● **INVITED REVIEW**

Spinal cord injury drives chronic brain changes

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Abstract

Only a few studies have considered changes in brain structures other than sensory and motor cortex after spinal cord injury, although cognitive impairments have been reported in these patients. Spinal cord injury results in chronic brain neuroinflammation with consequent neurodegeneration and cognitive decline in rodents. Regarding the hippocampus, neurogenesis is reduced and reactive gliosis increased. These long-term abnormalities could explain behavioral impairments exhibited in humans patients suffering from spinal cord trauma.

Key Words: *spinal cord injury; brain neurodegeneration; neuroinflammation*

Introduction

Spinal cord injury (SCI) produces an extensive brain reorganization of the sensorimotor cortex due to cortical circuit deafferentation (Nardone et al., 2013). Concomitantly with the cortical plastic changes SCI leads to the atrophy not only of spinal cord (Lundell et al., 2011) but also of the sensorimotor cortex and corticospinal tract (CST) (Jurkiewicz et al., 2006; Wrigley et al., 2009). In particular, human magnetic resonance imaging (MRI) studies using voxel-based morphometry and diffusion tensor imaging have revealed that grey matter volume decreases in primary somatosensory (S1) and motor cortex (M1) in chronic SCI, which is consistent with atrophy and/or neuronal loss (Jurkiewicz et al., 2006; Wrigley et al., 2009; Freund et al., 2011, 2013a, b). In addition, these studies have demonstrated that axonal and myelin integrity of CST is reduced following spinal cord trauma (Wrigley et al., 2009; Freund et al., 2012, 2013b). Concerning the survival of cortical axotomized motoneurons there is no uniform consensus. A number of reports on SCI animal models have shown apoptotic neurons on Lamina V of primary motor cortex (Hains et al., 2003; Lee et al., 2004) while others have demonstrated that the number of large pyramidal neurons remains invariable (Wannier et al., 2005; Brock et al., 2010; Nielson et al., 2011). Despite this controversy regarding the survival of the upper-motoneuron both positions agree with the fact that those neurons suffer changes as atrophy and shrinkage following SCI (Tseng and Prince, 1996; Wannier et al., 2005; Brock et al., 2010; Nielson et al., 2011).

Crucially, the decrease of CST integrity and cortical grey matter volume is directly correlated with spinal cord atrophy in humans (Freund et al., 2012, 2013a) suggesting that trauma-induced spinal degenerative process spreads towards the brain.

According to human MRI studies SCI can cause progressive reduction in grey matter volume not only in the sensorimotor cortex but also in regions not directly connected to the injury site, such as insular, cerebellar, medial prefrontal, anterior cingulate and temporal cortices, which are crucial for the processing of emotional information and the modulation of attentional states (Nicotra et al., 2006; Wrigley et al., 2009).

In this regard there have been several reports about long-term cognitive impairments in humans after SCI. Standardized neuropsychological tests have identified performance impairments in span memory, executive functioning, memory function, concentration ability, attention, processing speed, and learning (Roth et al., 1989; Murray et al., 2007; Lazzaro et al., 2013; Craig et al., 2015). As comorbid traumatic brain injury (TBI) can result in cognitive impairments, it is worth mentioning that the stated reports exclude people with concomitant TBI. Sixty percent of spinal cord injured patients suffer not only from cognitive impairment but also from depression (Shin et al., 2012) and anxiety (Post and van Leeuwen, 2012) conditions which result in a general decrease in quality of life (Boakye et al., 2012). A prospective longitudinal neuropsychological study has shown that cognitive impairment in spinal cord injured patients was associated with elevated depressive mood, anxiety and fatigue only when patients returned to society, where there is less support and substantial challenges (Craig et al., 2015).

Since human behavior is very complex, factors other than TBI might also contribute to lower cognitive performance such as chronic pain, taking multiple medication and alcohol and substance abuse. In this context, Faden and colleagues´ work is very significant as it reveals that SCI in both mouse and rat causes impairment of spatial and retention memory and depressive-like behavior as demonstrated by diminished performance in the Morris water maze, Y-maze, novel objective recognition, sucrose preference and tail suspension tests (Wu et al., 2014a, b). One recent report has provided evidence for a relationship between the up-regulation of peripheral and hippocampal cytokine levels and

the increase of depression or anxiety-like signs following rodent spinal cord contusion (Maldonado-Bouchard et al., 2016).

There is compelling evidence suggesting that chronic SCI results in a widespread brain neuroinflammation (Felix et al., 2012; Wu et al., 2014a, b; Maldonado-Bouchard et al., 2016; Jure et al., 2017). Indeed, trauma to spinal cord frequently causes neuropathic pain associated with chronic inflammation in both the dorsal horn and spinothalamic projection sites in the thalamus (Hulsebosch et al., 2009; Zhao et al., 2007). Microglial cells and astrocytes under pathological conditions (chronic stress, injury, neurodegenerative diseases, diabetes, aging, infection, *etc.*) become reactive and develop a neuroinflammatory response leading to functional consequences for learning and memory (Sierra et al., 2014). In this regard, Faden's group have demonstrated that microglia is activated in cerebral cortex, thalamus and hippocampus in a rodent model of SCI (Wu et al., 2014a, b, 2016). The authors have described that there is a significant decrease in the number of resting microglia displaying ramified cellular morphology and an increase in the number of activated microglia displaying a bushy and hypertrophy cellular morphology. The latter changes in microglia morphology are associated with M1 pro-inflammatory cytokine profile expression and are observed both in the acute and chronic phases post trauma (Wu et al., 2014a, b). Pro-inflammatory cytokines (TNFα, IL-6) and cell cycle genes (cyclin A1, A2, D1, PCNA) are chronically increased in the hippocampus after severe SCI (Wu et al., 2014a, b). In line with these findings, our results have shown a chronic increase of hyperthophic and bushy microglia in the molecular layer, subgranular zone (SGZ) and hilus of the hippocampal dentate gyrus (DG) after severe SCI (Jure et al., 2017). In the same report we have provided the first evidence for astrocyte activation in all the DG sub-regions mentioned, suggesting that astrocytes could articulate and develop the neuroinflammatory response alongside microglial cells (Jure et al., 2017)

Interestingly, glia reactivity is related to SCI intensity. Severe lesions induce reactive microglia and astrogliosis in all DG sub-regions. However, reactive microglia and astrogliosis develop only in the hilus and in the molecular layer respectively after moderate SCI while no changes are observed in the mildly injured rats (Jure et al., 2017). In accordance with our result, a recent report has shown microglia activation only after moderate and severe SCI and not in mildly injured mice in the cerebral cortex and hippocampus (Wu et al., 2016). Widespread brain neuroinflammation could lead to remote neurodegeneration after SCI. Indeed, neuroinflammation and microglia activation are common landmarks following normal aging, neurodegenerative diseases, chronic stress, and brain ischemia (Sierra et al., 2014). In this regard isolated thoracic SCI in both rat and mouse models has resulted in significant neuronal loss in the hippocampus, cortex, and thalamus only in the chronic phase but not at early time points (Wu et al., 2014a, b). Stereological analyses have demonstrated that moderate and severe - but not mild- SCI reduces neuronal survival and increases neuronal endoplasmic reticulum stress in important brain regions associated with cognitive decline and depression (Wu et al., 2016). In summary it could be stated that on the one hand there are no signs of either neuronal loss or neuroinflammation in mildly injured rats and on the other hand, neuroinflammation arises both in the acute and chronic phases preceding neurodegeneration which appears only at late time points, suggesting that inflammation leads to SCI-induced brain neurodegeneration.

The hippocampus is involved in the formation of memory and learning, processes that require extensive neuroplasticity (O´Keefe, 2007). In this regard, the incorporation of newborn neurons into the mature circuit enhances hippocampal-dependent learning performances in the DG (Kempermann and Gage, 1999). Microglia and astrocytes are important components of the neurogenic niche and a growing number of reports relate the activation of both cells to decreased neurogenesis (Belarbi and Rosi, 2013; Sierra et al., 2014). Indeed, a significant long-term neurogenesis reduction has been reported after chronic cervical and thoracic SCI that could be associated with microglia activation in the hippocampus (Felix et al., 2012; Wu et al., 2014a). In this regard, we have recently demonstrated that severe and moderate SCI down-regulates the production of newborn neurons in the same manner (Jure et al., 2017). However, neurogenesis in the mildly injured rats has remained unchanged suggesting that neurogenesis reduction could be an all-or-none response from a certain threshold. Notably, in line with these findings it has been shown that injured animals with moderate and severe SCI show the same outcome in cognitive tests and development of depression-like symptoms (Maldonado-Bouchard et al., 2016; Wu et al., 2016). In addition, neurogenesis appears to be more sensitive to SCI than astrocytes and microglial morphological responses, since moderately injured rats show a sharp newborn neuron decrease associated with no glial changes in the SGZ (Jure et al., 2017).

Convincing work has demonstrated that the brain is affected by SCI. However, exact mechanisms underlying those changes are completely unknown. On the one hand, the systemic immune function is markedly altered after SCI and this mechanism could affect the brain (Popovich and McTigue, 2009; Schwab et al., 2014) and on the other hand, corticosterone released in the acute phase after SCI could model the brain producing long-term alterations. It is well documented that the hippocampus and cerebral cortex are vulnerable to glucocorticoid actions (Lucassen et al., 2015). Finally, BDNF and other molecules that participate in neuron-glia communication as chemokines (Cardona et al., 2006; Wu et al., 2014b; Gundersen et al., 2015) could be involved in brain changes following SCI. In this regard, BDNF is known to regulate adult neurogenesis at the SGZ (Lee et

al., 2002; Scharfman et al., 2005; Fumagalli et al., 2009) and it has been shown that reduced hippocampal neurogenesis is correlated with the decrease of BDNF protein levels (Felix et al., 2012). However, other reports found that this factor remains unchanged after 4 and 12 weeks of injury (Fumagalli et al., 2009).

Regarding chemokines, CCL21 is produced by spinal cord neurons after nerve damage or glutamate exposure (Hulsebosch et al., 2009) and is delivered at more distant sites resulting in microglia activation and neuropathic pain generation (Zhao et al., 2007). In addition, CCL21 is up-regulated in neurons both in the acute and chronic phases after SCI in the thalamus, hippocampus and cerebral cortex (Wu et al., 2014a, 2016). Consistent with these results, the microglia activator CCL2 (Zhang et al., 2017) and its receptor CCR2 are chronically expressed in neurons after severe spinal contusion in the thalamus, hippocampus and periaqueductal gray matter, brain circuits associated with pain and emotional or memory functions (Knerlich-Lukoschus et al., 2011).

In conclusion, SCI results in chronic brain neuroinflammation that is remarkably similar to that reported after TBI producing a progressive delayed neurodegeneration and functional deficits as cognitive impairment and depressive-like behavior (Faden et al., 2016). Those long-term brain abnormalities and the reported diffuse neuroinflammation associated could explain behavioral impairments exhibited in patients suffering from spinal cord trauma (Davidoff et al., 1992; Dowler et al., 1997; Lazzaro et al., 2013). Future rehabilitation strategies should be oriented to improving not only sensorimotor skills but also cognitive function. Given that SCI drives chronic brain changes, it will be necessary to consider cognitive and emotional patient impairments as a consequence of SCI *per se* and not as a consequence of the lifestyle resulting from the disability. Therefore, future therapies should include the inhibition of post-traumatic brain inflammatory response to avoid cognitive and emotional deficits.

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