SOMATOMEDIN C (IGF-1) IN BRAIN TRAUMA: POTENTIAL EFFECT ON NEUROPROTECTION. A NARRATIVE REVIEW

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Abstract

In recent years, through experimental studies, the effects of various neurotransmitters, as well as proteins, enzymes, and hormones involved in the inflammatory response during and after traumatic brain injury, have been investigated in depth, finding a substance called insulin-like growth factor type I (IGF-1), this protein, has shown to be important in processes of neuroprotection, synaptogenesis, myelination, and prevention of apoptosis, among others.

This article aims to clarify the role of Somatomedin C or type I insulin-like factor and its potential neuromodulatory function after head trauma. Factors such as age, sex, physical activity, diet, and the influence of other hormones have been related to the brain's levels, and functioning of somatomedin C. IGF-1 receptors are found in higher concentration in some specific regions of the nervous system where neuronal tissue is more susceptible and have binding proteins that regulate the degradation of this substance, which in inflammatory conditions such as brain trauma has been shown to promote angiogenesis and attenuate the production of proinflammatory cytokines.
KEYWORDS: Brain trauma; C somatomedin; Insulin-like growth factor I; Traumatic brain injury.

Resumen

En los últimos años, mediante estudios experimentales se ha investigado a profundidad los efectos de diversos neurotransmisores, así como proteínas, enzimas y hormonas involucradas en la respuesta inflamatoria durante y posterior al trauma craneoencefálico, encontrando una sustancia denominada factor de crecimiento similar a la insulina tipo I (IGF-1), esta proteína, ha demostrado ser importante en procesos de neuroprotección, sinaptogénesis, mielinización, prevención de apoptosis, entre otros.

El objetivo de este artículo consiste en esclarecer el papel de la Somatomedina C o factor similar a la insulina tipo I y su potencial función neuromoduladora posterior al trauma craneoencefálico. Factores como la edad, sexo, actividad física, la alimentación y la influencia de otras hormonas se han relacionado con los niveles y el funcionamiento de la somatomedina C a nivel cerebral. Los receptores de IGF-1 se encuentran en mayor concentración en algunas regiones específicas.
del sistema nervioso donde el tejido neuronal es más susceptible y cuentan con proteínas de unión que regulan la degradación de esta sustancia, que en condiciones inflamatorias como el traumatismo cerebral ha demostrado promover la angiogénesis y atenuar la producción de citoquinas proinflamatorias.

Introduction

Somatomedin C, or IGF-1 (insulin-like growth factor 1), is a small insulin-like peptide (1). Its receptor, IGF-1R (insulin-like growth factor receptor 1), is widely distributed throughout the human body, including in different areas of the central nervous system (CNS), such as the hippocampus (2, 3). IGF-1 and insulin have structural similarities in the receptor and signaling pathways but different cellular responses, such as metabolism, maturation, migration, and regeneration of neurons and other CNS cells (3, 4). This peptide is produced in the liver and the brain in low concentrations that vary according to age, sex, nutrition, physical activity, recent trauma, and severity of trauma (5-11).
Cranioencephalic trauma (TCE) due to external kinetic force generates brain dysfunction due to intracellular and extracellular structural and functional damage that can be perpetuated for months or years (1, 10, 12). The compensatory physiological response to TBI seeks cellular homeostasis through mechanisms such as angiogenesis, growth, proliferation, and cell migration, thanks to peptides such as IGF-1, hormones, and factors with tropism for cells in the affected brain tissue (8, 13-15). It has been shown in studies that after brain damage, the levels of IGF-1 and its receptor increase in oligodendrocytes, endothelial cells, and astrocytes (16, 17); Similarly, it has shown a neuroprotective effect on myelination, synaptogenesis, and increase in the dendritic tree in neurons, reflected in increased neuronal survival during TBI and even before trauma (11, 18-20).

IGF-1 has recently acquired clinical relevance thanks to its beneficial action on many cells, especially on neuronal tissue, being able to be considered as a future therapeutic target for the damage caused by brain trauma, in addition to its pleiotropic effect at a nutritional, cognitive, and psychological level (5-9, 15, 21, 22).
This narrative review aims to investigate the role of IGF-1 (also known as somatomedin-C) in brain trauma; given its neuroprotective properties in the pathophysiology of traumatic brain injury, it is believed that IGF-1 could become a therapeutic alternative for this entity.

**Methods**

The research and bibliographic review were carried out from January 2022 to September 2022 in search engines and databases such as PubMed, Cochrane Library, ScienceDirect, Google Scholar, and Redalyc, published between 1993-2022. There were used all a combination of the words "IGF-1", "Somatomedin C," "Insulin-like growth factor 1" in combination with "craniocerebral trauma," "cranial trauma," "brain trauma" using specific link words (and, in, or) to optimize the search. It was found a total of more than 100,000 documents. The inclusion criteria were all the papers related to biochemistry, physiology, and pathology of IGF-1 with TBI, as well as neuroinflammation secondary to head trauma.
The exclusion criteria were all the articles not related to TBI and papers published before 1993.

A total of 39 articles were used to write this narrative review regarding the effect of IGF-1 and its future considerations to improve the outcomes of patients with brain trauma.

**Discussion**

IGF-1 (insulin-like growth factor 1) is a 70 amino acid peptide with a similar structure to insulin and is encoded by a gene with six exons. This substance is related to the receptor of the same name, the IGF-1 receptor (IGF-1R) (1), which can induce the differentiation of neural cells in vitro, including neurons, astrocytes, oligodendrocytes, and endothelial cells (23).

Growth hormone (GH) released by the anterior pituitary stimulates IGF-1 production in hepatocytes and neuronal tissue. Once synthesized, IGF-1 interacts with its transmembrane receptor tyrosine kinase, consisting of two alpha and two beta chains. These receptors are found in greater concentration in regions...
such as the cerebral cortex, the hippocampus, and the thalamus, while in olfactory bulbs, hypothalamus, cerebellum, striatum, midbrain, and brainstem, they have a medium or low concentration (1-3, 10, 17) (See figure 1). IGF-binding proteins (IGFBPs) protect IGF-1 from degradation and increase its half-life and proper disposition in the IGF-1R (24).

IGF-1 levels depend on age, sex, physical activity, and diet, among other factors; where it is found to a greater extent during early periods given brain development and decreases with age, it is slightly increased in men and is expressed more efficiently and in greater quantity during aerobic exercise (5-9). Despite being like insulin and cross the blood-brain barrier via active transport (25, 26), IGF-1 have different physiological effects on neuronal growth.

The binding of IGF-1 explains its cellular function to its receptor. IGF-1R phosphorylates and activates two adapter proteins, IRS-1 (insulin receptor substrate 1) and SHC (Src homologous collagen protein), which activate multiple pathways such as PI3K-AKT (phosphatidylinositol 3-kinase pathway) and MAPK (protein kinase pathway, mitogen activity) responsible for
protein synthesis, cell survival and proliferation (1, 3, 27). (See figure 2 and 3).

Cranioencephalic trauma (TCE) is a brain dysfunction triggered by an external force leading to focal or diffuse lesions at a macroscopic level (10). The primary lesion is due to direct impact causing diffuse or focal alterations as well as damage or death of oligodendrocytes, decreased dendritic ramifications, myelin degradation by axonal proteases, and axonal edema (13). A secondary lesion is the loss of autoregulation of one or several cellular functions after the primary mechanism, generating changes in the inter and intracellular biochemical environment, alterations in glucose metabolism (28), neurotransmitters, ions, as well as the release of reactive oxygen species and nitric oxide thus activating inflammatory and pro-apoptotic pathways (proteases, caspases, free radicals). Events that can start in a matter of hours and last up to days or months (1, 12).

It has also been detected that somatomedin C is an essential regulator in post-trauma angiogenesis since IGF-1 and VEGF
(Vascular Endothelial Growth Factor) increase endothelial cell proliferation to create new ones. Blood vessels and thus improves the blood supply to the compromised area (16, 29, 30).

At the end of the secondary injury, the brain activates one of its post-traumatic remodeling mechanisms: Neuroplasticity, where it tries to repair the damage caused through synaptogenesis, angiogenesis, neurogenesis, gliogenesis, among others, through neurotrophic factors and endogenous hormones, some of which is IGF-1 (8). It has been seen that increases in Somatomedin C have been demonstrated in contusion, edema, and perilesional sites of direct damage. Its levels may vary depending on the anatomical site. It is essential to clarify that IGF-1 levels will vary according to the production of hormones at the pituitary level and that if there are lesions in this gland, its levels will be altered (31).

In different studies carried out in mice where the injury is induced in endothelial cells with induction of lipopolysaccharides (LPS) compared to a control group, it has been shown that as IGF-1 levels increase, nitric oxide synthase RNA (eNOS) levels decrease, indicating a considerable decrease in
this reactive oxygen species (ROS) (32). It has also been found that IGF-1, after brain injury, regulates different metabolic functions, cell proliferation, cell survival, myelination, and growth of neurons. It has been shown that with increasing IGF-1 levels, proinflammatory factors such as IL-1β, TNF-α, and IL-6 decrease (32).

In recent years, with the advent and deepening of studies on the development of therapeutic agents to counteract secondary damage in head trauma, IGF-1 (insulin-like growth factor 1) or Somatomedin C has shown a neuroprotective effect. In rodent models, it has been demonstrated that this peptide increases the expression of glucose transporters in cells by activating AKT, which improves glucose uptake in neurons 4) (8), promotes the proliferation, survival, and differentiation of oligodendrocytes by stimulating the myelin synthesis or preventing its degradation (8, 11, 20). Likewise, it favors the survival of immature neurons in addition to increasing neuronal differentiation (24, 33). An effect has been shown on the generation of axons and dendrites in the central and peripheral nervous system (8, 18, 19, 34, 35), as well as the activation of antiapoptotic and neuroprotective...
mechanisms after mild brain lesions and lesions in peripheral nerve cells (21, 36).

IGF-1 as a therapeutic alternative in TBI

Even though early intervention in traumatic brain injury has improved the mortality rate in these patients, it remains a challenge to establish the proper balance in the metabolic demands associated with the damage, so it is essential to recognize the impact that IGF-1 represents on the brain and its influence on metabolism, proliferation, and repair (37). Advances in research on the effect of this protein have promoted the development of studies that seek to highlight IGF-1 as a therapeutic alternative; Some of these were carried out in rodents, where after being subjected to traumatic brain injury, they were administered a central infusion of IGF-1 during the seven days after the damage was induced (33). The samples taken at the cortical and hippocampal levels and the follow-up with motor function scales were able to conclude that the administration of IGF-1 improves cognitive and motor function and neuronal density in the hippocampus (33). However, in terms of ranges of benefit and efficacy, it is unknown if a longer or...
shorter period of this therapy can produce the same results and if a prolonged administration can cause a deleterious effect on the metabolic balance.

On the other hand, randomized clinical trials in patients with traumatic brain injury have shown promising results. The study was designed as a prospective, randomized, double-blind investigation to compare the effectiveness of combination IGF-I/GH therapy with placebo treatment. The study included 97 patients who had experienced TBI, and they were randomly assigned to receive either combination IGF-I/GH therapy or a placebo. Nutritional support was provided to all patients, and the administration of insulin-like growth factor-I was done through continuous intravenous infusion at a rate of 0.01 mg/kg/hr, while GH was administered subcutaneously at a rate of 0.05 mg/kg/day (37). For the control group, a normal saline solution was administered instead of both agents. Throughout the 14-day treatment period, nutritional and metabolic monitoring was carried out for all patients.

The effects of subcutaneous administration of growth hormone (GH) and continuous infusion of IGF-1 in conjunction with nutritional support regimens versus placebo have been compared within 72
hours of trauma (37), finding that combination therapy of these agents produced improvement in nutritional and metabolic demands and did not increase the risk of complications that do occur when GH is administered in isolation (sepsis, hypertension, hyperglycemia, impaired liver function, among others) (38). Additionally, combined therapy maintained IGF-1 levels above physiological values compared to isolated treatment. The treatment group attained a positive nitrogen balance within the initial 24-hour period, and this positive balance persisted throughout the treatment duration, with a p-value of less than 0.05 (37). This increase was related to better nutritional parameters and attenuating the refractory nitrogen loss during brain trauma (38,39).

Conclusion

Somatomedin C has a neuroprotective and proliferative effect on post-trauma neuronal tissue and neurovascular structures, triggering physiological changes that promote blood flow and cell repair, making IGF-1 an attractive therapeutic alternative in...
brain trauma. More human studies are required to establish somatomedin C as a therapeutic target for patients with traumatic brain injury.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals in this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.
Figure 1. IGF-1 production sites in the human body. Growth hormone (GH) insulin-like growth factor type I (IGF-1).
Figure 2. Diagram the most relevant pathways for IGF-1 binding to its receptor. Insulin-like growth factor-1 (IGF-1), insulin receptor substrate 1 (IRS-1), Src homologous collagen protein (SHC1), phosphatidylinositol 3-kinase (PI3K-AKT) pathway, protein

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kinase (MAPK-ERK), protein serine/threonine kinase (mTOR),
glycogen synthase kinase-3 beta (GSK3B).

Figure 3. Neuroprotective effects associated with IGF-1 during or after brain injury. Insulin-like growth factor type 1 (IGF-1).
Images References

Images with original authorship using Reactome tools, consult:


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