Chapter

Introductory Chapter: Trends in Therapeutic Strategies after Spinal Cord Injury

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1. Epidemiology

Spinal cord injury (SCI) continues to be a diagnosis without a straightforward treatment plan, even in today's advanced medical-technological time. This is a problematic pathology not only for the patient but also for the health system since, aside from causing individual disability, it also originates an important economic cost. This is due—in great part—to the age group most affected by this type of injury, which regularly involves an average age of injury of 37.1 years old [1].

Spinal cord injury can lead to fatal consequences when autonomic processes such as respiratory or cardiovascular function are altered by injury. Otherwise, the most common repercussions are those affecting motor and sensitivity skills. This generates a scenario where the patient's clinical prognosis may vary from complete paralysis to an optimum case of injury where the patient could only need physical therapy for rehabilitation [2].

The reported prevalence as of 2017 is between 440 and 526 cases per million population, with a mortality rate as high as 22% in both developed and non-developed countries [3]. Regarding its incidence, there are 130,000 new cases reported every year [4]. And even though it may not seem like a large group of patients, it accounts for more than approximately a million dollars' worth of treatment for every case reported, thus becoming an important target for research toward finding an effective treatment that can limit symptomatology as well as complications due to SCI [3].

SCI pathophysiology encompasses an important number of phenomena that mainly contribute to SC-tissue destruction and/or regeneration inhibition.

2. Pathophysiology

The understanding of the pathophysiology of acute and chronic SCI is essential to the development of new therapeutic techniques that can effectively stop damaging mechanisms and promote beneficial effects.

Primary lesion is caused by the physical consequences of injury: contusion, compression, or laceration [5]. This leads to demyelization and hemorrhage, which by itself causes ischemia and necrosis affecting nearby cells in the central nervous system. With this process comes edema which develops hours after the insult and continues to expand for several days afterward. Finally in this stage, inflammatory response, cells such as neutrophils and macrophages approach the affected area to phagocytize the apoptotic and necrotic waste [6].

After this immediate response to the injury, there is a second phase with further effects on neural degeneration and tissue restoration:

- *Vascular changes*. These are due—in great part—to the ischemia that takes place, especially in the gray matter structures, and are aggravated by the hypotensive state of hypovolemia. This could be followed by a reperfusion phase that contributes to a secondary injury and the release of free radicals [7, 8].

- *Oxidative stress*. Free radicals have important effects on DNA and proteins by damaging the cell membrane through lipid peroxidation, as well as promoting apoptosis, resulting in a strong inhibition of Na-K ATPase [9, 10]. These are important consequences to keep in mind being that several treatment options available today such as methylprednisolone are related directly to this damaging mechanism [6, 11].

- *Excitotoxicity*. Glutamate, an important neurotransmitter in the central nervous system, also plays a role in the pathophysiology of SCI, as the extensive release of this molecule allows calcium entrance and the accumulation of intracellular Na and Cl (using its NMDA receptor), which in turn results in cytotoxic edema [12]. Therefore, NMDA receptor blockade becomes a therapeutic option to further explore.

- *Immune response*. As an immune-privileged site, the central nervous system is not known for having a large immune cell presence. Nonetheless, after a SCI, microglia suffers activation, and cytokines are rapidly released. There is an increase in the amount of TNF-α and arachidonic acid metabolites that can be found in cerebral spinal fluid. This, however, is a positive effect since TNF-α has been shown to increase levels of interleukin-10 which counteracts free radicals and stimulates axonal regeneration, making it a target for stimulation as a treatment option [13, 14].

- *Activation of Rho pathway*. SCI activates Rho pathway, which in turn inhibits the re-growth of axons and causes apoptosis. By inhibiting this activation, recovery improves substantially; however, there is no therapy for this purpose that has been approved yet [15].

- *Depletion of cAMP*. After injury an important reduction of cAMP in neurons occurs; this alteration inhibits neuron regeneration [16].

- *Glial scar and astrocyte activation*. The formation of a glial scar after injury represents a barrier to growing axons [17–20]. Additionally, activated astrocytes—the main cells conforming glial scar—express chondroitin sulfate proteoglycans (CSPGs) and extracellular matrix molecules like phosphocan and neurocan that, when downregulated, have shown to improve axonal regeneration, thereby proving their role in regeneration inhibition [17, 21].

At the moment, there is enough evidence about the deleterious effects exerted by each one of the abovementioned phenomena. That is why, several investigation groups are working on developing therapeutic strategies to induce neuroprotection and subsequently promote SC regeneration.

3. Neuroprotective therapies

As secondary lesion mechanisms are so abundant and have such a long-term effect on the patient's outcome; they have become the main target for SCI therapy. All of these potential treatment options are involved in various research proposals as to find suitable possibilities and improve recovery:

- *Cyclooxygenase inhibitors*. COX is a pro-inflammatory enzyme that leads to the production of prostanoids and therefore increased inflammation. This is the basis for the neuroprotective role of cox-inhibitors such as indomethacin (inhibits COX-1/COX-2 and the activity of select leucocytes, thereby preventing inflammation aggravation and edema) [22].

- *Immunophilin ligands*. These proteins are abundantly found in neural tissue and bind immunosuppressants like cyclosporine A and their analogs which are known as ligands [23]. When these ligands bind to immunophilins, they inhibit rotamase and calcineurin activity. These effects decrease immune responses such as cytokine production and neutrophil motility [24]. Ultimately, cyclosporine A binding to immunophilin slows down the demyelination process and stops the spreading of inflammation [25].

- *Antioxidants*. One of the most damaging pathophysiological mechanisms of SCI is perhaps the increased release of free radicals [26]. Methylprednisolone, currently the primary treatment for acute SCI, is aimed toward inhibiting lipid peroxidation and lactate accumulation. However, there are still concerns about it being a risk factor for pneumonia development [27].

- *Calpain inhibitors*. Calpain is a calcium-dependent cysteine protease that promotes apoptosis through enzyme degradation of cytoskeletal and membrane proteins. Researchers have found this to be associated with the increased concentration of intracellular calcium following SCI [28]. The two main classes include aldehyde-calpain and oxirane inhibitors, of this last one the primary example is E-64-d. This therapeutic option has demonstrated its neuroprotective effects in SCI models. By blocking calpains, apoptosis could be reduced [29].

- *Apoptosis inhibitors*. Caspase-3 and caspase-9 are key mediators for apoptosis after acute SCI; by inhibiting these molecules, there has been a proven clinical improvement in previous studies using minocycline. Minocycline is a second-generation tetracycline that has demonstrated to have anti-inflammatory and neuroprotective qualities in experimental studies in SCI, stroke, and neurodegenerative diseases. Talking about its antiapoptotic effects, minocycline decreases caspase 1 and caspase 3 availability, cytochrome c release, mitochondrial calcium uptake, and the release of apoptotic factors. By downsizing apoptosis in SCI, this drug reduces microglial activation [30].

- *Hormones*. Steroid hormones such as progesterone and estrogen have proven to be neuroprotective in SCI by showing decreased excitotoxicity, increased myelination, and enhanced antioxidant properties [31].

- *Na channel blockers*. Tetrodotoxin is the most investigated compound of this category; it has proven effects of better recovery by inhibiting fast Na channels and thereby lessening the continuous depolarized state of injured neurons [32].

4. Regenerative therapies

- *Pharmacological treatments*

    - *Rho pathway antagonists*. The Rho family has been associated with several pathways concerning cell proliferation, regeneration, and gene expression [33]. When activated, it leads to neurite growth blockade, especially when implicating Rho kinase (ROCK) [34]. This is why Rho-ROCK inhibitors are now under research as treatment options. These include C3 transferase, which modifies the Rho family thus minimizing its effect, and Y27632 which competes with ROCK for ATP receptors [35].

    - *Cyclic AMP enhancers*. The elevation of cyclic AMP levels is directly associated with a better neuronal response to myelin inhibitors. This has led to research for strategies that elevate cyclic AMP, for instance, the administration of dibutyryl cAMP (activating cAMP-dependent protein kinase) [36] or the inhibition of phosphodiesterase (PDE) using rolipram (a PDE-4 inhibitor that targets SNC tissue more specifically) has shown relevant effects on axonal regeneration [37].

    - *Glial scar inhibitors*. Being that the scar itself is an inhibiting factor for regeneration, several studies have tried to find a strategy to counteract this effect. Decorin is a proteoglycan molecule that has been linked to a reduction in the expression of inhibitory molecules such as brevican and neurocan as well as to the increased capability for axonal growth across myelin-rich environments [38].

    - *Hydrogels*. This type of material allows for healthy tissue to reconnect and therefore enable axonal growth across the injury. Hydrogels are usually made of hyaluronic acid or poly(2-hydroxyethyl methacrylate-co-methyl methacrylate); however, other options are being studied for their additional benefits. Some of these new prospects include poly(2-hydroxyethyl methacrylate-co-methyl methacrylate) which has shown improvement in locomotor function [39] and poly[N-(2-hydroxypropyl) methacrylamide] with evidence that it has axonogenic and angiogenic properties [40].

- *Scar removal*. Numerous research projects have proven that during chronic stages of injury (>2 weeks), there is a clear benefit when removing the glial scar given that it portrays a barrier both physically and chemically for axonal regeneration [21, 41].

- *Biocompatible matrices*. Tissucol (fibrin glue) is a fibrinogen and thrombin compound that's biocompatible and can therefore be used for cell transplant, as well as promoting growth [42]. Another alternative in this area is alginate, a biocompatible material obtained from bacteria and algae that promotes cell migration and axonal growth [43]. Other options in this category include Matrigel, polyethylene glycol, and hyaluronic acid [44].

- *Cell therapies*. In chronic stages of SCI, studies have shown that transplanting different cell types has improved recovery. Mesenchymal stem cells (MSCs) are the most promising ones so far, with the capacity to modulate the

microenvironment generated after SCI by secreting anti-inflammatory molecules and switching from M1 to M2 macrophage phenotype (protective and restorer phenotype) [45]. They also release neurotrophic factors that stimulate myelination and reduce apoptosis [46].

- *Combination therapies*. As there is a large amount of experimental therapies that target different physiopathological pathways, researchers have found it to be more effective to combine some of these options when it comes to tackling acute and chronic injuries [47]. Some examples of this are the combination of several growth factors and cell transplants, combining chondroitinase ABC and physical rehabilitation and the surgical removal of scar tissue along with immune modulatory therapy [48, 49].

So far, there is no definite treatment course for patients with SCI. This fact remains, although research over the years has developed several options that target the immunologic response that is triggered after an injury and that have both beneficial and damaging consequences as well as other mechanisms such as lipoperoxidation and cytotoxicity. Hence, there are several circumstances that need to be neutralized before a second strategy can intervene that can initiate remodeling and restoring the damaged tissue. So far, the understanding of pathophysiological mechanisms has been our most powerful tool into deciphering the best therapeutic plan. Neuroprotection is the current target for pharmacological as well as non-pharmacological therapies such as rolipram, MSCs, methylprednisolone, indomethacin, dibutyryl cAMP, and scar removal. The endpoint for all these treatment options is to encourage and enable neuroregeneration, and although as mentioned previously, there have been incredible advancements in this area, the search continues for new alternatives that offer better outcomes.

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