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THE IMPORTANCE OF THE AKT/CREB/ BDNF CELL SIGNALING AXIS FOR THE NEUROLOGICAL RECOVERY OF TRAUMATIC BRAIN INJURY PATIENTS

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Abstract: Traumatic brain injury is a high morbidity and mortality event and occurs when there is traumatic damage to the scalp, skullcap, cerebral cortex and subcortical areas. In these traumatic events, neurological protection mechanisms act in order to mitigate the deleterious consequences related to the inflammatory response of the nervous tissue, such as neuroplasticity, related to brain cell modeling as a reaction to external stimuli and which functions as an important neurological recovery event, being favored by the activation of the Akt/CREB/BDNF cell signaling axis. **Objective:** To explain the influence of the Akt/CREB/BDNF signaling axis on the neurological recovery of patients suffering from traumatic brain injury. **Methodology:** This study is a systematic review of the literature, with a qualitative approach, interpreting and analyzing the data obtained. The guiding question of the study was: "Contributions of the Akt/CREB/BDNF cell signaling axis in recovery from traumatic brain injury". This was followed by the following steps: identifying the topic, selecting the hypothesis or research question, establishing inclusion and exclusion criteria, defining the information and clinical studies to be included in this review study, interpreting the results and presenting the review with a synthesis of knowledge. **Discussion of results:** Through this work, it was possible to recognize the pathophysiological processes involved in brain injury mechanisms due to traumatic brain injury, specifically those related to neurological recovery from this type of brain injury. To this end, this study focused on the Akt/CREB/BDNF cell signaling axis, since its role in neurological processes such as neuroplasticity and promotion of neuronal survival has been proven. **Conclusion:** It is clear that traumatic brain injury is a health problem with high morbidity and mortality. Thus, the mechanisms of action of the Akt/

CREB/BDNF signaling axis on neuroplasticity and neuronal survival emerge as an important form of neurological recovery for patients who are victims of this subtype of trauma. Further research on this subject is crucial in order to develop possible therapeutic interventions based on this cascade of cellular responses, with the aim of providing a better prognosis for patients affected by traumatic brain injury.
Keywords: Neuronal plasticity; Cerebrovascular trauma; Neurosurgery.

INTRODUCTION

Traumas, defined as injuries to tissues and organs caused by external agents, are an important cause of morbidity and mortality worldwide, with a high probability of causing sequelae and disabilities, significantly affecting the patient's quality of life. In this context, traumatic brain injury (TBI) is a serious type of trauma and occurs when structures such as the cortex, subcortical regions, scalp and skullcap are injured. Some of the symptoms usually present in this type of injury are a lowered level of consciousness, headache, seizures, nausea, emesis and mydriasis. Treatment involves neurosurgical procedures and monitoring in an intensive care unit, where vasoactive drugs are usually administered, intubation for mechanical ventilation and monitoring of intracranial pressure (OLIVEIRA et al, 2018).

Patients who have suffered traumatic brain injury often have sequelae such as aphasia and motor and/or cognitive deficits related to brain damage caused by damaging mechanisms such as oxidative stress, vasogenic edema, necrosis and excitotoxicity. However, the chronification of damage related to the initial injury is minimized due to neuroplasticity, which is the ability of the central nervous system to adapt morphofunctionally to environmental, social and physical changes, as is the case with injuries caused by trauma. This adaptation can occur in various ways, such as changes in the level of release of certain neurotransmitters, reorganization of the brain's electrical circuit through synaptic changes, axonal regeneration and neurogenesis (BASTOS et al, 2017).

From this perspective, the Akt/CREB/BDNF activation axis has been an important target of studies, since it has been proven to promote neuroplasticity. This is a cell signaling pathway that begins with the activation of the protein kinase Akt (Protein Kinase B), which causes the phosphorylation of the CREB protein (CRE Element Binding Protein), which is an important transcription factor for genes related to neuronal plasticity. The phosphorylation of CREB increases the expression of BDNF (Brain-Derived Neurotrophic Factor) which, in turn, triggers numerous processes at cellular level, such as neurogenesis, neuronal survival, synaptic plasticity and the formation of new synapses (JIN YAN et al, 2022).

Thus, this study focuses on the role of the Akt/CREB/BDNF activation axis in the neurological recovery process of patients suffering from traumatic brain injury (TBI), with the aim of understanding the neuroprotective mechanism that this cell signaling pathway exerts on the nervous tissue of patients undergoing this clinical condition. This topic was chosen as the object of research due to the epidemiological importance of this type of trauma, both in terms of morbidity and mortality and incidence rates. In this sense, we were interested in contributing to the development of scientific knowledge about this cell signaling pathway, with the aim of fostering a better understanding of brain responses to traumatic events and stimulating research into the therapeutic uses of this signaling axis.

OBJECTIVES

General objective: To explain the influence of the Akt/CREB/BDNF signaling axis on neurological recovery in patients suffering from traumatic brain injury.

Specific objectives:

-To characterize the pathophysiological events involved in brain injuries caused by traumatic brain injury;

-To describe the processes of neuroplasticity related to the repair of neurological damage caused by trauma;

-Analyze the physiological mechanism of the Akt/CREB/BDNF signaling axis in nervous tissue.

MATERIAL AND METHODS

This study is a systematic review of the literature, with a qualitative approach, interpreting and analyzing the data obtained. The study's guiding question was: "Contributions of the Akt/CREB/BDNF cell signaling axis in recovery from traumatic brain injury". This was followed by the following stages: identification of the topic, selection of the hypothesis or research question, establishment of inclusion and exclusion criteria, definition of the information and clinical studies to be included in this review study, interpretation of the results and presentation of the review with synthesis of knowledge.

Stage 1: Identification of the topic and selection of the research question: First, the topic was defined in order to start the integrative review and move on to the subsequent stages of the study, formulating the guiding question. Thus, in relation to the chosen topic, the guiding question was: "What are the contributions of the Akt/CREB/BDNF cell signaling axis in recovery from traumatic brain injury?".

Stage 2: sample selection criteria: A systematic literature review was carried out, based on a survey of scientific articles found on the main scientific article search platforms: ScienceDirect, PubMed, SciELO and BIREME, from 2017 to 2023, establishing inclusion and exclusion criteria, defining the information and clinical studies to be included in this study. Terms from the Health Sciences Descriptors (DeCS) were used, namely: cerebrovascular trauma, neuronal plasticity, neurosurgery, in Portuguese and English, together with the Boolean operator "e" in all databases, eventually associating the terms with the use of quotation marks (""). Given the need to carry out a broader search, these keywords and the Boolean operator were always used in the search field related to the abstract. These descriptors were combined in order to find as many suitable publications for the review as possible. We selected studies written between 2017 and 2023, written in Portuguese, Spanish or English, which were free to access and did not have duplicate versions. Articles that did not meet all the inclusion criteria mentioned were excluded, and 17 articles were selected after selective analysis.

JUSTIFICATION

Considering that traumatic brain injury represents an important cause of disability and mortality worldwide, especially in young adults, it is worth emphasizing that this study is relevant insofar as it contributes to the dissemination of knowledge about an important mechanism involved in the recovery of patients who are victims of this health problem, being crucial for the future development of therapeutic modalities related to the subtype of trauma addressed, contributing to the reduction of mortality and disability caused by it.

RESULTS AND DISCUSSION

Traumatic brain injury is epidemiologically a type of trauma with a high incidence and high morbidity and mortality rates. The mechanisms involved in the pathophysiology of this health problem are complex and involve cellular and biochemical processes that culminate in the impairment of nervous tissue homeostasis, causing neuronal death by necrosis, which affects the patient's neurological functions, especially when the prognosis includes high risks of disability.

In this context, the action of the Akt/CREB/BDNF axis on the physiological processes of neuroprotection has emerged as an important research topic due to its contribution to the neurological repair of lesions resulting from the intense inflammatory process intrinsic to TBI.

Studies have identified phytochemical compounds with the potential to stimulate the activation of this cell signaling axis and provide its neuroprotective mechanisms, such as regulating the synaptic network, promoting neuroplasticity and increasing neuronal survival by inhibiting apoptosis. However, research is still needed to develop new therapeutic modalities involving these nutraceuticals and their relationship with the Akt/CREB/BDNF axis.

TRAUMATIC BRAIN INJURY

An injury is classified as traumatic when it occurs as a result of some external agent, which can be mechanical, electrical, chemical or thermal in nature. In the case of traumatic brain injury, these injuries can affect structures such as the skullcap, scalp, meninges, cerebral cortex and subcortical regions. In epidemiological terms, this health problem is quite representative, with an incidence of around 69 million cases per year, and is more prevalent in young adults due to car accidents. In the elderly population, on the other hand, falls are usually the most common etiology. It is an important cause of morbidity, mortality and disability worldwide, and the third leading cause of death in Brazil (MAGALHÃES et al, 2017).

The kinesiology of traumas that cause cranioencephalic injuries involves acceleration/deceleration mechanisms, in which the brain's inertia causes it to collide with the skullcap. In addition, direct penetration events can also be the cause of the trauma. Regardless of the triggering factor, inflammatory events are always present and occur through the release of pro-inflammatory substances, such as IL-6 (one of whose functions is to activate B lymphocytes), IL-8 (which acts as a chemokine to recruit neutrophils and macrophages) and TNF alpha (which promotes increased endothelial adhesion, facilitating diapedesis, stimulates angiogenesis by increasing the synthesis of Vascular Endothelial Growth Factor and also recruits leukocytes). When these inflammatory phenomena occur in an unregulated manner, they are responsible for complications associated with traumatic brain injury, such as cerebral edema. In addition, other clinical manifestations related to this clinical condition include hypoxia, arterial hypotension, hypercapnia, intracranial hypertension, lowered level of consciousness, dyspnea, headache, seizure, nausea, emesis and mydriasis, as well as possible sensory, motor, cognitive and linguistic impairments (ISRAEL et al, 2019).

Morphologically, injuries related to traumatic brain injury can be divided into three groups: extracranial injuries, injuries to the skullcap and intracranial injuries. Extracranial injuries correspond to external damage to the skullcap and are represented by subgaleal hematoma (accumulation of blood between the periosteum and epicranial aponeurosis) and scalping (laceration of the scalp). Injuries to the skullcap involve fractures of the

neurocranium, which can involve a single bone fragment (linear fracture), multiple bone fragments (comminuted fracture) or a bone sink (depression of the skullcap). Finally, intracranial injuries are internal damage to the skullcap, such as subdural hematoma, epidural hematoma, intraparenchymal hematoma and cerebral edema (VELASCO et al, 2019).

Traumatic brain injury is an emergency situation and should be managed by assessing the level of consciousness using the Glasgow coma scale, hemodynamic stabilization using vasoactive drugs, controlling oxygenation through mechanical ventilation and monitoring intracranial pressure (FEDERIZZI et al, 2017).

MECHANISMS OF NEURONAL DAMAGE

The brain injuries caused by a TBI are the result of pathophysiological processes that can begin at the time of the trauma or continue for days afterwards. Initially, the traumatic injury causes tissue damage and deregulation of the blood flow to the nervous tissue, compromising its metabolism. As a result, the anaerobic metabolic pathway is activated, leading to an accumulation of lactic acid. When this metabolic mechanism fails, a state of adenosine triphosphate (ATP) insufficiency begins, causing ionic pump failures which culminate in increased permeability of lipoprotein membranes, cellular edema, oxidative stress and excitotoxicity (CANCHILA et al, 2023).

The neurological injuries that can affect a TBI patient can be divided into primary and secondary injuries. In terms of time, primary injuries are those whose onset occurs at the time of the traumatic event and are closely related to its kinesiology. Primary injuries in penetrating trauma caused by firearms or bladed weapons occur as a result of the direct impact of these instruments on the brain mass. However, in traumas of a different kinetic nature, such as those in which there is no contact with the encephalic parenchyma, primary injuries can be caused by inertial acceleration and deceleration mechanisms, and can occur as a result of the impact of the encephalon on the skull cap itself, since these two structures respond differently to the inertia of the impact due to their different densities, which can cause laceration of brain tissue due to the shock to the bone structure, as well as rupture of vessels that drain into the dural sinuses. In addition, the central region of the encephalon, which is attached to the brainstem, has a smaller range of movement compared to the peripheral encephalic regions, so the different rates of displacement of these regions during trauma can cause stretching of axons and blood vessels (DIXON, 2017).

On the other hand, secondary injuries occur days or even weeks after the accident and are a consequence of the relationship between intra- and extracerebral factors, which can cause neurological damage through hypercarbia, anemic hypoxia, arterial hypotension, hypoglycemia, respiratory hypoxia, as well as hydroelectrolytic disorders. In addition, intracranial hemodynamic changes, infectious processes, cerebral edema, intracranial hypertension, hydrocephalus and neurotoxicity can be cited as late complications of TBI (KAUR; SHARMA, 2018).

These two subtypes of injury are correlated through cell death mechanisms, which can occur both at the time of the trauma and at a later stage. From this perspective, apoptosis is one of the main mechanisms of cell death. It occurs physiologically in the cell cycle and can be triggered by processes such as oxidative stress, which can lead to partial DNA damage. Since apoptosis causes little inflammatory response, its influence on neuronal deaths secondary to TBI is minimal. On the other hand, necrosis, the main mechanism of neuronal loss in a TBI, occurs as a result of an energy failure that prevents the cell from

maintaining its homeostasis, generating intense inflammatory activity that can be caused by oxidative stress and excitotoxicity (DIXON, 2017).

In addition, excitotoxicity, a mechanism referring to glutamate's ability to cause neuronal death, is also an important tissue reaction that occurs as a consequence of TBI. Glutamate, the main excitatory neurotransmitter, acts on three main types of postsynaptic ionotropic receptors on cell membranes: N-methyl-D-aspartate (NMDA), Kainate and a-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA). In addition, it can also bind to metabotropic receptors linked to the G protein, activating ion channels through the release of second messengers. Under physiological conditions, glutamate concentrations in the synaptic clefts and in the extracellular medium are regulated by processes involving enzymes and glutamate transporter proteins, which act in the degradation and reuptake of this neurotransmitter, respectively. In pathological events, the concentration of glutamate can rise and cause neuronal excitotoxicity, as occurs in TBI, whose kinetic energy causes mechanical deformation of axons and the release of excitatory neurotransmitters such as glutamate. Subsequently, hypoxia and oxidative stress caused by reactive oxygen species (ROS) formed by the inflammatory response can reduce the cellular permeability of neurons and allow an even greater release of glutamate (PEARN et al, 2017).

The binding of glutamate to ionotropic receptors causes an influx of sodium ions, which generate cell edema as a result of the osmotic process. Subsequently, long-lasting calcium channels open and raise the intracellular calcium concentration, which leads to the activation of proteases and phospholipase A, which increase the permeability of the neuronal membrane and favor the formation of arachidonic acid and free radicals, which damage neuronal cells by oxidizing the double layer of lipids, intensifying the increase in cell permeability. The production of nitric oxide also occurs as a response to the increase in intracellular calcium, and is important for preserving cerebral blood flow in the early stages of trauma. However, later in the brain injury, nitric oxide causes intense vasodilation which leads to an increase in endothelial permeability, resulting in an increase in intracranial pressure due to vasogenic cerebral edema (PEARN et al, 2017).

NEUROPLASTICITY

Neuroplasticity is a term that refers to the capacity of the nervous system, especially the brain, to promote processes of adaptation and reorganization through stimuli from learning, injuries, new experiences and/or environmental changes. The discovery of this brain competence was extremely important for neuroscience, as it changed the old belief that the brain was a static organ with limited capacity to undergo changes (BASTOS et al, 2017).

In this context, it is known that this complex process can occur in various ways in the modeling of the brain's neural network, such as changes in the number of active synapses. In synaptogenesis, there is an increase in the number of active synapses, usually due to the presence of cognitive stimuli and new experiences. In synapse elimination, the number of active synapses decreases, which can occur due to damaging mechanisms or simply the destruction of synapses that have become useless due to environmental changes that have reduced the demand for a certain cortical area. It is also possible that there is just a change in the network of synaptic connections without necessarily a reduction in their quantity, as happens in the process of cortical remodeling. In addition, the

formation of new neurons (neurogenesis) can also occur in certain brain areas, such as the hippocampus, contributing to the process of neuroplasticity (CASTRO; GIL-MOHAPEL; BROCARDO, 2017).

In addition, there is long-term plasticity, a type of neuroplasticity event in which the intensity of synaptic communication between certain neurons changes over the long term. This synaptic connection can be weakened or stimulated, the latter being closely related to learning and long-term memory, since the neuronal stimulus provided by cognitive activity increases the sensitivity of the post-synaptic neuron to the neurotransmitters released into the synaptic cleft by the pre-synaptic neuron, generating an intensification of synaptic transmission and favoring the storage of information (CAIMAR; LOPES, 2020).

Neurotransmitters are also closely related to the process of neuroplasticity, given their ability to regulate neuronal depolarization events, with examples of excitatory (glutamate) and inhibitory (gamma-aminobutyric acid) neurotransmitters. Finally, some neurotransmitters can also act in the formation and development of neurons, such as brain-derived neurotrophic factor (BDNF), which is also important in the formation of synapses as it acts as a neuronal growth factor that directs the axons and dendrites of neurons towards the formation of neural connections (CAIMAR; LOPES, 2020).

AKT/CREB/BDNF CELL SIGNALING AXIS

The Akt/CREB/BDNF signaling axis is an intracellular signaling pathway that occurs in the brain parenchyma and has functions associated with synaptogenesis, neuronal development and the survival of neurons, attributions that justify the medical interest in this cellular pathway in the context of traumatic brain injury (JIA Y et al, 2021).

In this context, it is important to know the function of each component of this cell signaling axis and the cascade of events that occur during its activation process. Firstly, Akt (protein kinase B) is activated under the stimulus of growth factors and neurotransmitters, and its cellular expression is increased during events of stress and cell damage, which highlights its importance in maintaining neuronal survival. Akt acts as an enzyme that transduces cellular signals through phosphorylation reactions. In turn, CREB (CRE Binding Protein) is a transcription factor that is activated when it is phosphorylated by Akt. In its active form, CREB acts by regulating the translation of genes related to neuronal survival and neuroplasticity, such as BDNF (Brain-Derived Neurotrophic Factor), which stimulates neuronal survival by inhibiting cell death programmed by apoptosis, in addition to regulating the formation of the synaptic network, since it stimulates the growth of axons and dendrites for the formation of synapses, contributing to neuroplasticity through synaptogenesis (KANDEZI et al, 2020).

Thus, the Akt/CREB/BDNF cell signaling pathway can act in the recovery of neurological injuries by promoting neuronal survival by inhibiting apoptosis and stimulating synaptic plasticity, important events in a brain with structural impairment. In addition, the inflammatory process resulting from a brain injury mediated by interleukins and prostaglandins can be modulated by this cellular axis, which helps to prevent an excessive inflammatory event. These mechanisms provide a microenvironment that favors repair and regeneration processes, preserving injured neurons and reducing the functional consequences related to the injury event (JIN YAN et al, 2022).

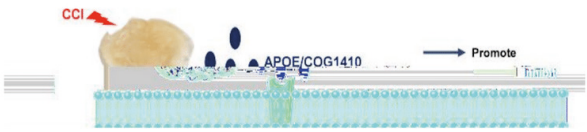

Figure 1: Schematic representation of the physiology of the Akt/CREB/BDNF axis (Adapted from: JIN YAN et al, 2022).

PHYTOCHEMICALS ACTING ON THE AKT/CREB/BDNF AXIS

Phytochemicals, secondary metabolites derived from plants with pharmacotherapeutic functions, have been studied as neuroprotective factors due to their anti-inflammatory, antioxidant and anti-apoptotic properties, making them possible therapeutic alternatives to prevent the progression of neurodegenerative conditions, such as those that occur in a TBI (ZARNESHAN; FAKHRI; KHAN, 2022).

Ginsenosides, bioactive compounds found in the roots of plants of the genus Panax, such as Panax ginseng and Panax quinquefolius, known generically as "ginseng", are the compounds responsible for the medicinal effects of these plants, which have been used in oriental medicine for centuries. These plant species are part of the Araliaceae family, which has more than 180 known species of ginsenosides. The antioxidant functions of this class of substances can help neutralize the free radicals produced in brain inflammation, protecting neurons from suffering oxidative stress and having the integrity of their membranes compromised. In addition, their anti-inflammatory properties act directly on the inflammatory process, preventing it from evolving into chronic inflammation that is potentially damaging to brain tissue. Ginsenosides also act to regulate the release of neurotransmitters such as glutamate, generating protection against the occurrence of excitotoxicity and consequent hyperstimulation of the neurons' ionotropic receptors (ZARNESHAN; FAKHRI; KHAN, 2022).

However, the neuroprotective effects of ginsenosides that most raise expectations in the scientific community are related to their ability to modulate the activation of the Akt/CREB/BDNF cell signaling axis, a property observed in some ginsenosides, such as Rg1 and Rb1. These bioactive compounds influence the neurotransmission related to the activation of this cell signaling pathway, triggering an increase in the expression of the Akt protein, which activates, through phosphorylation, CREB, which will act as a cellular transcriptor, favoring the translation of BDNF in the ribosomes, which will be responsible for the neuroprotective effects intrinsic to this axis, such as the promotion of neuroplasticity and neuronal survival. Despite these benefits, the pharmacokinetics of this compound are still a challenge for its use in clinical practice, since its oral bioavailability can be lower than 10% (ZARNESHAN; FAKHRI; KHAN, 2022).

Curcumin (diferuloylmethane) has also been studied as a compound with the potential to act beneficially on neurodegenerative processes. This substance is the main bioactive extracted from the rhizomes of the Curcuma longa plant and is a nutraceutical dietary phenol with anti-apoptotic, anti-inflammatory and antioxidant properties, as well as promoting an upregulation of mitochondrial function. Furthermore, studies show that this compound also has the potential to activate the Akt/CREB/BDNF axis, thus having neurogenic, neuronal repair and prevention effects against the occurrence of neurotoxic events (KANDEZI et al, 2020).

CONCLUSION

Traumatic brain injury patients are prone to developing various potentially life-threatening neurological complications, such as intracranial hemorrhages and elevated intracranial pressure, which justifies the importance of a better understanding of the neuroprotective mechanisms that act on the damaging processes resulting from trauma. In this sense, it is clear that the Akt/CREB/BDNF axis has considerable relevance in the physiological processes related to increased neuronal survival.

Therefore, studies investigating the clinical applications of this cell signaling cascade are important for promoting new therapeutic interventions that offer less deleterious prognoses for patients who are victims of this type of trauma.

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