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Regeneration of descending axon tracts after spinal cord injury

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Abstract

Axons within the adult mammalian central nervous system do not regenerate spontaneously after injury. Upon injury, the balance between growth promoting and growth inhibitory factors in the central nervous system dramatically changes resulting in the absence of regeneration. Axonal responses to injury vary considerably. In central nervous system regeneration studies, the spinal cord has received a lot of attention because of its relatively easy accessibility and its clinical relevance. The present review discusses the axon-tract-specific requirements for regeneration in the rat. This knowledge is very important for the development and optimalization of therapies to repair the injured spinal cord.

Keywords: Spinal cord injury; Axon tracts; Regeneration

Contents

Abbreviations: a-FGF, acidic-fibroblast growth factor; α-MSH, α-melanocyte stimulating hormone; BBB locomotor rating scale, Basso–Beattie–Bresnahan locomotor rating scale; BDA, biodextran amine; BDNF, brain derived neurotrophic factor; BPY, iron chelator 2,2′-bipyridine; C, cervical; CAM, cell adhesion molecule; ChABC, chondroitinase ABC; CNS, central nervous system; CNTF, ciliary neurotrophic factor; CoST, coerulospinal tract; CPG, central pattern generator; CSPG, chondroitin sulphate proteoglycan; CST, corticospinal tract; DβH, dopamine-β-hydroxylase; E, embryonic day; ECM, extracellular matrix; GAG, glycosamino glycan; GAP-43, growth associated protein-43; GDNF, glial derived neurotrophic factor; GFRα-1, GDNF-family receptor α-1; L, lumbar; LiCl, lithium chloride; LIF, leukemia inhibiting factor; MAG, myelin-associated glycoprotein; m-RNA, messenger RNA; NEP1-40, Nogo-66 (1-40) antagonist peptide; NGF, nerve growth factor; NgR, neuronal protein Nogo-66 receptor; NT-3, neurotrophin-3; NT-4/5, neurotrophin-4/5; OEC, olfactory ensheathing cell; OMgp, oligodendrocyte myelin glycoprotein; ONF, olfactory nerve fibroblast; P, postnatal day; PNS, peripheral nervous system; RaST, raphespinal tract; ReST, reticulospinal tract; RST, rubrospinal tract; SCI, spinal cord injury; T, thoracic; TH, tyrosine hydroxylase; trk, tyrosine kinase receptor; VST, vestibulospinal tract; WGA-HRP, wheat-germ agglutinin horseradish peroxidase

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1. Introduction

1.1. Outline of the review

In traumatic spinal cord injury (SCI), the impact on the spinal cord induces a primary injury site which consists of severed axons, dying neurons and glia, and a disturbed microvasculature. This primary injury triggers a cascade of pathological events referred to as secondary damage mechanisms including vascular and biochemical changes, hemorrhagic necrosis, inflammatory processes and delayed demyelination. As a consequence of the secondary injury mechanisms, the primary lesion area is extended. The pathological events that occur after the initial impact to the spinal cord render disturbed signal conduction along the severed axon tracts. This results in an impairment or loss of body functions mediated by these tracts. The loss or impairment of body functions is mostly permanent. This is mainly due to the environment of the adult mammalian central nervous system (CNS), which is very hostile to axon growth. In the adult CNS there is an optimal balance between growth permissiveness and inhibition. After injury to the CNS, this balance is disturbed resulting in the absence of axon regeneration. Severed neurons make initial attempts to regrow, attempts which are ultimately aborted. Hence, the severed axons will not reconnect to their former target cells. Consequently, functions that were mediated by the severed tracts are impaired or completely lost, depending on the severity of axon tract damage.

Functional recovery can be achieved by restoration of signal conduction across the level of the lesion. There are two main mechanisms by which this restoration of signal conduction can occur: (1) regeneration of severed axons, and (2) the formation of alternative pathways. The two mechanisms are illustrated in Fig. 1. (1) Axon regeneration includes all the processes leading to a functional reconnection of the severed axon to a specific target area (Joosten, 1997). This specific target area of the severed axon can be its original one or a distant area that is functionally connected to the original target area of the severed axon. Axon regeneration can be achieved in three ways: reconnection, relay, or rerouting to the original target area. For reconnection, a severed axon grows across the level of the lesion, reconnects to the original target area and is functionally active (Fig. 1A and A′). This implies that the original functional connection is reestablished. For relay, a severed axon grows