


A Review of Pharmacological and Cell-based Therapies in Spinal Cord Injury

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Abstract

Spinal cord injury (SCI) is a severe central nervous system trauma (CNS) that has two primary and secondary phases. The initial phase, which is irreversible, causes nerve tissue destruction and bleeding. Various factors in the second phase together aggravate the primary damage. One of the important factors of the second phase is the cascading of inflammatory factors, which, contribute to the further destruction of nerve tissue. In addition to surgical treatments, drug and cell-based or extracellular vesicles therapy, by modulating the immune system and reducing inflammatory factors at the lesion site, prevent further destruction of nerve tissue and help improve the patient's neurological and motor function. Researchers have provided many chemical and herbal medicines to reduce complications caused by spinal cord injury, many of which are currently being used and are also known as drugs of choice. However, sometimes the long-term use of these drugs causes side effects. Today, the new approach of cell therapy and the use of extracellular vesicles (EVs) is being investigated, which has minimized the side effects of drug treatments and helped to improve the function of nerve cells. Mesenchymal stem cells (MSCs), have a high ability to differentiate into different cells and to modulate the immune system by secreting paracrine factors. But since they cannot cross the blood-brain barrier (BBB), researchers solved this problem by extracting extracellular vesicles (EVs) derived from mesenchymal stem cells (MSCs), which also contain all paracrine factors. In this study, a brief overview of drug treatments, stem cells, and extracellular vesicular therapy in the treatment of spinal cord injury has been discussed.

Keywords: Spinal cord injury, SCI therapies, Stem cell, Extracellular vesicle, Neuroimmunology

Introduction

The largest part of the nervous system is central nervous system (CNS). Brain and spinal cord are two important of CNS. This system has a limited capacity to repair diseases and traumatic injuries. One of the most important CNS injuries is spinal cord injury (SCI). SCI due to natural or driving accidents, falls from a height, and fights, annually lead to a wide range of relative or permanent defects and lack of motor, sensory, and autonomic functions under the damaged area in humans and animals (Feigin et al, 2019). Most of SCI is related to contusion in the spinal cord, such as vertebral dislocation or fracture, can lead to seizures, neuropathic pain, bowel and bladder dysfunction, pressure sores, urinary and stool disorders, and other respiratory and cardiovascular complications. Therefore, spinal cord injury severely reduces the quality of life (Ma et al. 2019). Considering the complications that occur after spinal cord injury and the limited ability of the nerve tissue to repair itself, it is necessary to provide a solution that has the least

complications and helps the patient recover. In this study, we evaluate the pathophysiology of spinal cord injury and current and future therapies including pharmaceutical therapies, stem cell therapy, and extracellular vesicle therapy.

Pathophysiology of SCI

Traumatic spinal cord injuries cause pathological changes including cell death and axonal degeneration, ultimately leading to loss of sensory and motor function. (Parr et al. 2008). Following spinal cord injury, the primary and secondary phases of the disease occur. Pressure, contusion, tensile, or tearing of the spinal cord during the lesion leads to further mechanical destruction of the nervous tissue and also bleeding in the spinal cord, which is an irreversible process. Axon damage and disruption in the cell membrane cause the activation of a cascade of cellular and molecular changes and messenger paths that initiate the second phase of spinal injuries (Kang et al, 2018, Alizadeh et al, 2019). The formation of free radicals, the release of pro-inflammatory cytokines (TNF- α , IL-1b, and IL-6)

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and inflammatory cells (Monocytes, Neutrophils, and lymphocytes), and the oxidative stress are a complication of secondary injuries that causes the death of neurons, glial cells, and myelin degeneration. Following gliosis, astrocytes proliferate and take the place of damaged neurons, resulting in the appearance of a compressed glial scar that acts as a physical and chemical barrier and prevents axon regeneration. Also, following cavitation of the spinal cord, neurons, and glial cells are progressively reduced and destroyed (Tzekou and Fehlings, 2014; Tator and Fehlings, 1991). So, inhibition of inflammation and gliosis are treatment goals in SCI.

Pharmacological therapies

Corticosteroids

The use of methylprednisolone as the drug of choice in the treatment of spinal cord injury is still controversial because of its side effects, including hyperglycemia, gastrointestinal bleeding, and wound infection (Bracken et al, 1984; Galandiuk et al, 1993; Shepard and Bracken, 1994; Bracken et al, 1997; Pointillart et al, 2000; Matsumoto et al, 2001; Kwon et al, 2004; Evaniew et al, 2015). However, administering Methylprednisolone Sodium Succinate (MPSS) in the first 8 hours after the injury prevents secondary damage by reducing free radicals and oxidative stress, improving blood flow and modulating the immune response, improving motor function and preserving the structure of the spinal cord (Hall and Braughler, 1982; Bracken et al, 1990; Hurlbert et al, 2013).

Cyclooxygenase inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and meclufenamate reduces edema and inflammation of the spinal cord and cause axon sprouting and improvement of motor function with minimal side effects (Domon et al, 2018; Chaves et al, 2018; Lambrechts and Cook, 2021). But the comparison that was made in our previous study between methylprednisolone sodium succinate (MPSS) and meloxicam (COX-2 inhibitor), meloxicam had less motor function improvement compared to MPSS (Khodabakhshi Rad et al, 2022).

Minocycline

This drug crosses the blood-brain barrier and has neuroprotective, anti-inflammatory, antioxidant, and anti-apoptotic properties (Casha et al, 2012; Shultz and Zhong, 2017; Donovan and Kirshblum, 2018;

Zhang et al, 2021).

Chondroitinase ABC enzyme

Chondroitinase ABC (ChABC) with inhibition of Chondroitin sulfate proteoglycans (CSPG) as a regeneration failure agent (Fry et al, 2010; Kim et al, 2013; Anjum et al, 2020; Zhang et al, 2021), increases the expression of anti-inflammatory cytokines and decreases pro-inflammatory cytokines and regulates immunity, increases synaptic communication and improves motor performance (Bradbury et al, 2002; Didangelos et al, 2014).

Neuroimmunophilin ligands

Neuroimmunophilin ligands (Cyclosporin A and FK-506) increase neuron regeneration in the central and peripheral nervous system, and also have neuroprotective properties in ischemia, neurodegenerative disorders, and trauma (Liu et al, 1991; Kang et al, 2008; Kawakami, 2013; Zhang et al, 2021).

Anti-CD11d Antibodies

Anti-CD11d Antibodies reduce the infiltration of neutrophils and macrophages at the site of spinal cord injury (Mabon et al, 2000; Saville et al, 2004), improve motor function, and reduce pain and histopathological damage (Gris et al, 2004; Hurtado et al, 2012).

T cell targeting therapies (CXCL10 antagonisms and Fingolimod)

CXCL10 antagonisms, by reducing the infiltration of T cells in the lesion site, reduce neuronal death and increase axon regeneration (Ghirnikaret al, 2001; Glaser et al, 2006; Gonzalez et al, 2007). Fingolimod reduces the number of circulating lymphocytes and its local and systemic administration reduces reactive gliosis, cell death, and neuronal inflammation, and ultimately improves motor and bladder function (Chiba, 2005; Lee et al, 2009; Norimatsu et al, 2012; Wang et al, 2015; Healy et al, 2016; Putatunda et al, 2018).

Autologous macrophage therapy

It cleans tissue debris in the injured area, modulates the immune system, and affects neurons, glial cells, and immune cells. Although they may affect healthy tissue and cause cell death and increase the size of the lesion and functional disorders, they are vital for the healing and regenerating of axons (Bomstein et al, 2003; Knoller et al, 2005).

Hepatocyte growth factor (HGF)

HGF has neuroprotective effects, increases the regeneration of axons, oligodendrocytes, and the survival of neurons (Kitamura et al, 2007; Kitamura et al, 2011; Zhang et al, 2021), and helps to improve motor function by reducing the activity of astrocytes, glial scar, infiltration of leukocytes, and inflammation (Kitamura et al, 2011).

Fibroblast growth factors (FGF)

The application of FGF in the form of fibrin glue with acidic FGF has been shown in studies to have neuroprotective and immunomodulatory effects and to increase the level of interleukins 4, 10 and 13 (Kuo et al, 2011; Garcia et al, 2016). It reduces the production of free radicals and increases the survival and growth of different types of neurons (Koshinaga et al, 1993; Teng et al, 1999; Clarke et al, 2001; Rabchevsky et al, 2011; Zhou et al, 2018).

Among other drug treatments that are effective in healing spinal cord injury and have been presented in various studies are Monosialotetrahexosylganglioside (GM-1), Anti-Nogo-A antibodies (ATI-355), VX-210 (Cethrin), B-Cell depletion therapies, Neurotrophic factors, Granulocyte colony-stimulating factor, Vitamin E, Selenium, Dimethyl sulfoxide, Naloxone antagonist drug, Thyrotropin releasing hormone and etc (Anderson et al, 1985; Sterner and Sterner, 2022). Today, old drug treatments have given way to emerging therapeutic approaches (stem cell and extracellular vesicles therapy) in neuron protection in spinal cord injury of animal modeling, which has the least possible side effects and can be supplied systemically or locally.

Stem cell therapy for SCI

Different types of stem cells have been investigated in the healing of spinal cord injury. Some of these cells include Schwann cells, olfactory sheath cells, mesenchymal stem cells, neural progenitor cells, oligodendrocyte progenitor cells, and various induced pluripotent stem cells (Badner et al, 2017; Srivastava et al, 2021). MSCs are pluripotent stem cells that reside in mature tissues such as adipose tissue, bone marrow, dental pulp, Wharton's jelly, and endometrium. MSCs can differentiate into a variety of cells, including adipocytes, osteoblasts, and cartilage tissue cells (Viswanathan and Read, 2013). Because of their high biological safety, immunomodulatory

properties, and their ability to synthesize angiogenic and neurotrophic factors, MSCs have been proposed as a promising method to stimulate the regeneration of neurons in spinal cord injury (Mukhamedshina et al, 2019). MSCs exert a strong regulatory effect on the immune system by stimulating the secretion and production of a variety of inflammatory and non-inflammatory cytokines. Therefore, in reducing immune rejection, the treatment of inflammatory conditions and autoimmune diseases has been considered. Studies have shown that the immunomodulatory effect of MSCs is exerted through cell-cell contact and secretion of soluble factors. IDO1, TGF- β , PGE-2, and HGF are among the important mediators in the process of immune modulation by MSCs (Zhou et al, 2020). In addition, their multiple potentials and unique ability for self-renewal make them a suitable option for cell-based therapies. MSCs have a high ability in proliferation, differentiation, and regeneration of damaged tissue, remyelination, axon regeneration, inhibition of apoptosis, inhibition of inflammation, and change of macrophage phenotype (M1 to M2). Due to the immune-modulating feature, these cells can be transferred to damaged tissues after transplantation and at the same time guarantee cellular immunity and phenotypic stability (Hematti, 2008; Bagher et al, 2015; Bagher et al, 2016; Giacoppo et al, 2017; Ezquer et al, 2017; Berebichez-Fridman and Montero-Olvera, 2018; Fu et al, 2019; Pool et al, 2019).

Although MSCs have valuable effects in improving the condition of various diseases, their clinical use is limited by the possibility of malignancy, potential risk of tumor formation, profibrogenic ability, heterogeneity of MSC populations, entrapment in the lungs after infusion, poor grafting efficiency, low immunogenicity, short half-life and low production of antibodies after repeated administration is encountered. Also, the clinical use and creation of MSCs bank, like other types of cells, require strict conditions for storage and maintenance (Lee, 2018; Musiał-Wysocka et al, 2019; Navajas et al, 2019). Considering the limitations of MSCs, a new solution has been presented that does not have the mentioned limitations for clinical applications, and that is the use of extracellular vesicles.

Extracellular vesicle therapy

Extracellular vesicles, which are secreted by

almost all types of cells, have a double-layer membrane, and for this reason, they have good stability and permeability. After stimulating receptors on the surface of target cells or entering target cells, EVs can regulate cell function and messaging (Villarroya-Beltri et al, 2014). EVs are rich in lipids, proteins, and nucleic acids such as lncRNAs and miRNAs. They are between 30-50000 nm in diameter (Chiang and Chen, 2019; O'Brien et al, 2020) and are divided into three categories: exosomes (30-150 nm), microvesicles (100-1000 nm) and apoptotic bodies (1000-5000 nm) (Chukhchin et al, 2020).

Extracellular vesicles derived from MSCs have mediators of the paracrine effects of MSCs, for which tumorigenic properties have not been reported so far (Lai et al, 2018; Nooshabadi et al, 2020). In addition, many of the concerns that have been raised about the viability and maintenance of cell function do not exist in EVs (Colao et al, 2018; Wu et al, 2019). Due to their very small size, EVs are not a threat to pulmonary embolism and can easily cross physiological barriers such as the blood-brain barrier and show strong neuroprotective effects following central nervous system injuries (Yin et al, 2019; Mendt et al, 2019). Various studies have shown that systemic or local administration (in a hydrogel bed) of EVs with their immunomodulatory and immunoregulatory properties, reduces inflammation, edema, neuronal degeneration, glial scar, oxidative stress, and pro-inflammatory cytokines and increases angiogenesis, axonal regeneration, anti-inflammation cytokines and ultimately improves motor function (Guo et al, 2019; Li et al, 2020; Jia et al, 2021). Considering the valuable features of exosomes, it may be as a cell-free therapeutic approach in the treatment of spinal cord injury. EVs can be extracted from all MSCs of different origins, and they play a significant role in the treatment of spinal cord injuries. Zhou et al, 2022 showed that bone MSC-Exos improves pericyte coverage, and promotes axonal regeneration, and motor function by reducing leakage of BBB and edema (Zhou et al, 2022). Kang and Guo, 2022 reported that human umbilical cord MSCs derived from Wharton's jelly, with reducing apoptosis and inflammatory agents, and promoting angiogenesis and axonal growth, inhibit glial scar, and promote neuronal recovery (Kang and Guo, 2022). Moreover, human epidural adipose tissue mesenchymal stem cell-derived exosomes (ADSC-Exos) and human menstrual blood-derived mesenchymal stem cells (MenSCs) can modulate the inflammatory response

and promote polarization macrophage and microglia (Sung et al, 2022; He et al, 2022). Also, dental pulp stem cells- EVs showed a potential motor performance improvement through immunomodulatory effects (Liu et al, 2022). The widespread use of EVs in the treatment of spinal cord injury has been investigated in many experimental studies and is ongoing (Zhung et al, 2023).

Discussion

Spinal cord injury has a complex pathophysiology. The secondary phase that occurs after the primary phase of damage causes neuronal apoptosis, inflammatory response, vascular changes, accumulation of free radicals, and activation of astrocytes and glial scar formation. Among these events, inflammation is one of the main factors. To prevent these consequences, a chain of harmful reactions developing around the lesion must be blocked. Therefore, early timing for neuron protection by drugs should be a basic strategy. SCI management is mainly to prevent progressive degeneration and neutralize secondary damage at the site of the injury to reduce pain and symptoms and restore motor function. So far, various drugs and compounds have been prescribed at different times after the injury in acute SCI. The basis of these treatments should be to reduce the penetration of inflammatory cells, the release of pro-inflammatory cytokines, and free radicals, and by modulating the immune system, increase the occurrence of the anti-inflammatory phenotype of macrophages and the release of anti-inflammatory cytokines, so as to ultimately reduce the neuronal damage.

In recent decades, many immunomodulatory pharmaceuticals have been offered to improve motor function after SCI. Some of these drugs, such as NSAID/cyclooxygenase inhibitor, ChABC, and GCSF therapy after SCI, do not have harmful effects, but some drugs, such as methylprednisolone and GM-1, have minimal effects or have controversial side effects. However, drug treatments may not be able to cover all the inflammatory factors in the lesion site, and the combined and simultaneous use of stem cell therapies/extracellular vesicle therapies (systemic or local injection) can provide effective recovery for patients with spinal cord injury (Sterner and Sterner 2022; Zhang et al, 2023).

Conclusion

In this study, a number of medicinal treatments were presented and their number will be increased in

the future. Today, various studies have shown that the use of different mesenchymal stem cells that have the ability to differentiate into nerve cells and due to important paracrine features they have can help to treat spinal cord injury faster. Due to the fact that these cells do not have the ability to cross the blood and brain barrier, the extraction of extracellular vesicles from mesenchymal stem cells along with having paracrine characteristics can solve this problem. Many studies in the field of spinal cord injury treatment with extracellular vesicles have been reported in laboratory models with satisfactory results. It is hoped that one day we will see the application of these nanovesicles in the treatment of spinal cord injuries in humans.

Conflict of Interest

The authors declare that they have no conflict of interest.

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