Brain and spinal cord trauma: what we know about the therapeutic potential of insulin growth factor 1 gene therapy

Maria Jose Bellini¹, Florencia Labombarda², 3, *

Abstract
Although little attention has been paid to cognitive and emotional dysfunctions observed in patients after spinal cord injury, several reports have described impairments in cognitive abilities. Our group also has contributed significantly to the study of cognitive impairments in a rat model of spinal cord injury. These findings are very significant because they demonstrate that cognitive and mood deficits are not induced by lifestyle changes, drugs of abuse, and combined medication. They are related to changes in brain structures involved in cognition and emotion, such as the hippocampus. Chronic spinal cord injury decreases neurogenesis, enhances glial reactivity leading to hippocampal neuroinflammation, and triggers cognitive deficits. These brain distal abnormalities are recently called tertiary damage. Given that there is no treatment for Tertiary Damage, insulin growth factor 1 gene therapy emerges as a good candidate. Insulin growth factor 1 gene therapy recovers neurogenesis and induces the polarization from pro-inflammatory towards anti-inflammatory microglial phenotypes, which represents a potential strategy to treat the neuroinflammation that supports tertiary damage. Insulin growth factor 1 gene therapy can be extended to other central nervous system pathologies such as traumatic brain injury where the neuroinflammatory component is crucial. Insulin growth factor 1 gene therapy could emerge as a new therapeutic strategy for treating traumatic brain injury and spinal cord injury.

Key Words: cognitive impairments; gene therapy; hippocampus; insulin growth factor 1; microglial cells; neurodegeneration; neurogenesis; neuroinflammation; spinal cord injury; traumatic brain injury

Introduction
Spinal cord injury (SCI) leads to permanent motor, sensory and autonomic dysfunction given the inability of the central nervous system (CNS) to regenerate. Mechanic SCI occurs when the spinal cord is severely bruised, compressed, lacerated, or severed as a result of the traumatic impact. The mechanic impact leads to primary damage which involves cellular death, extracellular matrix changes, edema formation, and blood-brain barrier breakdown. This primary damage drives to the well-known secondary damage characterized by microglia and astrocyte reactivity, periphery immune cell invasion, inflammation, and oxidative stress. These events result in neuron and oligodendrocyte death, which generate a loss of function (Ahuja et al., 2017).

Traditionally, SCI investigation was focused on pathophysiological changes in the spinal cord with efforts being made to recover sensorimotor function and relief neuropathic pain. In this regard, several studies have shown anterograde and retrograde axonal degeneration, which lead to the atrophy of the deafferented sensorimotor cortex (Wrigley et al., 2009; Freund et al., 2013). However, studies considering brain areas other than the sensorimotor system are scarce although humans suffer from cognitive and emotional impairment (Murray et al., 2007; Lazzaro et al., 2013; Craig et al., 2015). Interestingly, animal models have shown that SCI results in cognitive deficits and depressive-like behavior, which correlate with hippocampal neurogenesis, neurogenesis reduction, and neuroinflammation (Wu et al., 2014a, b; Jure et al., 2021). Long-distal areas after SCI have been ignored for many years. Fortunately, this scenario has been changing lately. Compelling evidence suggests that SCI spreads to the brain affecting rostral distal areas and producing progressive neurodegeneration and neuroinflammation (Wrigley et al., 2009; Freund et al., 2013; Jure et al., 2021). In this regard, our group has defined this distal and rostral damage as Tertiary Damage.

Traumatic brain injury (TBI) pathophysiology also includes primary and secondary events. Primary injury is the consequence of the mechanical forces producing diffuse or focal damage. Secondary injury results from this early insult and it is characterized by a complex network of biochemical events that culminate in white matter damage and neurodegeneration contributing to behavioral morbidity. Curiously, glial alterations observed during Tertiary Damage resemble changes described in the brain after TBI. Indeed, chronic neuroinflammation is an important pathophysiological mechanism underlying neurodegeneration following TBI and it is associated with neurological, cognitive, and psychiatric disorders (Rodgers et al., 2014). The persistence of pro-inflammatory neurotoxic microglia might explain the progressive neurodegenerative and chronic brain atrophy described after TBI (Loane et al., 2014).

Given that chronic neuroinflammation and microglial activation are associated with chronic neurodegeneration and cognitive deficits, therapeutic strategies designed to modulate these processes should be addressed. In this regard, therapies based on insulin growth factor 1 (IGF-1) could be a promising possibility. IGF-1 is a hormone protein that plays an important role during development and adulthood as it is involved in the regulation of growth and cellular proliferation. This growth factor is predominantly released by the liver and its synthesis is stimulated by growth hormone. However, a variety of tissues produces IGF-1 at distinctive times. Particularly, in the CNS, it has neurotrophic and neuroprotective functions, playing an important role in neuronal rescue during neurodegenerative processes (Acaz-Fonseca et al., 2015; Labandeira et al., 2017).

Gene therapy appears as a fascinating option to treat CNS trauma and neurodegenerative diseases. This therapy potentially leads to neuroprotection, neurorestoration, and the correction of pathogenic mechanisms by inducing the expression of specific proteins (Sudhaker et al., 2019). Furthermore, gene delivery to the CNS using adenovirus results to be safe and well-tolerated (O'Connor et al., 2015). In this sense, a recombinant adenoval viral construct harboring the CDNA of rat IGF-1 (RAd-IGF1) has been used to treat neuroinflammation in aged rats and after experimental SCI (Falomir-Lockhart et al., 2019; Jure et al., 2021).

Firstly, in this review, we will discuss not only cognitive and emotional impairments observed after SCI but also evidence on hippocampal abnormalities. Secondly, IGF-1 gene therapy to treat behavioral and hippocampal alterations after SCI will be considered. Finally, the possibilities of IGF-1 gene therapy to deal with TBI will be analyzed.
Search Strategy and Selection Criteria

Studies cited in this review were published from 2000 to 2021 and were selected from the PubMed and Google Scholar databases using the following keywords: brain and spinal cord injury, IGF-1 gene therapy and IGF-1 and traumatic brain injury.

Cognitive and Emotional Consequences after Spinal Cord Injury

Although little attention has been paid to cognitive and emotional dysfunctions observed in patients after SCI, several reports have described impairments in executive functioning, concentration ability, memory function, attention, learning, and processing speed impairment (Murray et al., 2007; Lazzaro et al., 2013; Craig et al., 2015). Cognitive impairments were underestimated by the scientific community because sixty percent of spinal cord injury (SCI) patients with depressed mood and anxiety were not recognized as a consequence of SCI (Jure et al., 2020). Certainly, all these conditions contribute to decreasing quality of life, reducing social participation, and affecting cognition (Craig et al., 2015). Therefore, it is very complex to discern what the causes of their cognitive deficits are. It is crucial to develop animal models to study the biological changes in the brain after SCI that lead to cognitive changes and behavioral alterations.

In this regard, Faden’s work is very significant because it demonstrates for the first time that SCI causes emotional and cognitive deficits in rodents (Wu et al., 2014a, b). In their work, mice received a moderate contusion injury in the cervical spinal cord using the Y-Maze spontaneous alternation test, which implied locomotion. Contextual and emotional memory was evaluated using the step-down fear-avoidance test. Results show that lesioned mice demonstrated decreased immobility time during the tail suspension test and to reduce water sweet consumption during the sucrose preference, indicating depression-like behavior (Wu et al., 2014a).

Our group also has contributed significantly to the study of cognitive impairments after SCI. Recognition and working memory were evaluated using a compression model of spinal lesions, which let rats walk (Jure et al., 2021). Spatial working memory was evaluated by the Y-Maze spontaneous alternation test. Lesioned rats displayed a reduction of spontaneous alternation, indicative of dysfunctional spatial working memory (Jure et al., 2021). Recognition and working memory were evaluated by the Novel object recognition test (NOR) and results showed that lesioned rats spent less time exploring the novel object in the recognition phase than sham ones demonstrating that injured rats were not able to discriminate between the novel and the familiar object, an indicative of impaired recognition memory (Jure et al., 2021).

These findings are very significant because they demonstrate that cognitive and mood deficits are not induced by lifestyle changes, drugs of abuse, and combined medication. They are related to changes in brain structures involved in cognition and emotion, such as the hippocampus.

Hippocampal Abnormalities after Spinal Cord Injury

Hippocampal neurons

The hippocampus has an impressive capacity for adaptive plasticity since neuronal circuitry undergoes constant modifications in dendritic complexity. Numerous reports describe that hippocampal dysfunction generates cognitive impairment in hippocampal-dependent learning such as retention and spatial memory (Belarbi et al., 2012, Li et al., 2016). In this regard, hippocampal failure is associated with NOR and Y-maze performances (Broadbent et al., 2010). In line with these findings, depressive-like behaviors are reported using the sucrose preference and the force swim test after hippocampal ischemia in mice (Luo et al., 2019).

Since cognitive and emotional impairment described in humans and rodents after SCI is related to modifications of these circuits, one of the goals of our laboratory is to study the impact of SCI on this structure. We have recently demonstrated that SCI increased hippocampal vulnerability in mice. The number of mature neurons of both the dorsal granular cell layer (GCL) and pyramidal cell layer (CA1) remained unaltered during the acute phase, but neural density declined in the chronic phase following SCI (Jure et al., 2022). Faden’s group has also shown that the number of total hippocampal neurons remained unchanged in the acute phase and decreased in the chronic phase (Wu et al., 2014b).

Neurogenesis

The subgranular zone (SGZ) of the dentate gyrus of the hippocampus is one of the brain regions where the generation of new neurons continues throughout life due to the persistence of a neural stem cell (NSC) population (Toda and Gage, 2018). Normally NSCs are activated and produce highly proliferative life due to the persistence of a neural stem cell (NSC) population (Toda and Le, 2016). Neuronal circuits associated with encoding spatial information is also decreased during the recognition phase than sham ones demonstrating that injured rats were not able to discriminate between the novel and the familiar object, an indicative of impaired recognition memory (Jure et al., 2021).

These findings are very significant because they demonstrate that cognitive and mood deficits are not induced by lifestyle changes, drugs of abuse, and combined medication. They are related to changes in brain structures involved in cognition and emotion, such as the hippocampus.

Hippocampal neuroinflammation

Microglial cells alongside astrocytes manage the inflammatory response in the CNS. Microglia and astrocytes that are involved in the spread of molecules generating a different spectrum of functional properties (Tang and Le, 2016). Homeostasis recovery after injury depends on the fine-tuning polarization of microglia and astrocytes from pro-inflammatory towards anti-inflammatory phenotypes. Microglia are maintained in a surveillant state of activation through several inhibitory signaling between microglia and other cells (Frank et al., 2018).

Neurogenic niches are modified by surrounding microenvironments and pathological conditions. Indeed, neuroinflammation has been extensively reported to impact hippocampal neurogenesis (Sierra et al., 2014). In fact, neurogenesis decreases with aging, chronic stress, and neurodegenerative diseases, all conditions where neuroinflammation is a common landmark. For instance, pro-inflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor-alpha (TNFα) reduce the proliferation and survival of NSCs and ANPs (Kuzumaki et al., 2010). The recruitment of new neurons to hippocampal circuits associated with encoding spatial information is also decreased during chronic inflammation leading to cognitive impairment in rodents (Sierra et al., 2014).

Chronic neuroinflammation also generates hippocampal dysfunction altering synaptic plasticity, decreasing cognitive performance such as spatial and memory, and inducing depressive-like behavior (Belarbi et al., 2012). In this regard, treatment with anti-inflammatory drugs such as minocycline, cannabinoids, or TNFα inhibitors improves recognition memory evaluated by NOR and spatimated memory assessed by the Y-maze (Belarbi et al., 2012, Li et al., 2016). In addition, anti-inflammatory drugs improve fear memory, reduce anhedonia measured by the sucrose preference test and forced swim tests (Troubat et al., 2021).

There is compelling evidence demonstrating that SCI induces microglial...
changes in rodents (Wu et al., 2014a; Jure et al., 2017, 2021, 2022). For instance, our group has described that the number of microglial cells increased during the acute phase in the hilus, molecular layer, and GCL + SGZ of the dentate gyrus in mice. However, mRNA levels of pro-inflammatory cytokines remained unaltered in this phase (Jure et al., 2022). In agreement with these results, Faden’s group has shown an increase in the number of microglial cells concurrent with the up-regulation of mRNA expression of cytokines such as IL-1β, TNFα, IL-18 and IL-1β-TNFα (Wu et al., 2014b). It is described that microglial cells change their morphology from ramified to hypertrophic and bushy, indicative of microglia activation. Nevertheless, coinciding with our results, mRNA levels of pro-inflammatory cytokines experimented with no modifications 7 days post-injury (Felix et al., 2012; Wu et al., 2014b).

During the acute phase, microglial cells proliferate and acquire the morphology of an active cell although it is no production of pro-inflammatory cytokines. These characteristics are the hallmark of primed microglia, which has been described in a number of conditions such as infection, stress, and neurodegeneration (Frank et al., 2018). The scenario definitely changes during the chronic phase. In agreement with Faden’s results, we have shown that mRNA levels of pro-inflammatory cytokines such as IL-1β, TNFα, IL-1β, and IL-1β-TNFα were re-regulated. Furthermore, microglial cells presented an activated morphology displaying hypertrophic and bushy forms instead of the surveilled ramified phenotype in the Hilus, molecular layer, and SGZ + GCL (Jure et al., 2021). A further analysis using the expression of arginase 1 (ARG), an enzyme associated with a non-inflammatory profile, showed that these hypertrophic microglia in the hippocampus belonged to a pro-inflammatory phenotype after SCI (Jure et al., 2022).

Microglial activation may be due to neuron release of chemokines after SCI. In this regard, some studies have shown that CA1, CA3, and hilar neurons increased the expression of CCL2, CCR2, CCL3, and CCL21 in the chronic phase (Li et al., 2020). The effects of CCL2 and CCL21 on microglial activation and the key role of these chemokines on neuron-glia communication are well-known (Lockhart et al., 2020). On the other hand, astrocytes also play a critical role in regulating neuroinflammation, and the number of activated cells increases in the hilus, molecular layer, and SGZ + GCL after both acute and chronic SCI (Jure et al., 2022).

Neuroinflammation in the chronic phase could also be responsible for the death of hippocampal neurons since it is common to various neurological disorders such as epilepsy, degenerative diseases, and multiple sclerosis where several neurons are usually lost. In fact, pro-inflammatory microglia release TNFα, nitric oxide, and reactive oxygen species, which produce neuronal death (Kandil et al., 2012).

Based on this evidence, chronic neuroinflammation and the activation of microglia could cause cognitive and emotional impairment neurodegeneration, which lead to cognitive and emotional impairment in hippocampal-dependent behaviors after SCI. It is important to clarify that although both cognition and emotional behavior involve the hippocampus, these functions also depend on other brain regions such as the amygdala, the hypothalamus as well as the prefrontal and perirhinal cortices (Spelman et al., 2015).

**Insulin Growth Factor 1 Gene Therapy for Treating the Encephalopathy Caused by Spinal Cord Injury**

Gene therapy appears as an interesting option to treat CNS trauma, especially when clinical treatment implies a constant supply of any peptide. Modified associated demers have been used to deliver genes of interest to the brain. Delivery methods in the CNS include intraparenchymal injection (directly into the brain or spinal cord) or injection into the cerebrospinal fluid either intracerebroventricular (ICV) or intrathecal. The delivered gene can target the specific gene causing the disease or can modify the underlying pathogenic mechanism. In the second case, neurorestorative therapies are focused on attempting to restore cellular functions affected by the disease. This strategy has followed the delivery of genes that code for growth factors, such as glial-derived neurotrophic factor, nerve growth factor, and IGF-1 (Sudhakar et al., 2019). Indeed, the delivery of these genes is a powerful tool for treating neurodegenerative diseases such as amyotrophic lateral sclerosis, Parkinson’s disease, and Alzheimer’s disease. In this regard, an associated adenovirus coding for glial-derived neurotrophic factor applied to the striatum and substantia nigra resulted in better clinical scores in a model of Parkinson’s disease (Sudhakar et al., 2019). In addition, IGF-1 gene therapy administered into the perihilar region of the amygdala in a model of amnestic mild cognitive impairment and delayed motor decline and extended survival (O’Connor et al., 2015). On the other hand, for treating SCI gene therapy focuses on growth factors that either stimulate regeneration, increase the plasticity of the spare tissue and stimulate the intrinsic regenerative program of the injured spinal cord (Franz et al., 2012).

Given that patients present cognitive impairments, it is important to find therapies to reverse the hippocampal abnormalities described after chronic SCI. The fine-tuning polarization from pro-inflammatory towards anti-inflammatory microglial phenotypes represents a potential strategy to treat the neuroinflammation that supports tertiary damage. In this regard, IGF-1 arises as a good candidate because it induces the polarization of microglial cells towards neuroprotective and anti-inflammatory phenotypes (Labandeira-Garcia et al., 2017). In addition, IGF-1 is considered a pleiotropic molecule with both neuroprotective and regenerative potential. IGF-1 has critical implications in re-attaining brain function by displaying axonal and dendritic morphology and improving synaptic function (Bianchi et al., 2017). IGF-1 exerts its neuroprotective actions under different conditions in the nervous system (Kumar and Loane, 2012) and it is thought that this protein promotes a potent anti-inflammatory molecule reducing reactive gliosis after brain injury (Labandeira et al., 2017; Morel et al., 2017). Furthermore, this factor has been used successfully as a therapeutic agent in different experimental models of neurodegeneration and traumatic brain damage (Pardo et al., 2016; Falomir-Lockhart et al., 2019; Herrera et al., 2021). Among the variety of functions regulated by IGF-1, metabolic functions, cell proliferation, neuron survival effects, and neurite outgrowth are significant in the context of brain damage (Zheng et al., 2017).

In this regard, the use of a recombinant adenovirus vector (RAd) overexpressing the coding region for rat IGF-1 (RAd-IGF1) in rodents has been attempted in an effective approach to reduce negative outcomes related to aging, neuroinflammation, and reactive gliosis after TBI and SCI (Nishida et al., 2011; Morel et al., 2017; Falomir-Lockhart et al., 2021; Herrera et al., 2021; Jure et al., 2021).

**ICV IGF-1 gene therapy has resulted in an effective route of IGF-1 administration since the RAd-IGF-1 vector transduces brain ependymal cells with high efficiency releasing IGF-1 to the cerebrospinal fluid (Herenu et al., 2007).** Compelling evidence has demonstrated that this route of administration regulates glial and neuron function in the brain parenchyma (Pardo et al., 2016; Morel et al., 2017; Falomir-Lockhart et al., 2019). Our laboratory has shown that RAd-IGF-1 gene therapy applied during the chronic phase after SCI reverts the inhibition of neurogenesis (Jure et al., 2021). Recently, as we have already mentioned, neurogenesis reduction results from the inactivation of NSCs (Jure et al., 2022). On this subject, IGF-1 enhances NSCs proliferation and differentiation by acting through the IGF-1 receptor (IGF-1R) (Cui et al., 2012) and Zheng, 2013. IGF-1R promotes the rise in the number of DCX* cells induced by IGF-1 gene therapy in the aged hippocampus (Pardo et al., 2016).

Surveillance ramified microglia turns into activated hypertrophic microglia after SCI (Jure et al., 2021). This morphological transformation is accompanied by the loss of ARG expression. ARG- hypertrophic microglia is normally related to neuroinflammation, aging, and neurodegenerative diseases (Stratulis et al., 2019). Our data clearly shows that RAd-IGF-1 therapy, applied during the chronic phase after SCI, polarizes microglia to an anti-inflammatory, neuroprotective phenotype, stimulating ARG- hypertrophic microglia to switch to ARG-expressing ramified cells (Jure et al., 2021). Curiously, in the neurogenic niche, RAd-IGF-1 administration increases the number of hypertrophic microglia, which expresses ARG. However, neuroprotective actions of hypertrophic microglia have been demonstrated (Mathieu et al., 2010; Kyoto et al., 2012). Therefore, ARG* activated microglia could release pro-neurogenic factors to neural stem cells and recover neurogenesis. In line with this result, reactive microglial cells in the striatum are increased and motor deficits are reduced by RAd-IGF-1 treatment in aged rats (Nishida et al., 2011; Falomir-Lockhart et al., 2019).

Interestingly, our laboratory has recently demonstrated that the reversion of hippocampal abnormalities after RAd-IGF-1 therapy is accompanied by the restoration of cognitive abilities. Indeed, the administration of RAd-IGF-1 during the chronic phase recovered recognition and functional working memory and measured by the Barnes, NOR (Jure et al., 2021). These results are consistent with previous studies showing that RAd-IGF-1 gene therapy improves spatial and recognition memories in aged rats (Pardo et al., 2016; Morel et al., 2017). Correlation studies show a positive relationship between the number of ARG microglia, cognitive function, and neurogenesis. These results indicate a relationship between ARG* microglia and the improvement of hippocampal functions.

Concerning IGF-1 mechanism of action, several reports have described that IGF-1 is necessary for the expression of ARG and full adoption of the microglial anti-inflammatory phenotype via the activation of the STAT6/Akt signaling pathway (Barrett et al., 2008). Additionally, the expression of IGF-1R is upregulated in microglia in different cell types beyond microglia (Martinez-Rachadell et al., 2019), thus, pleiotropic mechanisms of action should be considered.

**Insulin Growth Factor 1 Gene Therapy Associated with Traumatic Brain Injury**

There is extensive literature particularly focused on TBI and its relation with impaired behavior and neuroinflammation (Kumar and Loane, 2012; Blesch et al., 2016; Herrera et al., 2021). Although it is beyond the aim of this work to review all the research related to TBI, we will discuss IGF-1 therapeutic approaches in this pathology.

In this regard, previous research has established that IGF-1 plays an important role in neurogenesis after TBI as conditional IGF-1 overexpression in regions of neuronal damage results in an increase in immature neuron density after cortical injury (Carlson et al., 2014), and it also improves cognitive function (Madathil et al., 2013). Nevertheless, IGF-1 based therapy used after brain injury has been associated with adverse side effects, such as increased tumor growth and weight gain (Ito et al., 2012). Therefore, further studies are needed to understand the potential benefits and risks associated with IGF-1 gene therapy for TBI.
injury shows different results. In a model of brain trauma, using PEG-IGF-1 administration to improve IGF-1 stability and half-life, Sama et al. (2018) have found that modified IGF-1 was not effective in ameliorating early neuronal loss and/or contusion. However, Santì et al. (2018) have proven that peripheral IGF-1 exogenous administration is necessary to fully restore sensorimotor function after TBI.

It is worth mentioning that in a contusion model of TBI, there is a decrease in IGF-1 serum levels after the injury that correlates with hippocampal neuron loss and spatial memory deficits (Ozdemir et al., 2012). In addition, IGF-1 overexpression inhibits apoptosis induced by various stimuli involved in TBI such as hypoxia and excitotoxicity (Madathil et al., 2015). Furthermore, IGF-1/ICV injection after a penetrating brain injury reduces cell death, hippocampal neurodegeneration and promotes neuronal survival after TBI (Madathil et al., 2013).

As we have previously mentioned, IGF-1 has pleiotropic effects in the brain, being a potent mitogen with well-described trophic and anti-apoptotic effects on neurons. IGF-1 promotes projection neuron growth, dentritic arborization, and synaptogenesis. At a mechanistic level, this peptide has pro-survival effects on damaged neurons through the PI3K-AKT pathway (Madathil et al., 2015). Seminal observations established IGF-1/AKT signaling as a key pro-survival route in neurons. Moreover, serum IGF-1 protects neurons against maladaptive inflammation by blocking the action of inflammatory cytokines (Fernandez et al., 2017).

In line with these findings, our group has reported that both ICV and peripheral IGF-1 gene therapy administration are able to modify hippocampal neuroplasticity (Pardo et al., 2016; Falomir-Lockhart et al., 2019). As IGF-1 is actively transported from cerebrospinal fluid to the brain parenchyma by an unknown mechanism (Guan et al., 1996; Carro et al., 2000), the ICV route is a convenient strategy to deliver IGF-1 gene therapy to the brain. Coinciding with this affirmation, IGF-1 gene therapy ameliorates neuroinflammation (Nishida Neuroscience, 2011; Falomir-Lockhart 2019) on different experimental models such as aged rodents (Herenu et al., 2007; Falomir-Lockhart et al., 2019; Herrera et al., 2019, 2020) and the encephalopathy caused by SCI (Jure et al., 2021, 2022).

However, peripheral administration emerges as a less invasive route of RAd-IGF-1 delivery. Recently, we have demonstrated that intramuscular IGF-1 gene therapy enhances IGF-1 serum levels and decreases microglia reactivity after cortical stab wound injury, and prevents the concomitant cognitive impairment (Herrera et al., 2021). Similarly, IGF-1 brain increase after TBI is related to the enhanced entrance of circulating IGF-1 (Santi et al., 2018).

All these works strongly support the therapeutic use of IGF-1 based therapies (both systemic and ICV) for preventing the unfavorable outcomes of traumatic damage.

Conclusion

It is time to consider SCI as a brain neurodegenerative disease and not only as an event circumscribed to the spinal cord. Indeed, the hippocampus is deeply and chronically altered as a consequence of spinal cord damage. Alterations in these structures might lead to cognitive and mood disorders seen in rodents and even in humans. This approach is opening a new area in neurobiology since therapeutic strategies are focused on preventing secondary injury and ignoring the encephalopathy that develops at rostral sites. Future rehabilitation strategies should emphasize not only sensorimotor and cognitive functions but also cognitive functions in general.

In this sense, IGF-1 emerges as a new therapeutic option as it modulates microglia towards an anti-inflammatory phenotype decreasing neuroinflammation and restoring cognitive function in animal models of CNS injuries (both systemic and ICV) for preventing the unfavorable outcomes of traumatic brain injury. The authors declare no conflicts of interest.

Acknowledgments: FL and MJB have designed and written the manuscript. Both authors also collected, analyzed and discussed the data, and approved the final version of the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons AttributionNonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

References

Açac-Fonseca E, Duran JC, Carrero P, Garcia-Segura LM, Arevalo MA (2015) Sex differences in gliia reactivity after cortical brain injury. Glia 63:1966-1981.

Ahuja CS, Wilson JR, Nonsi S, Kotter MRN, Druschel C, Curt A, Fehlings MG (2017) Traumatic spinal cord injury. Nat Rev Dis Primers 3:17018.

Arruda-Carvalho M, Sakaguchi M, Akers KG, Josselyn SA, Frankland PW (2011) Posttraining ablation of adult-generated neurons degrades previously acquired memories. J Neurosci 31:15113-15127.

Barrett JP, Milone AM, Falvey A, Lynch MA (2015) Involvement of IGF-1 and Akt in M1/ M2 activation state in bone marrow-derived macrophages. Exp Cell Res 335:258-268.

Beattie MS, Farooqui AA, Bresnahan JC (2000) Review of current evidence for apoptosis after spinal cord injury. J Neuropauma 17:915-925.

Belardi K, Arellano C, Ferguson R, Jopson T, Ross S (2012a) Chronic neuroinflammation impacts the recruitment of adult-born neurons into behaviorally relevant hippocampal networks. Brain Behav Immun 26:18-23.

Bellini MJ, Herenu CB, Goya RG, Garcia-Segura LM (2011) Insulin-like growth factor I gene reduces astrocytes into their inflammatory response to lipopolysaccharide. J Neuroinflammation 8:21.

Bergami M, Rimondini R, Santì S, Blum R, Gotz M, Canossa M (2008) Deletion of TrkB in adult progenitors alters newborn neuron integration into hippocampal circuits and increases anxiety-like behavior. Proc Natl Acad Sci U S A 105:15570-15575.

Bianchi VE, Locatelli V, Rizzi L (2017) Neurotrophic and neuroregenerative effects of GH/ IGF-1. Int J Mol Sci 18:2441.

Blennow K, Brody DL, Koehanek PM, Levin H, McKee A, Davies GM, Yaffe K, Zetterberg H (2016) Traumatic brain injuries. Nat Rev Dis Primers 2:16094.

Brodthorst NJ, Gaskin S, Squire LR, Clark RE (2010) Object recognition memory and the rodent hippocampus. Learn Mem 17:5-11.

Carlson SW, Madathil SK, Sama DM, Gao X, Chen J, Saatman KE (2014) Conditional overexpression of insulin-like growth factor-1 enhances hippocampal neurogenesis and restores immature neuron dentritic processes after traumatic brain injury. J Neuroatroph Exp Neurol 73:744-746.

Carro E, Nunez A, Busiguina S, Torres-Aleman I (2000) Circulating insulin-like growth factor I mediates effects of exercise on the brain. J Neurosci. 20:2926-2933.

Craig A, Nicholas Perry K, Guest R, Tran Y, Dezarnaulds A, Hales A, Efraums C, Mitchell J (2015) Prospective study of the occurrence of psychological disorders and comorbidities after spinal cord injury. Arch Phys Med Rehabil 96:1426-1434.

Dehler S, Lou WP, Gao L, Skabbim M, Dallenbach S, Neumann A, Martin-Villallba A (2018) An immune-CNS axis activates remote hippocampal stem cells following spinal transection injury. Front Mol Neurosci 11:443.

Falomir-Lockhart E, Dolcetti FJ, Garcia-Segura LM, Herenu CB, Bellini MJ (2019) IGF-1 gene therapy modifies microglia in the striatum of senile rats. Front Aging Neurosci 11:48.

Felix MS, Popa N, Jeljoul M, Boucouet J, Gauthier P, Bauer S, Matazazo VA (2012) Alteration of forebrain neurogenesis after cervical spinal cord injury in the adult rat. Front Neurosci 6:45.

Fernandez-Arias MDM, Grondona JM, Granados-Duran P, Fernandez-Llebrez P, Lopez-Avalos MD (2017) Microglia morphological categorization in a rat model of neuroinflammation by hierarchical cluster and principal components analysis. Front Cell Neurosci 11:235.

Franz S, Weidner N, Bleisch A (2012) Gene therapy approaches to enhancing plasticity and regeneration after spinal cord injury. Exp Neurol 235:62-69.

Frank MG, Fonken LK, Annis JL, Watkins LR, Maier SF (2018) Stress disribits microglia via down-regulation of CDO20: A mechanism of neuroinflammatory priming. Brain Behav Immun 69:62-73.

Freund P, Weiskopf N, Ashburner J, Wolf K, Sutter R, Altmann DR, Friston K, Thompson A, Curt A (2013) MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: a prospective longitudinal study. Lancet Neurol 12:873-881.

Guan J, Skinner SJ, Beilharz EJ, Hua KM, Hodgkinson S, Gluckman PD, Williams CE (1996) The movement of IGF-I into the brain parenchyma after hypoxic-ischaemic injury. Neuroreport 7:632-636.

Hashimoto K, Nakashima M, Hamano A, Gotoh M, Ikeshima-Kataoka H, Murakami-Murofushi K, Miyamoto Y (2018) 2-carba cyclic phosphatidic acid supresses inflammation via regulation of microglial polarisation in the stab-wounded mouse cerebral cortex. Sci Rep 8:9715.

Herenu CB, Cristina C, Rimoiji O, Becu-Villalobos D, Cambiaggi V, Portiansky EL, Goya RG (2007) Restorative effect of insulin-like growth factor I gene therapy in the hypothalamus of senile rats with dopaminergic dysfunction. Gene Ther 14:237-245.

Herrera ML, Basadjian OM, Falomir-Lockhart E, Dolcetti FJ, Herenu CB, Bellini MJ (2019) Novel adenoviral IGF-1 administration modulates the association between depressive symptoms and aging: Does gender matter? Behav Brain Res 372:112050.

Herrera ML, Basadjian OM, Falomir-Lockhart E, Dolcetti FJ, Herenu CB, Bellini MJ (2020) Sex frailty differences in ageing mice: neuropathologies and therapeutic projections. Eur J Neurosci 52:2827-2837.

Herrera ML, Bandin S, Champanini LG, Herenu CB, Bellini MJ (2021) Intramuscular insulin-like growth factor-I gene therapy modulates reactive microglia after traumatic brain injury. Brain Res Bull 175:196-204.
Hood KN, Zhao J, Redell JB, Hylin MJ, Harris B, Perez A, Moore AN, Dash PK (2018) Endoplasmic reticulum stress contributes to the loss of newborn hippocampal neurons after traumatic brain injury. J Neurosci 38:2372-2384.

Jure I, Pietranera L, De Nicola AF, Labombarda F (2017) Spinal cord injury impairs neurogenesis and induces gli activity in the hippocampus. Neurochem Res 42:2178-2190.

Jure I, Lockhart EF, De Nicola AF, Bellini MJ, Labombarda F (2021) IGF-I gene therapy reversed cognitive deficits and restored hippocampal alterations after chronic spinal cord injury. Molecular neurobiology.

Jure I, De Nicola AF, Encinas JM, Labombarda F (2022) Spinal cord injury led to hippocampal gli alterations and neural stem cell activation. Cell Mol Neurobiol 42:197-215.

Kaidi AM, Degos V, Peinaune S, Goudon E, Chvor H, Loron G, Le Charpentier T, Josserand J, Ali C, Vivien D, Collingridge G, Lombert A, Issa L, Rene F, Loeffler JP, Kavelaars A, Verney C, Manzt J, Gressens P (2012) Activation of microglial N-methyl-D-aspartate receptors triggers inflammation and neuronal cell death in the developing and mature brain. Ann Neurol 72:536-549.

Kiyota T, Ingraham KL, Swan RJ, Jacobsen MT, Andrews SJ, Ikeshu T (2012) AAV serotype 2/5-mediated gene delivery of anti-inflammatory interleukin-10 enhances neurogenesis and cognitive function in APP+PS1 mice. Gene Ther 19:724-733.

Kumar A, Loane DJ (2012) Neuroinflammation after traumatic brain injury: opportunities for therapeutic intervention. Brain Behav Immun 26:1191-1201.

Kuzumaki N, Ikegami D, Imai S, Narita M, Tamura R, Yajima M, Suzuki A, Miyashita K, Niikura K, Takeshima H, Ando T, Ushijima T, Suzuki T, Narita M (2010) Enhanced IL-1beta production in response to the activation of the hippocampal gli cells impairs neurogenesis in mice. Nat Neurosci 6:721-728.

Labandeira-Garcia JL, Costa-Besada MA, Labandeira CM, Villar-Cheda B, Rodriguez-Perez A (2013) Central correlates of impaired information processing in people with spinal cord injury. J Clin Neurophysiol 30:69-76.

Lazzaro I, Tran Y, Wijesuriya N, Craig A (2013) Central correlates of impaired information processing in people with spinal cord injury. J Clin Neurophysiol 30:69-76.

Lucassen PJ, Oomen CA, Naninck EF, Fitzsimons CP, van Dam AM, Czeh B, Korosi A (2015) Neuroinflammation and neurodegeneration, and cognitive impairment after spinal cord injury. Neuron 84:63-75.

Loane DJ, Kumar A, Stoica BA, Cabatbat R, Faden AI (2014) Progressive neurodegeneration of spinal cord injury causes brain inflammation associated with cognitive and affective changes: role of cell cycle pathways. J Neurotrauma 31:487-497.

Santì A, Genis L, Torres Almen I (2018) A coordinated action of blood-borne and brain insulin-like growth factor-I in the response to traumatic brain injury. Cereb Cortex 28:2007-2014.

Sierra A, Encinas JM, Deudero J, Chancey JH, Enikolopov G, Overstreet-Wadiche LS, Turka SE, Maletić-Savatic M (2010) Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. Cell Stem Cell 7:483-495.

Sierra A, Beccari S, Díaz-Aparicio I, Encinas JM, Comeu S, Tremblay ME (2014) Surveillance, phagocytosis, and inflammation: how never-resting microglia influence adult hippocampal neurogenesis. Neuron 2014:610343.

Sierra A, Martin-Suarez S, Valcarcel-Martín R, Pascual-Brazo J, Aveloet SA, Abíego O, Deudero JJ, Brewer AL, Bernales I, Anderson AE, Baekelandt V, Maletić-Savatic M, Encinas JM (2015) Neuronal hyperactivity accelerates depletion of newborn stem cells and impairs hippocampal neurogenesis. Cell Stem Cell 16:488-503.

Spelman T, Rigotti M, Almami SE, Fusi S, Gogos JA, Jordan JA (2015) Hippocampal-prefrontal input supports spatial encoding in working memory. Nature 522:309-314.

Sudhakar V, Richardson RM (2019) Gene therapy for neurodegenerative diseases. Neurotherapeutics 16:166-175.

Tang Y, Le W (2016) Differential roles of M1 and M2 microglia in neurodegenerative diseases. Mol Neurobiol 53:1181-1194.

Toda T, Gage FH (2018) Review: adult neurogenesis contributes to hippocampal plasticity. Cell Tissue Res 7:201303.

Troubat R, Barone F, Leman S, Desmidt T, Cressant A, Anatasova B, Bizarda BR, El Hage W, Surget A, Belzung C, Camus V (2021) Neuroinflammation and depression: a review. Eur J Neurosci 53:151-171.

Wrigley PG, Huston SA, Arda MN (2012) Relationship between circulating IGF-1 levels and traumatic brain injury. J Neurotrauma 29:274-285.

Zhao B, Zheng Z (2017) Insulin growth factor-1 protects neural stem cells against apoptosis induced by hypoxia through Akt/mitogen-activated protein kinase/extracellular signal-regulated kinase (Akt/MAPK/ERK) pathway in hypoxia-ischemic encephalopathy. Med Sci Monit 23:1872-1879.

Zheng P, Tong W (2017) IGF-1: an endogenous link between traumatic brain injury and Alzheimer disease? J Neurosurg Sci 61:416-421.

C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y