaths. However, unlike the Schwann cells of the PNS, the oligodendrocytes are sluggish in their phagocytosis of myelin after CNS nerve injuries and the oligodendrocytes do *not* support CNS nerve regeneration (Busch & Silver, 2007; Fawcett, 2006; Fenrich & Gordon, 2004; Li, Field, & Raisman, 1999; Moreau-Fauvarque et al., 2003). The oligodendrocytes express three known inhibitors of axon growth. These are Nogo-66, myelin associated glycoprotein (MAG) and oligodendrocyte myelin glycoprotein (Omgp) that bind to the receptor complex on neurons of NgR1 or NgR2, $p75^{NTR}$ or TROY, and LINGO-1, three receptors that act via Rho activation in neurons to inhibit axon outgrowth (Fig. 1) (Gonzenbach & Schwab, 2008; Hunt, Coffin, & Anderson, 2002; Schwab & Caroni, 2008).

2. Experimental strategies to encourage regeneration of injured axons in the central nervous system

2.1. Introduction

2.1.1. Raising cAMP is sufficient to promote nerve growth in the central nervous system

A series of experiments by Filbin and her colleagues established that elevation of cAMP in neurons *in vitro* and/or priming of the neurons with neurotrophic factors is sufficient to promote neurite outgrowth on the normally inhibitory substrate of central myelin (Fig. 1). The fact that immature neurons have high levels of cAMP when they retain the capacity to grow on the normally inhibitory CNS myelin, was their first clear finding leading to the elaboration of the intracellular pathways responsible for bypassing Rho inhibition and promoting axon outgrowth via protein kinase A