

# Pathophysiology of Neurodegeneration Following Traumatic Brain Injury

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## ABSTRACT

Acute neuropathological conditions, including brain and spinal cord trauma, are leading causes of death and disabilities worldwide, especially in children and young adults. The causes of brain and spinal cord injuries include automobile accidents, accidents during recreational activities, falls and violent attacks. In the United States of America alone, around 1.7 million people each year seek medical care for some kind of head injury. Fifty-two thousand of these people will die, while the same number will present with permanent functional disability. Considering the high worldwide prevalence of these acute pathological conditions, research on the mechanisms underlying central nervous system damage is of extreme importance. Nowadays, a number of experimental models of acute neural disorders have been developed and the mechanisms of tissue loss have been investigated. These mechanisms include both primary and secondary pathological events contributing to tissue damage and functional impairment.

**Keywords:** Acute neural injury, cell death, neurodegeneration, secondary damage

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The main secondary pathological mechanisms encompass excitotoxicity, ionic imbalances, inflammatory response, oxidative stress and apoptosis. The proper elucidation of how neural tissue is lost following brain and spinal cord trauma is fundamental to developing effective therapies to human diseases. The present review evaluates the main mechanisms of secondary tissue damage following traumatic brain and spinal cord injuries.

## **INTRODUCTION**

Acute neuropathological conditions, including brain and spinal cord trauma, are the leading causes of death and disabilities worldwide, especially in children and young adults (1–4), and the third most common cause of death in Europe and the United States of America (USA), only after cancer and cardiovascular diseases (4). Every year, more than 1.7 million people seek medical care with some kind of head or spinal cord injury in the USA (5). About 52 000 of these people will die, while the same number presents a permanent functional disability (4, 6), commonly requiring prolonged intensive and specialist medical treatment (7). The leading causes of traumatic brain injury (TBI) in the USA are related to firearms, automobile crashes, recreational activities and falls (5).

In the United Kingdom, around 500 000 patients are admitted in the hospital with mild to severe head and neck injuries every year, with 35% of cases ultimately resulting in death (8). The incidence of brain and spinal cord trauma is three times higher than schizophrenia, mania and panic disorder. In Australia, the lifetime cost of new cases of brain and spinal cord injury has been estimated to be 10.5 billion Australian dollars in 2008 (9). In the USA, the annual cost of traumatic brain injury has been estimated to be 60 billion dollars (10). Lifetime costs for a young North American adult suffering a severe spinal cord injury would be about 3 million dollars (11). In Latin America and the Caribbean, TBI also appears as a critical public health problem (12, 13). Considering the high worldwide prevalence of these acute pathological conditions and the above-mentioned socio-economic burden associated, research on the mechanisms underlying central nervous system (CNS) damage are of extreme importance (14).

One of the most significant events associated with TBI is defined as secondary neuronal degeneration (SND). The SDN consists of a downstream cascade of destructive events that may affect cells that were not or were only marginally affected by the initial wound (15, 16). The primary neuronal injury induces an immediate process of degeneration and cell death by a mechanical disruption of the nervous tissue, with the release of chemical mediators to the extracellular environment that, acting on the neighbouring cells initially spared by the primary insult, promote a further cell loss (15, 16). The primary lesion induces structural modifications in the blood-brain barrier (BBB), leading to tissue oedema associated with neuronal and glial cell swelling (17). In addition, an additional injury of neurons may occur while these harmful substances persist in the extracellular milieu. The degree of secondary neuronal damage is proportional to the extension of the initial injury, so that the more vigorous and lasting the primary insult, the more intense will be the release of mediators of SND. These events occur simultaneously, so that at some point the same region possesses cells degenerating through the primary neuronal degeneration, the secondary injury and also neuronal cells that remain intact, spared from the primary aggressive stimulus (16, 18, 19).

Numerous evidence point to the participation of some key factors in the pathophysiology of SND following traumatic brain/spinal cord injury. Among these, excitotoxicity, inflammatory response and oxidative stress seem to be widely involved in tissue loss (20–25). The present review evaluates the general mechanisms of secondary tissue damage following traumatic brain and spinal cord injuries.

## **Excitotoxicity after traumatic neural injury**

In the mammalian nervous system there are several substances acting as neurotransmitters, with either excitatory or inhibitory functions. Glutamate, the brain's chief excitatory neurotransmitter, is physiologically present in small concentrations (23). Its postsynaptic response occurs through the pharmacological action of inotropic and metabotropic receptors with distinct features. The metabotropic receptors are coupled to a system involving the participation of G proteins, which work through the release of second messengers that elicit the mobilization of calcium channels in cell membrane (23). The inotropic glutamatergic receptors are further classified into three subtypes according to their selective agonists: N-methyl-D-aspartates (NMDA),  $\alpha$ -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) and kainic acid (Kainato). Each is an ion channel activated by glutamate, and may be permeable to sodium, potassium and calcium ions (23).

In physiological conditions, extracellular glutamate concentration is regulated by mechanisms involving enzymes and transporters in neurons and glial cells (26, 27). However, during pathological events, including traumatic injury of the brain and spinal cord and ischaemia, these mechanisms are ineffective in maintaining physiological concentrations of glutamate in neural tissue (20, 23, 25, 28). As a result, its concentration becomes higher than is physiologically tolerable by the tissue, inducing cell damage by a phenomenon defined as excitotoxicity (20, 24, 29), a term employed to define the ability of glutamate and its agonists to mediate neuronal death (30).

The high concentration of extracellular glutamate induced by traumatic injury in the nervous system results in a high activation of inotropic glutamatergic receptors and, consequently, dysfunction of the sodium/potassium pump with an influx of sodium and chloride

ions leading to an increased uptake of water, with a resulting enhancement in cell body volume. The influx of calcium can trigger a secondary increase of its intracellular concentration. This influx or the release of ionic intracellular storage can elevate their cellular level, thus exceeding the capacity of their regulatory mechanisms. These events can cause metabolic impairment, with consequent activation of various enzymes as proteases, lipases, phosphatases and endonucleases that directly damage the cellular structure, inducing the formation of free radicals that in turn can mediate cell death (29, 31), ultimately leading to a functional impairment of the affected tissue.

### **Oxidative stress and traumatic neural injury**

Oxidative stress is one of principal pathological attributes during pathological conditions, including mechanical trauma (32). Oxidative stress results from the generation of a large amount of derivatives of reactive oxygen species (ROS) during the pathological condition, which may induce degradation of proteins, lipids and nucleic acids (33), resulting in cell death by necrosis or apoptosis.

When the amount of ROS exceed their normal levels, they can contribute to an indiscriminate impairment of structural and functional integrity of cells, and modification of cellular DNA, proteins and lipids (34). Nevertheless, cells have a variety of antioxidant mechanisms for defense and repair against the action of ROS produced during the anaerobic metabolism of the brain. In some circumstances, however, these systems fail, leading to oxidative stress where the production of oxidizing ROS suppresses the body's defenses because of a dysfunction in balancing the production of pro-oxidants and free radicals.

Among the ROS generated following acute trauma and with deleterious properties in the brain, nitric oxide (NO) is one of the more studied. Nitric oxide is a very small and highly diffusible molecule which can act as a non-conventional neurotransmitter (35). Nitric oxide is synthesized by three distinct isoforms: neuronal (nNOS), endothelial (eNOS) and inducible (iNOS). Their functional or noxious effects are mainly determined on its concentration levels and the identity of the acting enzymatic isoform (36, 37). Low levels of NO generated by the nNOS and eNOS are associated with the cell signalling activities of NO (35). Conversely, the high levels of NO generated by iNOS are responsible for an increase in the level of both RNOS and ROS (38). The toxic effects of NO are mainly mediated by its oxidation products, particularly the biological oxidant peroxynitrite (39).

### **Inflammation after traumatic lesion**

Inflammation can be defined as the first response of the immune system to invasion of pathogens or in response to alterations in the tissue homeostasis, safeguarding the tissue from these noxious agents and promoting healing, being generally beneficial to the organism, by limiting the survival and proliferation of destructive agents, promoting tissue repair and recovery and keeping the energy levels needed for survival of the tissue (40, 41) including chronic alterations in the tissue milieu (42). Nonetheless, a prolonged and exacerbated inflammatory response mediated by pro-inflammatory cytokines potentially cytotoxic such as interleukin-1 beta (IL-1 $\beta$ ), tumour necrosis factor alpha (TNF- $\alpha$ ), NO and cyclooxygenase 2 (COX-2), can be highly harmful to both peripheral and nervous tissue (40).

The inflammatory response may be involved in mechanisms responsible for the exacerbation of the SND in brain trauma and spinal cord injury, characterized by a substantial cell loss associated with severe functional deficits (43–46). During the acute inflammatory response in the CNS, there is the recruitment of neutrophils and macrophages to the site of injury. The microglia (resident macrophages of the CNS) has an important role during this process. After the injury, the endothelial cells express adhesion molecules as P-selectines and E-selectines (47, 48) which interact with receptors found in the membrane of neutrophils, adhere to the endothelium, cross the vascular wall and penetrate the nervous system parenchyma (49). The microglia then responds quickly to the injury, retracts their extensions and assumes an amoeboid-like form. These cells are important phagocytes for the elimination of debris and release of a large number of pro-inflammatory mediators (50).

Despite its important phagocytic function, evidence points to microglial cells contributing to the phenomenon of SND in traumatic brain injury in *in vivo* and *in vitro* models (14, 49). The microglial cells can synthesize and release substances potentially harmful such as NO, free radicals, proteolytic enzymes, TNF- $\alpha$  and IL-1 $\beta$  (22, 51). It has been reported that during excitotoxic injury, microglial cells release NO and IL-1 $\beta$ , which could contribute to the process of SDN (52, 53).

## **CONCLUSIONS**

Acute neuropathological conditions are the leading causes of death and disabilities worldwide, with an important socio-economic burden associated. Excitotoxicity, inflammatory response and oxidative stress are events widely involved in tissue loss after traumatic brain injury. Studies

focussing on the mechanisms underlying these events are of extreme importance in developing effective therapies.

## **ACKNOWLEDGEMENTS**

The author thanks Associação Alberto Santos Dumont para Apoio a Pesquisa (ASSDAP) – Brazil for its financial and logistical support. The author declares the inexistence of any financial interests or other dual commitments that represent potential conflicts of interest related to the present manuscript.

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