J Biochem Technol (2023) 14(4): 19-24
https://doi.org/10.51847/fHjZDJorr4
ISSN: 0974-2328

Spinal Cord Injury Physiopathology and Its Causative Models: A Review Study

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Received: 06 September 2023 / Received in revised form: 05 December 2023, Accepted: 07 December 2023, Published online: 16 December 2023

Abstract

Spinal cord injury is a disabling neurological disease. Despite recent clinical improvements in the methods of diagnosis, survival, and well-being of patients with injuries, there are still serious problems in the treatment of neurological and functional disorders of these patients. This slow progression is mainly because of the complexity of the pathophysiology of spinal cord injury and the extensive and numerous physiological and biochemical changes that happen in the injured spinal cord. For this reason, in the last few decades, significant efforts have been made by researchers to identify the pathophysiology of spinal cord injury and to discover the molecular and cellular mechanisms of tissue destruction and repair in the damaged spinal cord. In this regard, several animal models have been applied to create secondary and primary spinal cord injuries and to study their progress. In this article, we will first review the recent advances in understanding spinal cord injury physiopathology. Then, the existing animal models that have been used to identify the spinal cord injury mechanisms and create treatment strategies for this disease will be presented. Despite extensive studies and presentation of various models, there are still some major problems in understanding spinal cord injury, which are: (1) lack of coordination and sufficient anatomical and physiopathological similarity between experimental spinal cord injury and clinical spinal cord injury, (2) inconsistency of pathobiology spinal cord injury between different species and races, (3) difficulty in interpreting the results measured in animals when choosing the appropriate animal model to solve specific research problems.

Keywords: Spinal cord injury, Physiopathology, Causative models, Neurological disease

Introduction

Spinal cord injury or SCI for short is a sensory and motor disorder that is associated with temporary or permanent disability and reduced life expectancy (Fodor *et al*., 2023a). The annual incidence of spinal cord injuries in the world has varied from 1.13 to 163.4 cases per million people (Kang *et al*., 2018). A sudden blow to the spine that breaks, dislocates, crushes, or compresses the vertebrae may cause spinal cord injury due to trauma. A gunshot or stab wound may also sever the spinal cord (Alshammari *et al*., 2023). Diseases such as arthritis, cancer, inflammation, infections, or disc wear of the spinal vertebrae are among the causes of non-traumatic injuries of the spinal cord (Kang *et al*., 2018; Bashir *et al*., 2021; Vagabov *et al*., 2021).

Clinical outcomes of spinal cord injury are related to the location and severity of the lesion and may include complete or partial loss of motor function or sensory below the injury level (Chen *et al*., 2013). Spinal cord injury usually affects the spinal cord cervical level (50%), the most common level being the fifth cervical vertebra (Hachem *et al*., 2017). Other injuries include the chest area (35%) and lumbar area (11%). Lesions below the thoracic vertebrae can cause paraplegia, while lesions at the level of the cervical vertebrae are associated with quadriplegia (Fodor *et al*., 2023b). With recent advances in medical practices and patient care, patients with spinal cord injuries often survive these traumatic injuries and live years after the initial injury (Middleton *et al*., 2012; Cañete *et al*., 2022; Domiaty, 2022).

The life expectancy of spinal cord injury patients is highly dependent on the injury level and preserved functions (Tatiana *et al*., 2023). For example, patients with ASIA disability scale D who need a wheelchair for daily activities have a 75% normal life expectancy. However, patients who do not need a wheelchair can have a life expectancy of up to 90% (Shavelle *et al*., 2015). Explanation that the degree of spinal cord injury is graded based on the ASIA (American Spinal Injury Association) grading scale that describes the injury severity. This scale is graded based on letters (A, B, C, D, and E) (Maynard *et al*., 1997).

In most developing countries, the majority of patients are young adults (20-40 years old), so they impose a great burden on these countries. Men are exposed to this disease four times more than women (DeVivo, 2012; Bernard *et al*., 2021; Osipchuk *et al*., 2023).

The lack of effective treatments for spinal cord injury is caused by the complexity of physiopathology and the mechanisms involved in the development of the lesion (Karunakaran *et al*., 2023). For this reason, it is essential to do a study in the field of identifying cellular and molecular events that lead to functional damage and can suggest new therapeutic solutions. Modeling in laboratory animals is one of the research methods to identify spinal cord injury mechanisms and find new treatment methods. Considerable research has been done worldwide to develop animal models, and based on that, many therapeutic strategies have been explored. In

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this article, we review various animal models of spinal cord injury and evaluate their advantages and disadvantages for further studies.

Progression of Spinal Cord Injury

The Initial Stage of Spinal Cord Injury

A spinal cord injury is generally caused by a sudden blow to the spine that causes a fracture or dislocation of the vertebrae. The damage caused by the initial mechanical forces that are applied to the spinal cord at the injury time is known as the primary injury, in which "displaced bone fragments, discs, or ligaments in the spinal cord tissue are torn"(Dzhidzalov *et al*., 2023).

Many injuries do not result in complete spinal cord severing. The four main types of primary injury are (1) trauma with continuous pressure on the spinal cord tissue, (2) trauma with transient pressure, (3) incomplete spinal cord transection, and (4) spinal cord transection. The most common form of primary injury is trauma with continuous pressure, which usually puts pressure on the spinal cord as a result of broken bone fragments (Rowland *et al*., 2008; Erdag, 2022). Regardless of the type of initial injury, these forces damage the descending and ascending pathways of the spinal cord and disrupt the function of cell membranes and blood vessels, causing accumulation, ion imbalance, ischemia, vasospasm, systemic hypotension, and spinal shock (Figley *et al*., 2014; Osman *et al*., 2022). To date, the most important clinical treatment to reduce tissue damage after primary injury is surgical decompression of the injured spinal cord (less than 24 hours after injury). In general, the amount of primary injury determines the spinal cord injury severity (Wilson *et al*., 2011; Ghaffar *et al*., 2021).

Secondary Stages of Spinal Cord Injury

Secondary injury happens within minutes of the primary injury, and continues for months or weeks, causing progressive damage to the spinal cord tissue around the injury site. The secondary spinal cord injury concept was first proposed in 1911 by Alfred Reginald Allen. While studying spinal cord injury in dogs, he stated that hematomyelia removal after injury improves neurological outcomes. He assumed that some biochemical factors present in the hemorrhagic lesion cause more destruction to the spinal cord (Allen, 1911; Anushree *et al*., 2022). The term secondary injury refers to a set of biochemical, molecular, and cellular phenomena that destroy the spinal cord tissue following self-destruction and prevent neurological recovery after injury of the spinal cord (Oyinbo *et al*., 2011).

Secondary damage can be divided into three stages: chronic, subacute, and acute. The acute phase happens immediately after spinal cord injury and includes ion imbalance, vascular damage, accumulation of neurotransmitters (toxicity from hyperstimulation), free radical formation, influx of high amounts of calcium, inflammation, lipid peroxidation, and cell death. With injury progression, the subacute phase of injury happens, which includes residual axon demyelination, apoptosis, Wallerin degradation, retrograde axonal degeneration, and glial scar formation around the injury place. Changes in the chronic stage of injury include cystic cavity formation, retrograde and progressive axonal degeneration, and glial scar enlargement and maturation (Oyinbo *et al*., 2011). In the following, we will review the main stages of secondary damage that play a role in spinal cord injury physiopathology.

Vascular Damage and Spinal Cord Tissue Ischemia

Vascular disorders of the spinal cord and decreased blood supply are the primary consequences of spinal cord injury. Larger vessels, such as the anterior vertebral artery, usually remain healthy, whereas smaller vessels rupture subject to traumatic injury resulting in leakage of red blood cells and leukocytes. Increased tissue pressure in the damaged vasospasm and spinal cord caused by bleeding in healthy vessels further disrupts the blood flow to the spinal cord (Tator & Koyanagi, 1997; Couillard-Despres *et al*., 2017). In the spinal cord injury models of laboratory mice and monkeys, in the first few hours after the injury, there is a gradual decrease in blood flow in the center of the lesion, which rests low for up to 24 hours (Rivlin & Tator, 1978). Gray matter is more susceptible to ischemic injury compared to white matter because the density of capillary beds is five times higher in gray matter. Ischemia and hemorrhage ultimately cause destruction and cell death through several mechanisms such as oxygen deficiency, adenosine triphosphate loss, ion imbalance, cell death, and free radical formation. Cell necrosis and cytoplasmic contents release increase extracellular glutamate levels, which causes glutamate toxicity. In addition, the blood flow reestablishment in ischemic tissue causes further damage through the production of inflammatory and free radicals responses (Hayashi *et al*., 1983; Anwar *et al*., 2016).

Ion Imbalance, Oxidative Damage, and Toxicity of Nervous Overstimulation

A few minutes after the primary spinal cord injury, events such as direct cell damage and hypoxia-ischemia cause a significant increase in extracellular glutamate (the vital excitatory neurotransmitter) in the central nervous system (Oyinbo *et al*., 2011). Kainate receptors and glutamate bind to ionotropic receptors and metabotropic receptors cause the entry of high amounts of calcium into the cells. The impact of glutamate is not only limited to nerve cells and by binding to its receptors on the surface of glial and endothelial cells, it affects a wide range (Xu *et al*., 2004). On the other hand, with the increase of intracellular calcium levels, astrocytes can release excess glutamate outside the cell. Decreased activated astrocyte ability to reabsorb glutamate from the interstitial space, because of lipid peroxidation, leads to more glutamate accumulation in the environment of spinal cord injury (Couillard-Despres *et al*., 2017). According to Panter *et al*.'s study, an increase in glutamate was observed in the first 20-30 minutes after spinal cord injury and returned to baseline after 60 minutes (Panter *et al*., 1990). In the white matter, intoxication caused by glutamate stimulation is caused by the occurrence of ionic imbalance. However, in the gray matter, this process is largely related to the NMDA receptor activity. In the laboratory, when a white rat was examined it seems that the activation of NMDA receptors and as a result calcium overload induces intrinsic apoptotic pathways in oligodendrocytes and neurons and further

cell death in the first week of spinal cord injury (Alfaifi *et al*., 2023). Administration of 801-MK (NDA receptor antagonist) shortly after spinal cord injury has been associated with functional improvement (Wada *et al*., 1999). In neurons, during glutamate toxicity or stimulation, NMDA receptor overactivity causes the overload of mitochondrial calcium, which in turn can cause necrosis or programmed cell death (apoptosis). Mitochondria play a vital role in calcium-dependent neuronal death. Shortly after spinal cord injury, calcium enters mitochondria (Duchen, 2012). Accumulation of calcium in mitochondria hinders mitochondrial respiration and as a result, decreases ATP interrupts, Na^+/K^+ ATPase pump activity, and ultimately increases intracellular sodium. In addition, the excessive amount of intracellular sodium reverses the activity of the calcium/sodium exchange pump, which will result in more entry of high amounts of calcium. Cell depolarization activates voltage-dependent sodium channels, and the entry of chlorine ions and water along with Na causes cell swelling (Regan & Choi, 1991). An increase in excessive sodium concentration increases the activity of the Na+/H exchange pump and causes an increase in intracellular H+, and an increase in membrane permeability to calcium ions, which aggravates the ionic imbalance caused by damage (Agrawal & Fehlings, 1996).

Cell Death Following Spinal Cord Injury

Cell death is an important event in mechanisms of secondary injury that affect glia and neurons after spinal cord injury. Cell death can occur by multiple mechanisms and in response to different injury mediators. Apoptosis and necrosis were originally recognized as the two main mechanisms of cell death after spinal cord injury (Zhang *et al*., 2012). Following spinal cord injury, the glial and nerve cells die by necrosis as a result of mechanical damage caused by the initial injury, which continues to the subacute and acute stages. Cell necrosis occurs due to many reasons, including the accumulation of toxic substances in the blood, toxicity due to glutamate overstimulation and ion imbalance, ATP depletion, the release of pro-inflammatory cytokines by lymphocytes and neutrophils, and the formation of free radicals (Liu *et al*., 2015).

Apoptosis is the main mechanism for cell death after spinal cord injury. Apoptosis is programmed cell death that happens within hours of initial injury. The cell shrinks and is finally phagocytized without causing an inflammatory response. Normally, apoptosis happens in areas far from the site of injury and a delayed manner and affects oligodendrocytes more. In spinal cord injury in laboratory white mice, apoptosis starts 4 hours after the damage and reaches its peak within 7 days (Masoudi *et al*., 2017). At the injury site, most oligodendrocytes are missing within 7 days after spinal cord injury. However, apoptosis can continue at a slower rate for weeks after spinal cord injury (McTigue *et al*., 2001). Astrocytes and microglia also undergo apoptosis. In spinal cord injury, apoptosis is primarily caused by the influx of high amounts of calcium caused by the injury, which activates calpain and caspases (enzymes involved in the cellular proteins breakdown) (Regan & Choi, 1991). In addition, it is believed that neuron death and oligodendrocytes in areas far from the center of the lesion can be caused by cytokines such as tumor necrosis factor-alpha, free radical damage, and toxicity caused by stimulation. Because the calcium released from the damaged cells at the site of the injury hardly reaches these remote areas.

Spinal cord injury also leads to a dysregulated autophagy. Regularly, autophagy plays a vital role in maintaining the cell's homeostasis by helping the organelles and proteins cycle. In autophagy, defective, harmful, or unnecessary cytoplasmic proteins and organelles are degraded by cells through a lysosomal-dependent mechanism. The autophagy process begins with the autophagosome formation around organelles and proteins that are labeled for autophagy. In the next step, the phagosome fuses with the lysosome to form an autolysosome, which begins the recycling process. In response to endoplasmic reticulum stress and cell damage, autophagy is activated and by destroying toxic proteins and damaged mitochondria, it makes the cell survive (Abbaszadeh *et al*., 2020).

Glial Scar

Following a spinal cord injury, a glial scar tissue forms around the center of the injury. Activated astrocytes play a major role in glial scar formation. Scar-forming cells create a biochemical zone and heterogeneous cellular in and around the lesion (Yuan & He, 2013). Inflammatory cells by producing cytokines (for example interleukins 1-IL and 6-IL and enzymes and chemokines that activate glial cells or disrupt the blood-spinal barrier) lead to the glial activation process and scar formation (Cregg *et al*., 2014). Activated macrophages/microglia produce proteolytic enzymes such as MMPs (matrix metalloproteinases), which cause greater vascular permeability and more disruption of the spinal cord blood barrier (Noble *et al*., 2002).

Inhibition of enzymes improves neuronal protection and improves function in animal models of spinal cord injury. Ependymal cells, glial cells, progenitors, and fibroblasts are also present in the glial scar structure. Fibroblasts help the production of laminin, collagen, and fibronectin in the extracellular matrix of the injured spinal cord. The tracking of these cells has shown that perivascular cells and fibroblasts transfer to the injury place and form a fibrotic core at the wound site, which matures within 2 weeks after the injury. In the mature scar glial, activated macrophage microglia occupy the innermost part near the center of the lesion. While the reactive astrocytes are located in a distant place and form a cell barrier (Cregg *et al*., 2014). In humans, scarglial begins to form in the first hours after spinal cord injury, which remains for a long time after (Huang *et al*., 2014). The presence of scarglial has been reported up to 42 years after the injury in the injured human spinal cord (Cregg *et al*., 2014).

Animal Models of Spinal Cord Injury

Laboratory animals that have been used to study spinal cord injury mainly include rodents, dogs, rabbits, pigs, and larger mammals, especially primates, which are close to humans in terms of size, neuroanatomy, and physiology (Kjell & Olson, 2016; Nardone *et al*., 2017). The larger the size of the laboratory animal, the more suitable research platform is provided for introducing the effectiveness of drugs, discovery and innovation of bioengineering, electrophysiological studies, and empowerment. The use of rodents as models of spinal cord injury has numerous

advantages. Including the fact that these small animals are relatively cheap and their maintenance requires limited facilities that are easily available to researchers in most research centers. Genetic changes can easily be made in these animals. Rodent models make it possible to understand how neural circuits change after spinal cord injury and how they recover.

For the aforementioned reasons, before the start of long and expensive clinical trials, an animal model of spinal cord injury that is intermediate between the characteristics and the rodent model and human spinal cord injury will be a valuable research resource for the preclinical evaluation of new treatments. An ideal animal model should have the following conditions: (1) simulate an injury that is similar to a clinical spinal cord injury, (2) be controlled, reproducible, and stable, (3) be simple to perform and easy to study, (4) the equipment used to make the model should be simple.

The animal models of spinal cord injury are diverse and include the spinal cord ischemia-reperfusion injury model, traumatic spinal cord injury, and spinal cord injury caused by a photochemical agent, complete or partial transversal cutting of spinal cord tissue. The model of spinal cord injury caused by contusion and pressure on the tissue is seen more often in the clinical models of spinal cord injury in humans. Some of these models are used to investigate physio-pathological mechanisms and others to investigate tissue engineering methods and spinal cord reconstruction (Stokes, 1992; Cheriyan *et al*., 2014; Friedli *et al*., 2015; Kjell & Olson, 2016; Nardone *et al*., 2017; Petteys *et al*., 2017).

Treatment strategies vary based on the stage of spinal cord injury. If the spinal cord injury is in an acute stage, drug-based treatments are recommended, and if it is in a more advanced stage, the suggested treatment includes the use of nerve cells or neurotrophic factors (Rivlin & Tator, 1978; Venkatesh *et al*., 2019). Overall, despite significant advances in treatment, there is still no effective method for spinal cord injury. Therefore, there is a need to better understand the mechanisms responsible for the various stages of injury and its progression, as well as the pathobiology of spinal cord injury.

Conclusion

Our deep understanding of the primary and secondary spinal cord injury mechanisms leads to the development of appropriate methods of spinal cord injury treatment. Designing suitable animal models helps to better understand the involved molecular pathways and develop effective treatment strategies for spinal cord injuries. None of the animal models presented so far can be an accurate model of clinical spinal cord injury. Some animal models, including contusion, compressive, tensile, photochemical, inflammatory injury, and ischemia-perfusion injury models, have been mostly used to investigate the spinal cord injury pathophysiology. While spinal cord injury models with spinal cord tissue cut are commonly used for tissue engineering and spinal cord reconstruction. Despite extensive studies and presentation of various models, there are still some major problems in understanding spinal cord injury, which are: (1) lack of coordination and sufficient anatomical and physio-pathological similarity between experimental spinal cord injury and clinical spinal cord injury, (2) inconsistency of pathobiology spinal cord injury between different species and races, (3) difficulty in interpreting the results measured in animals when choosing the appropriate animal model to solve specific research problems.

It is essential to consider different factors such as the animal type, age, size, and gender of animals, and the possibility of evaluating their sensory and motor performance. There is a need for more research regarding the standardization of suitable species and breeds of animals for spinal cord injury. Providing appropriate environmental conditions can reduce some of the problems related to conducting and interpreting behavioral tests and lead to improved comparisons between studies. Standardization of laboratory methods for different species and breeds may also reduce the differences between the biochemical parameters of normal and injured spinal cords.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

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