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Review

Anti-Nogo-A and training: Can one plus one equal three?

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ABSTRACT

Following spinal cord injury (SCI) the adult central nervous system (CNS) has a limited but substantial capacity for repair and plastic reorganisation. The degree of reorganisation is determined by a number of factors such as the extent and location of the lesion, the remaining circuit activity within the CNS and the age at injury. However, even in the best cases this spontaneous reorganisation does not lead to full recovery of the affected behaviour but instead often results in a functionally successful but compensatory strategy. Current SCI research focuses on enhancing fibre tract (re-)growth and recovery processes. Two currently promising approaches are the neutralisation of CNS growth inhibitory factors, and rehabilitative training of remaining networks. Independently, both approaches can lead to substantial functional recovery and anatomical reorganisation. In this review we focus on Nogo-A, a neurite growth inhibitory protein present in the adult CNS, and its role in regenerative and plastic growth following SCI. We then discuss the efforts of rehabilitative training and the potential combination of the two therapies.

Contents

Introduction

Despite a growing list of potential future treatments for SCI, there is still a great need to precisely understand the underlying mechanisms. This is especially important when thinking about combinatorial approaches to aid recovery from SCI. It is hoped that an understanding, from the cell biological point of view, of the complex physiological and pathophysiological processes following SCI, rehabilitation, training and regeneration enhancing pharmacological treatments will allow an insight into how to optimally combine these manipulations to maximise functional recovery. In this review we focus first on the spontaneous adaptive changes that occur in the spinal cord and brain circuitry following SCI. Next, we summarise two strategies that can enhance this reorganisation and thus lead to extensive functional recovery: neutralising the growth inhibitory protein Nogo-A and rehabilitative training. Blocking the function of Nogo-A following SCI allows regenerative growth of damaged axons

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and promotes plastic sprouting of intact fibres along with improved functional recovery. Rehabilitative training strategies are widely used experimentally and in the clinic. Recent findings with combinations of growth enhancing interventions and various training paradigms produced unexpectedly complex outcomes. These results point to a great need for a better understanding of the underlying mechanisms in order to best optimise future therapeutic strategies.

Processes of spontaneous recovery after SCI

The adult CNS has a limited but substantial capacity for spontaneous plastic reorganisation after injury (Merzenich et al., 1983b; Bareyre et al., 2004; Frigon and Rossignol, 2006; Edgerton et al., 2008; Darian-Smith, 2009; Ghosh et al., 2010; Ramer, 2010; Rosenzweig et al., 2010). Long distance regeneration of injured neurons does not occur spontaneously, but spared fibres, and surviving circuits in the brain and lower spinal cord can sprout, reorganise and contribute to functional recovery and compensation.

Spontaneous reorganisation of the sensory and motor forebrain cortex following injury

The forebrain cortex is capable of spontaneous reorganisation following injury in adulthood to peripheral nerves or the spinal cord. The majority of early data came from peripheral nerve lesion experiments in primates (Merzenich et al., 1983a; Merzenich et al., 1983b; Donoghue et al., 1990; Kaas, 1991): areas of the cortex corresponding to the lesioned nerve initially became silenced, but were rapidly "filled in" by responses from surrounding, intact areas (Merzenich et al., 1983a; Merzenich et al., 1983b; Sanes et al., 1988). Similar reorganisation was observed in the adult rat sensory and motor cortex following SCI (Fig. 1B1); following partial SCI in adult rodents neighbouring, intact areas of the cortex spontaneously expanded into the regions that had lost their targets, as observed with intracortical microstimulation (Fouad et al., 2001; Martinez et al., 2009), electrophysiology (Aguilar et al., 2010), trans-synaptic tracing (Bareyre et al., 2004), functional magnetic resonance imaging (fMRI) (Endo et al., 2007; Ghosh et al., 2009; Nishimura and Isa, 2009; Ghosh et al., 2010), voltage-sensitive dye imaging (VSD) (Ghosh et al., 2009; Ghosh et al., 2010) and retrograde tracing (Ghosh et al., 2010). Cortical plasticity following partial SCI has also been observed in humans with positron emission tomography (Bruehlmeier et al., 1998; Curt et al., 2002b) and fMRI (Curt et al., 2002a); for review see (Endo et al., 2009). In addition, it was shown in monkeys that recovery of hand function following partial cervical SCI was accompanied by the re-emergence of the cortical map of the hand (Schmidlin et al., 2004). The above observations suggest that the detailed structure of cortical maps is dynamically maintained throughout life, and that maps are able to rapidly respond to changing inputs. However, the exact mechanism(s) underlying these changes are not known but may involve long-term potentiation (Hess and Donoghue, 1994; Rioult-Pedotti et al., 2007), unmasking of horizontal connections (Hess and Donoghue, 1996; Adesnik and Scanziani, 2010), removal of inhibition (Hendry and Jones, 1986; Jacobs and Donoghue, 1991; Brasil-Neto et al., 1993; Aguilar et al., 2010), and/or sprouting and growth of new connections (Kleim et al., 2004; Kim et al., 2008; Ghosh et al., 2010).

Spontaneous reorganisation of spinal connections following injury

While functional and anatomical plasticity in the neocortex are well studied, recent observations suggest that the spinal cord is capable of

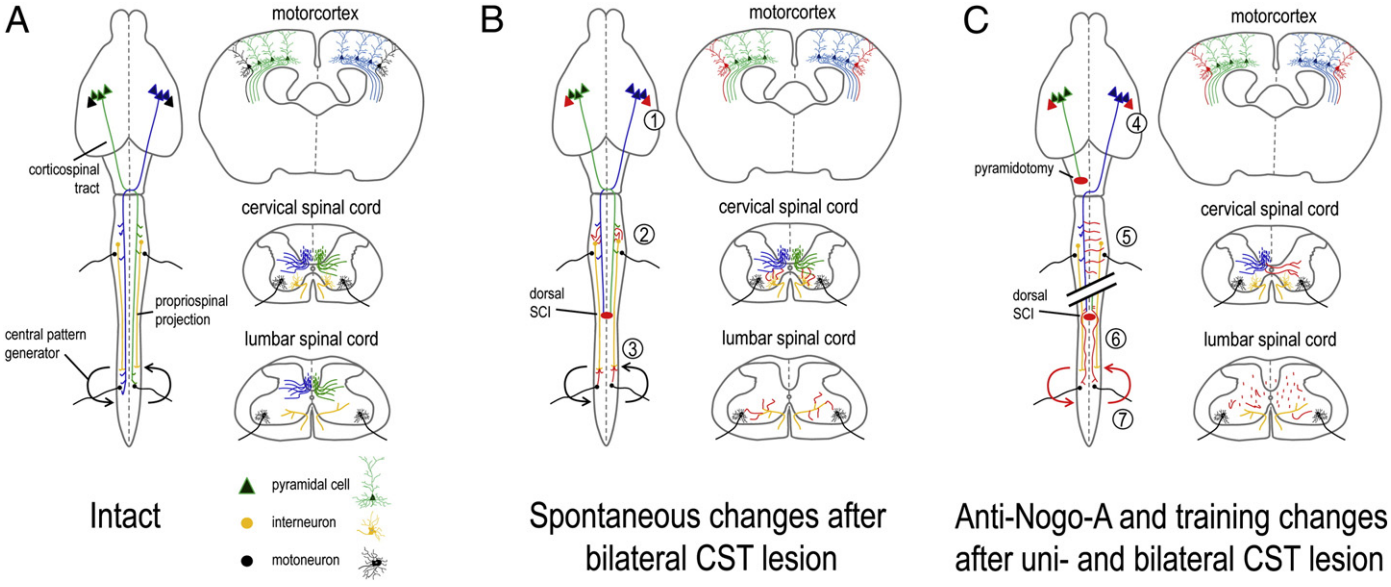

Fig. 1. Anti-Nogo-A treatment and rehabilitative training induce anatomical changes post-SCI. **A**, Intact adult CNS of a rat. Layer V pyramidal cells (green and blue) composing the CST send crossed projections from the motor cortex to the spinal cord. Axons from the pyramidal cells terminate in the cervical (from the forelimb motor cortex) and lumbar (from the hindlimb motor cortex) spinal cord grey matter. For illustrative purposes, two spinal cell types are shown. Long descending propriospinal interneurons (yellow) project from the cervical to the lumbar spinal cord. Motoneurons (black) are typically located in the ventral horn of the cervical and lumbar spinal cord and innervate the muscles of fore- and hindlimbs. Circular arrows indicate the spinal central pattern generator networks. **B**, Spontaneous changes occurring after bilateral CST lesion in the adult rat. In the absence of long-distance regeneration considerable functional recovery occurs spontaneously, mediated by: 1) undamaged motor cortex cells (red pyramidal cells) taking over the function of damaged neurons; 2) injured fibres disconnected from their original target in the lumbar spinal cord sprouting into the cervical spinal cord (red sprouts) and connecting onto local long propriospinal neurons (yellow), which bridge the lesion site; and 3) these propriospinal neurons increasing their terminal arborisation (red sprouts) in the lumbar spinal cord. **C**, Effects of anti-Nogo-A treatment and rehabilitative training following unilateral (illustrated in the upper part of the cartoon) and bilateral (illustrated in the lower part of the cartoon) CST lesion: 4) anti-Nogo-A treatment cells allows sprouting and enhanced growth of cortical neurons (red pyramidal cells); training allows growth of dendritic spines; 5) following unilateral CST lesion, both removal of Nogo-A and enhanced activity induce bilateral innervation (red fibres) of the cervical spinal cord by intact fibres; 6) after SCI, anti-Nogo-A treatment produces increased sprouting of lesioned fibres rostral to the lesion site and long-distance regeneration of injured axons (red fibres), 7) rehabilitative training induces adaptations in central pattern generator networks (red arrows).