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Review article

Differential regenerative ability of sensory and motor neurons

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ABSTRACT

After injury, the adult mammalian central nervous system (CNS) lacks long-distance axon regeneration. This review discusses the similarities and differences of sensory and motor neurons, seeking to understand how to achieve functional sensory and motor regeneration. As these two types of neurons respond differently to axotomy, growth environment and treatment, the future challenge will be on how to achieve full recovery in a way that allows regeneration of both types of fibres simultaneously.

Contents

1. Introduction

After spinal cord injury (SCI), long-distance axon regeneration in the adult mammalian CNS is a challenging task. There is a vast diversity of axonal tracts in the spinal cord that need to grow for long distances and contact appropriate targets. This review compares the regenerative responses of sensory and motor neurons, focusing particularly on their differences and on what this teaches us about regeneration.

For sensory neurons, we focus on dorsal root ganglion (DRG) neurons which are the afferent neurons relaying sensory information from the periphery to the brain. With cell bodies in the peripheral nervous system (PNS) and axons in both the PNS and CNS, DRG neurons give us insights as to why axons regenerate differently in the PNS and CNS environments [1]. For motor neurons, we focus on upper motor neurons, particularly the corticospinal tract (CST) whose neurons are located in the deeper layers of the sensorimotor cortex with axons projecting down the spinal cord.

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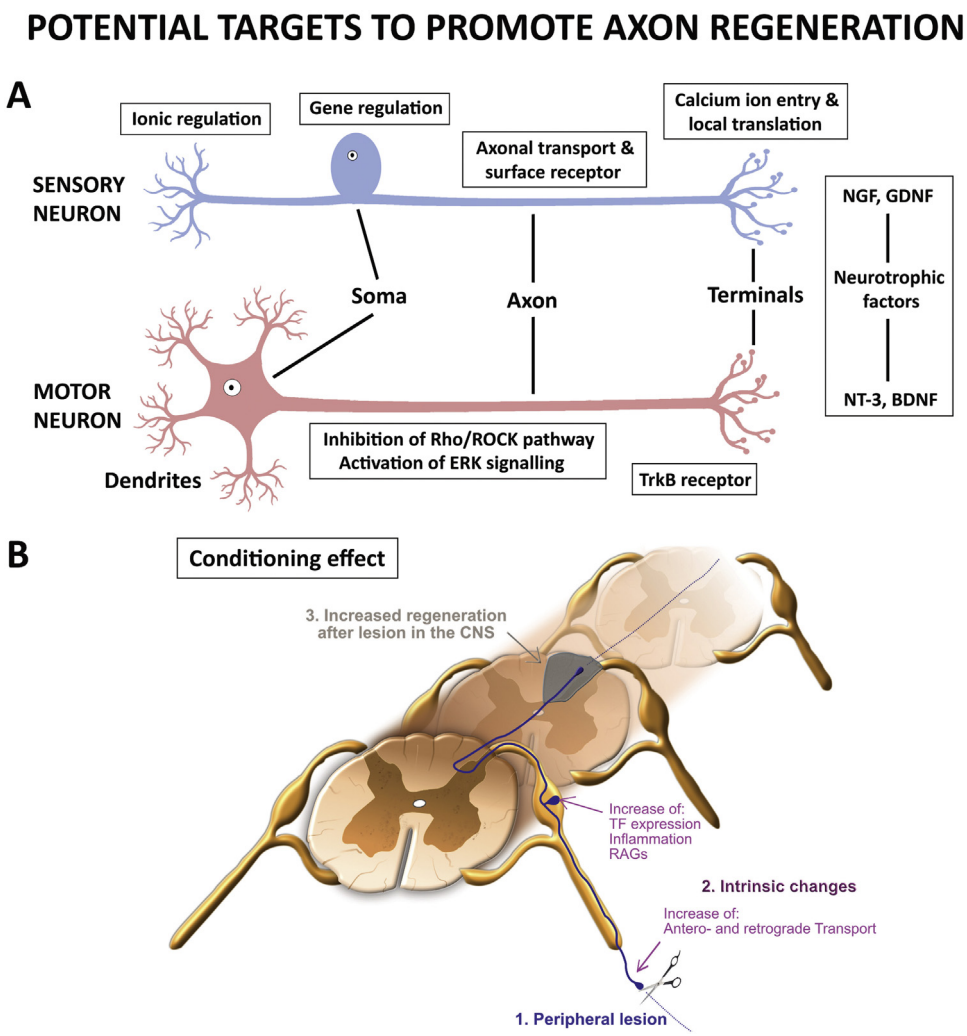

Fig. 1. Potential targets to promote axon regeneration.
(A) Sensory and motor neurons can be targeted differently for regeneration. (B) Conditioning effect facilitates sensory regeneration in the CNS due to intrinsic changes in the DRG neuron and axon following peripheral lesion.

Sensory and motor neurons are different from each other in many aspects: anatomy, surrounding environment, response to injury, and growth requirements. In this review, we aim to decipher some of these differences, analyzing how these two types of neurons respond to injury, and therefore provide an insight into how they can be stimulated to promote regeneration (Fig. 1A).

2. Intrinsic differences

Sensory and motor neurons have different developmental origins which arise during neurulation. The neural tube gives rise to components of the brain and spinal cord including motor neurons, while the neural plate border develops the neural crest to form components of the PNS including DRG neurons. During dorsal-ventral patterning of the neural tube, the roof plate is exposed to a concentration gradient of bone morphogenic proteins (BMPs) whereas the floor plate to an opposing gradient of Sonic Hedgehog (SHH) [2]. As both BMPs and SHH are morphogens with cell-fate-determining activity [3], they critically affect the development of sensory and motor tracts in the spinal cord, long before the presence of a functioning nervous system. Anatomically, motor neurons have a single axon and multiple dendrites, while sensory neurons lack dendrites but their axon splits into a central and peripheral branch destined to exist in different environments.

2.1. Early events after injury

2.1.1. Ionic changes

Axotomy disrupts the axonal membrane resulting in extracellular Ca^{2+} influx, which stimulates axonal degeneration and regeneration initiation. The Ca^{2+} rise is two-phasic, first a leak into the proximal axon, then a delayed entry through Ca^{2+} channels. This results in trains of action potentials in both sensory and motor neurons [4]. Ca^{2+} influx is crucial for resealing the impaired plasma membrane, intracellular ionic regulation and growth cone formation [5]. As demonstrated in DRG neurons, the lack of Ca^{2+} influx after axotomy significantly reduces their regenerative capacity [1] and local protein synthesis essential for growth cone initiation [6]. Physiological responses to injury can include changes to the resting membrane potential and membrane polarization [7]. These changes can be triggered by the Na^{+}-K^{+}-$2Cl^{-}$ type 1 cotransporter (NKCC1). As NKCC1 can regulate the concentration of intracellular Cl^{-}, it has a substantial effect in changing the resting membrane potential and modulating GABAergic activity [8]. This results in GABA having a depolarising effect on DRG and immature neurons,

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