Experimental Neurology 254 (2014) 195–199

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Commentary

Thinking outside the brain: Structural plasticity in the spinal cord promotes recovery from cortical stroke

Kelly A. Tennant*

Division of Medical Sciences, University of Victoria, Victoria, British Columbia V8W 2Y2, Canada

ARTICLE INFO

Article history:
Received 7 January 2014
Accepted 2 February 2014
Available online 8 February 2014

ABSTRACT

Neuroanatomically connected regions distal to a cortical stroke can exhibit both degenerative and adaptive changes during recovery. As the locus for afferent somatosensory fibres and efferent motor fibres, the spinal cord is ideally situated to play a critical role in functional recovery. In contrast to the wealth of research into cortical plasticity after stroke, much less focus has previously been placed on the role of subcortical or spinal cord plasticity in recovery of function after cortical stroke. Little is known about the extent and spatiotemporal profile of spinal rewiring, its regulation by neurotrophins or inflammatory cytokines, or its potential as a therapeutic target to improve stroke recovery. This commentary examines the recent findings by Sist et al. (2014) that there is a distinct critical period of heightened structural plasticity, growth factor expression, and inflammatory cytokine production in the spinal cord. They suggest that neuroplasticity is highest during the first two weeks after stroke and tapers off dramatically by the fourth week. Spinal cord plasticity correlates with the severity of cortical injury and temporally matches periods of accelerated spontaneous recovery of skilled reaching function. The potential of treatments that extend or re-open this window of spinal cord plasticity, such as anti-Nogo-A antibodies or chondroitinase ABC, to dramatically improve recovery from cortical stroke in clinical populations is discussed.

Introduction

Stroke-induced impairments in motor, sensory and cognitive function improve over time, likely due to rewiring of damaged neural circuitry in connected areas of the central nervous system (CNS). Post-stroke plasticity includes physiological and anatomical changes that provide a favourable environment for rewiring of lost synaptic connections (Brown and Murphy, 2008; Brown et al., 2007, 2009, 2010; Carmichael and Chesselet, 2002; Carmichael et al., 2001; Li and Murphy, 2008; Li et al., 1998; Risher et al., 2010; Stroemer et al., 1995; Winship and Murphy, 2009; Zhang and Murphy, 2007; Zhang et al., 2010) and remapping of lost function onto surviving ipsilateral brain regions (Castro-Alamancos and Borrel, 1995; Cicinelli et al., 1997; Dancause et al., 2005; Friel et al., 2000; Frost et al., 2003; Gharbawie et al., 2005; Kleim et al., 2003; Nudo and Milliken, 1996; Remple et al., 2001; Traversa et al., 1997). Neuroplasticity of contralateral homotopic cortex has also been found in cases of particularly large strokes which damage much of the typical substrate for ipsilateral plasticity (Abo et al., 2001; Adkins et al., 2004; Bestmann et al., 2010; Biernaskie et al., 2005; Brown et al., 2009; Cao et al., 1998; Chollet et al., 1991; Dijkhuizen et al., 2001, 2003; Hsu and Jones, 2006; Luhmann et al., 1995; Mohajerani et al., 2011; Takatsuru et al., 2009; Weber et al., 2008; Wei et al., 2001; Winship and Murphy, 2008). In contrast to the wealth of research into cortical plasticity after stroke, much less focus has been placed on the role of subcortical or spinal cord plasticity in recovery of function after cortical stroke, although this is beginning to change. For example, Mohajerani et al. (2011) found that pharmacological thalamic inactivation prior to stroke prevented rapid interhemispheric redistribution of sensory processing from the ipsilateral to the contralateral somatosensory cortex after stroke. This suggests that existing subcortical connections mediate rapid redistribution of sensory-evoked activity and play a critical role in stroke recovery.

Spinal plasticity before and after cortical injury

In the intact brain, motor skill learning and strength or endurance training are capable of inducing modifications in reflex physiology within the spinal cord (Adkins et al., 2006). Notably, whilst skill training also induces reorganization of cortical movement representations (Kleim et al., 1998), strength training fails to alter movement representations (Remple et al., 2001) but induces synaptogenesis within the spinal cord (Adkins et al., 2006). This demonstrates that behavioural demands dictate the type and location of plasticity across the CNS, and typically involve plasticity of both brain and spinal circuits. Similarly, neuroanatomically connected regions distal to a cortical stroke can exhibit both degenerative and adaptive changes during recovery. As the locus for afferent somatosensory fibres and efferent motor fibres,

* Division of Medical Sciences, University of Victoria, PO Box 1700, STN CSC, Victoria, British Columbia V8W 2Y2, Canada. Fax: +1 250 853 3964.
E-mail address: tennantk@uvic.ca.

0014-4886/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.expneurol.2014.02.003

the spinal cord is ideally situated to play a role in functional recovery. After all, sensory input and motor output, the keys to interacting with our environment, depend crucially on a functional spinal system. It makes sense then that plasticity in the spinal cord would play a critical role in recovery of sensorimotor function after stroke. However, the mechanism and spatiotemporal dynamics underlying spinal cord plasticity remain largely unknown, especially in the context of cortical injury.

Degeneration and regeneration in the spinal cord

Direct injury to the spinal cord itself is followed by acute Wallerian degeneration (WD) of axons below the site of injury that are disconnected from their cell bodies. WD begins with breakdown of axonal structures followed by infiltration of macrophages and degradation of myelin and finally ends with gradual fibrosis and atrophy of fibre tracts. WD can affect many tracts including the descending corticothalamic tract and ascending thalamocortical tract in the brain and descending corticospinal tract (CST) and ascending medial lemniscal and spinothalamic tracts in the spinal cord, depending on the location of the injury. In this way, stroke in the sensorimotor cortex induces secondary degeneration of the descending axons that form the CST in the spinal cord (Weishaupt et al., 2010). Within weeks of the stroke, secondary damage extends past the cervical spinal cord (CSC) and progressive and delayed degeneration of descending CST fibres is observed in the thoracic spinal cord (TSC). Activation of immune cells is also observed in the CSC within one week of infarction, and Weishaupt et al. (2010) suggest that the release of pro-inflammatory and cytotoxic proteins from infiltrating microglia is a likely mechanism of secondary damage to CST fibres after cortical stroke.

Previously, the spontaneous regenerative capacity of the CST in the adult system after spinal cord injury was thought to be negligible. However, recent research has shown that even in the absence of intervention, the CST is able to spontaneously regenerate after a partial lesion (Lundell et al., 2011), with spared fibres sprouting and circumventing the injury site (Rosenzweig et al., 2010; Steward et al., 2008). Neuroanatomical tracers have recently been used to investigate axonal sprouting in the spinal cord induced by cortical stroke and its role in stroke treatment and recovery. For example, CST axonal projections from the uninjured hemisphere exhibit increased midline crossing and innervation of spinal grey matter on the stroke-affected side (Lapash Daniels et al., 2009; Liu et al., 2009). Spontaneous behavioural recovery after stroke was associated with an increase in axonal labelling in the stroke-affected CSC one month after stroke (Liu et al., 2009). Treatments that improve functional recovery also increase the number of CST fibres originating in the uninjured sensorimotor cortex that cross the midline and innervate the stroke-affected side of the CSC. For example, bone marrow stromal cells (Liu et al., 2007, 2008, 2011), anti-Nogo antibody infusion (Tsai et al., 2007; Wiessner et al., 2003), and inosine (Zai et al., 2011) are all associated with spinal cord plasticity and functional recovery. Whilst the importance of spinal plasticity in recovery from cortical injury is supported by these and other studies, little is known about the extent and spatiotemporal profile of spinal rewiring, its regulation by neurotrophins or inflammatory cytokines, or its potential as a therapeutic target to improve stroke recovery.

Spatiotemporal dynamics of structural plasticity throughout the CNS after cortical stroke

Sist et al. (2014) have recently expanded on previous research by identifying a time-limited period of heightened post-stroke structural plasticity in the brain and spinal cord that correlates with the severity of cortical injury and promotes behavioural recovery. They investigated the effect of partial forelimb sensorimotor cortex (FL-SMC) lesions, which destroyed much of forelimb motor cortex (FLM1) and the medial half of forelimb somatosensory cortex (FLS1), versus complete FL-SMC lesions that additionally encompassed the remaining FLS1 and extended into hindlimb somatosensory cortex (HLS1). Reaching impairments on the Montoya Staircase Task were, as is to be expected, greater in animals with larger infarcts. Animals with partial lesions recovered to control levels by 28 days post-stroke. Although animals with complete lesions were more initially more impaired, they were able to make limited gains in behavioural improvement but failed to recover to control levels.

In order to investigate the underlying plastic mechanisms occurring in the brain and spinal cord during recovery, the authors chose to analyse growth-associated protein-43 (GAP-43) expression as an index of periods of heightened structural plasticity, reflecting greater neuronal growth and branching (Benowitz and Routtenberg, 1997; Bomze et al., 2001; Hoffman, 1989; Leu et al., 2010; Zuber et al., 1989). Consistent with Carmichael et al. (2005) and Stroemer et al. (1995), GAP-43 expression was elevated in the ipsilesional cortex (IC), peaked at two weeks post-stroke and remained elevated at least 1 month after injury. This time course is temporally similar to rates of synapse formation after stroke in peri-infarct tissue (Brown et al., 2007, 2008, 2009). Structural remodeling was not restricted to peri-infarct cortex, as GAP-43 expression was also upregulated in contralesional cortex (CC) and spinal cord after both partial and complete lesions. This is especially interesting given that clinical data suggest that reorganized activation in novel ipsilateral sensorimotor areas is associated with improved recovery after stroke (Calautti et al., 2010; Fridman et al., 2004; Johansen-Berg et al., 2002a,b).

FL-SMC lesions also increased GAP-43 expression in the spinal cord in a time-limited and lesion size dependent manner. Expression peaked one week after stroke and was restricted to the CSC after partial lesions. Complete lesions were associated with more pronounced expression that peaked two weeks after stroke and increased the spatial extent of plasticity such that GAP-43 expression was also seen in the lumbar spinal cord (LSC) after complete cortical lesions, reflecting the involvement of HLS1 in the cortical damage. Changes were time-limited and returned to baseline by four weeks after stroke. Interestingly, Sist and colleagues found that peak GAP-43 expression in the spinal cord overlapped with periods of spontaneous recovery of forelimb function and return to baseline expression occurred as recovery plateaued.

Furthermore, cortical stroke was associated with upregulation of other growth-promoting factors in the spinal cord. Brain derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) have previously been found to promote neuronal survival and axonal sprouting in the spinal cord (Bradbury et al., 1999; Bregman et al., 1997; Di Giovanni et al., 2003; Grill et al., 1997; Hammond et al., 1999; Hayashi et al., 2000; Schnell et al., 1994; Song et al., 2001; Vavrek et al., 2006; Ye and Houle, 1997). Complete FL-SMC lesions resulted in a transient increase in BDNF in the CSC 3 days after stroke, which precedes GAP-43 expression upregulation, suggesting BDNF as a signal for initiating structural plasticity in the spinal cord. The temporal profile of NT-3 expression correlated with GAP-43 levels in the CSC throughout recovery. Together, these results suggest a critical period for functional recovery after stroke that is associated with a period of heightened structural plasticity and growth factor expression in the spinal cord during the first two weeks after brain injury.

Spatiotemporal dynamics of inflammatory cytokine expression after stroke

To examine if periods of heightened structural plasticity in the spinal cord were additionally associated with increased expression of inflammatory cytokines, Sist et al. (2014) measured tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) protein levels in the CSC after complete FL-SMC injury. Analysis was focused on TNF-α and IL-6 because they are well-characterized inflammatory markers that also have known roles in synaptic plasticity, neuroprotection and regeneration (Hakkoum et al., 2007; Marchetti et al., 2004; Oshima et al., 2009; Suzuki et al., 2009; Turrin and Rivest, 2006; Yang et al., 2012). For example, TNF-α deficient transgenic mice do not exhibit increased axonal sprouting or behavioural