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ABSTRACT

Growth hormone is responsible for stimulating the growth and differentiation of cells of various tissues and cell types contribute to protein synthesis and the mobilization of fatty acids. At the nervous system level, it stimulates the regeneration of neurons, astrocytes, endothelial cells, oligodendrocytes, and even neuronal myelination. Traumatic brain injuries can alter the secretion of this hormone, due to the deformation of brain tissue and the alteration of neurometabolism by the subsequent ischemia. Knowing the basic aspects of pituitary disorders in this type of patient allows early identification and management to avoid complications.

INTRODUCTION

Growth hormone (GH), synthesized in the adenohypophysis, is responsible for the stimu-lation of cell growth and differentiation, its

synthesis and release is related to growth hormone releasing hormone (GHRH) which is responsible for stimulating the process of synthesis and release of GH, while somatostatin hormone is responsible for inhibiting the synthesis and release, thus performing a negative feedback. It has been shown that the highest serum levels of this hormone are found during sleep [1,2] GH secretion occurs in the form of pulses, and its serum concentrations may vary according to sex and individual conditions [3]. Different brain injuries can alter GH metabolism, taking into account that different trauma mechanisms can produce damage to the brain parenchyma as inflamma-tory or ischemic damage [4,5]. Considering the relevance and impact of neuroendocrine disorders on neurological integrity and quality of life, the aim of this review is to present basic concepts for the understanding and early detection of growth hormone deficiency in traumatic brain injury.

GROWTH HORMONE GENERALITIES

GH is synthesized in the lateral zones of the adenohypophysis by somatotropic cells. This hormone is a protein consisting of 191 amino acids with an approximate weight of 22650 Daltons. The synthesis and release of this hormone depends on two neurohormones loca-ted in the hypothalamus: GHRH and somatostatin [2,3]. The first one has a stimulating character, while the latter has an inhibitory character. Its release is rhythmic and alterna-ting, occurring when the amount of GHRH in plasma predominates. The peaks of GH re-lease occur in the slow wave phase of sleep, with a maximum amplitude hypothalamic-pituitary rhythm [2].

GROWTH HORMONE SYNTHESIS

Growth hormone synthesis is directly influenced by hypothalamic and peripheral factors which act on somatotrophs. Both act by binding to specific receptors located on the surface of somatotroph cells [3,6]. GHRH binds to a metabotropic receptor, which are receptors with 7 transmembrane domains that couple to second messengers via G proteins, which upon ligand-induced activation causes intracellular stimulation of cyclic adenosine monophosphate (cAMP), leading to GH synthesis [2]. Hypothalamic somatostatin has five receptor subtypes (SSTR1-SSTR5). Among which SSTR2 and SSTR5 are responsible for signaling suppression of pituitary GH and thyrotropin secretion [7].

Other regulators have been described, such as IGF-1, which in addition to mediating the peripheral actions of GH, is also capable of inhibiting GH secretion. Nutritional status can also influence the synthesis and secretion of GH, since it has been described that it can be increased in malnourished or fasting individuals [3,8]. Although, in states of hyperglyce-mia, hormones such as leptin are able to inhibit GH secretion. It has also been found to be associated with ghrelin, which is an intestinal peptide responsible for the induction of GH secretion, its receptor is expressed in the anterior pituitary, this peptide is produced mainly in the stomach, although small amounts are obtained from intestinal tissue, pitui-tary, placenta and pancreas, it is of great relevance because it is a nutritional regulator of GH secretion, its function is to maintain blood glucose levels during starvation [3,8].

EXCRETION

GH excretion is pulsatile, its serum concentration can be detected if an ultrasensitive as-say is used. These pulses are regulated by the reduction of inhibition by somatostatin. Therefore, serum GH measurement should be done in a 20-minute sampling during 24 hours, which would allow accurate assessment of serum GH concentrations; it was found that on average, serum GH during the night ranges between 1. 0 ± 0.2 ng/mL, while day-time concentrations average 0.6 ± 0.1 ng/mL in unimpaired adults; these levels may be lower in adults and obese persons, and higher during puberty and in neonates [2,8,9].

The maximum serum GH concentration ranges from 4.3 ± 0.7 ng/mL at night to 2.7 ± 0.5 ng/mL during the day, with the highest peak GH excretion occurring 1 hour after the onset of deep sleep. Physical activity, trauma and septic states increase GH secretion in the ran-ge of 20 to 30 ng/mL (3).

RECEPTORS

GH acts by binding to a specific receptor which is a homodimer located mainly in the li-ver, and induces intracellular signaling through a phosphorylation cascade by the JAK/STAT pathway which are activators of signal transcription. Its main action is to sti-mulate hepatic synthesis and secretion of IGF-1, which contributes to cell growth and dif-ferentiation [2,3].

The GH receptor is a 70 kd protein, belonging to the cytokine/hematopoietin superfamily. It consists of a single extracellular ligand-binding domain which spans the membrane and a cytoplasmic signaling component. Circulating GH-binding proteins are fragments of the receptor that bind to GH [6]. It has been observed that a single GH molecule is able to form complexes with two GH receptor molecules, leading to rapid internal turnover and activation of the JAK2 tyrosine kinase, which allows phosphorylation of several cyto-plasmic signaling molecules that determine cell proliferation and differentiated function [6].

On the other hand, it has been observed that STAT proteins, which are cytoplasmic pro-teins, represent important signaling components for GH action. They are phosphorylated by JAK2 and translocate directly to the cell nucleus, triggering GH-specific target gene effects at this level by binding to the nucleotide DNA. Within this group of proteins, it has been observed that STAT 1 and 5 interact most directly with the GH receptor [10,11]. The function of this receptor can be directly inhibited by IGF-1, as well as GH secretion, which is due to negative feedback [2,5].

GH receptor mutations have been described to be associated with partial or complete GH insensitivity and growth failure (Laron dwarfism), which is associated with normal or high serum GH concentrations, decreased serum GH-binding protein concentrations, and decreased serum IGF-1 concentrations [2,3].

PHYSIOLOGICAL FUNCTIONS

Unlike the other hormones produced by the pituitary gland, growth hormone does not act in a specific gland, but in the whole organism. This hormone stimulates the growth and differentiation of cells of various tissues and cell types. Its anabolic effects are remar-kable, stimulating protein synthesis and the mobilization of fatty acids for use as a source of energy [3,6]. It is also known to promote a diabetogenic state by decreasing glucose uptake by peripheral tissue, stimulating glucose secretion in the liver, and in turn insulin secretion [3]. In bone, it promotes protein deposition by bone growth-inducing cells, con-tributes to the rapid growth of bone cell lines, and is known to stimulate the conversion of chondrocytes into osteogenic cells, resulting in the pre-dominance of the rate of bone

ma-trix apposition over the rate of bone resorption [3,12]. At the level of the central nervous system, it has been proven that this hormone exerts important functions related to neuro-nal function and differentiation; its contribution to the regeneration of neurons, astrocytes, endothelial cells, oligodendrocytes, and even neuronal myelination has been studied. It has also been implicated in processes such as migration and survival of neurons [1].

The current concept of the diagnosis of growth hormone deficiency in the adult is based on the absence of growth hormone secretion following the administration of pharmacolog-ical agents, which normally trigger hormone secretion. This is due to the fluctuation of hormone over a 24-hour period. However, serum IGF-1 levels lack diurnal fluctuation and reflect the action of GH. Therefore, the usefulness of the latter has been investigated in the diagnosis of growth hormone deficiency [13]. In children in some cases, clinical risk factors are identified and taken into account, which may provide evidence of growth hor-mone deficiency, without the need for continuous stimulation testing. However, for con-firmation of the diagnosis in most countries of the world the latter test is required [14].

TRAUMATIC BRAIN INJURY
Pathophysiology

Primary and secondary lesions in traumatic brain injury divide the pathophysiology of trauma into two distinct phases. The first phase is characterized by mechanical deforma-tion of brain tissue and the second by brain biochemical changes that occur from the time of injury and last from days to months. The first phase is produced by the forces of accele-ration, deceleration, and impact forces, which will lead to loss of polarity of neurons, da-mage to blood vessels and axons. Ischemia is explained in the alteration of the architectu-re and functionality of the blood vessels, evidencing compromise in terms of tissue perfu-sion due to the lack of vascular bed density, added to other physiological phenomena such as arterial hypotension due to the loss of intrinsic capillary regulation, deficit of nitric oxide production and excess of prostaglandins, which will promote vasoconstriction [4,5,15]. Post-traumatic vasospasm is the result of an imbalance of vasodilator and vaso-constrictor factors, and is an aggravating factor of ischemia and hypoxia. Due to

the state of anaerobiosis, the increase in lactic acid will directly alter cell membrane permeability [4,5,15]. The water and electrolyte imbalance will contribute to the formation of cerebral edema, with subsequent endocranial hypertension. The second phase of traumatic brain injury will initiate an inflammatory cascade characterized by the presence of inflamma-tory cytokines and the presence of excitatory neurotransmitters that will alter calcium homeostasis and other electrolytes. The excess of intracellular calcium, together with an environment rich in inflammatory substances, will lead the neuron to the activation of internal pathways of self-destruction, represented by proteases and caspases that will de-grade the cytoskeleton proteins, irreversibly activating programmed cell death, or earlier, necrosis, with subsequent release of inflammatory substances into the extracellular environment [4,5,15].

Pathophysiology of hypopituitarism induced by traumatic brain injury

Although the exact pathophysiology of hypopituitarism following traumatic brain injury is unclear, several pathological mechanisms have been proposed as responsible for this dysfunction [16]. One of the main hypotheses is based on the argument of their anatomi-cal location. The pituitary gland, the hypothalamus and the vessels that irrigate these structures are fragile and vulnerable to significant changes in the characteristics of the environment in which they are located, which is the case in traumatic brain injury. Me-chanical alterations secondary to trauma can lead to different situations such as edema, rupture of blood vessels, hematoma, increased intracranial pressure, displacement of the hypothalamus, tearing and fracture of bones that destabilize the function of the gland [5].

Several studies have found genetic predisposition and immunity to be factors responsible for this condition. High levels of antihypophysis and antihypothalamic antibodies have been found in patients with this pituitary dysfunction after traumatic brain injury. Tanri-verdi et al [17], showed a strong association between the presence of high titers of anti-pituitary antibodies and anti-thalamic antibodies five years after traumatic brain injury [17]. Damage to the gland has been found, ranging from 26 to 86%, in patients who died after trauma. It is not

uncommon to find infarcts in segments of the pituitary gland, such as anterior neocrosis of the gland in patients who died less than a week after traumatic brain injury. Mechanisms such as ischemia and intracranial pressure may be responsible for this damage to the pituitary gland [15]. The vascular hypothesis is supported by imaging studies that have demonstrated severe pathological changes in relation to vascular injury. This hypothesis is also related to patterns of hormone loss, through studies showing that the most frequent hormone loss is somatotropin and gonadotropins, excreted in specific sites irrigated by pituitary portal vessels. The genetic polymorphism could also be associated with hypopituitarism [18]. Medications used in the intensive care unit could be responsible for having an impact on endocrine function.

Growth hormone deficiency secondary to traumatic brain injury and its effect on quality of life

The prevalence of hypopituitarism and quality of life in patients who survive traumatic brain injury is subject to factors such as skull fracture, duration of ventilatory support, initial imaging related to Marshall's classification and coma [19]. Although head trauma is common in certain high-risk occupations such as military service, a clear association between pituitary hormone dysfunction and head trauma in the military has not been es-tablished, but a long-term negative psychological effect may possibly be generated [14,20,21,22]. In a meta-analysis it was also analyzed that 12 months after a head trauma, about one third of patients were at high risk of suffering post-traumatic pituitary deficien-cy [23]. In a prospective study, it was recognized that in children, unlike adults, the preva-lence of hypopituitarism after traumatic brain injury remains controversial [16]. However, it has been established that children after trauma suffer a challenge in terms of rehabilita-tion and reintegration to their life as it was prior to the traumatic injury. This finding is directly related to the severity of the brain injury, which in turn affects the resilience of children after trauma [24-28].

Reduced growth hormone production in the context of pituitary dysfunction following head trauma is common. During a crossover, double-blind, placebo-controlled study, physical changes, resting energy expenditure, fatigue, sleep

disturbance and neuropsycho-logical status were observed in 18 patients with growth hormone deficiency secondary to trauma. Additionally, changes in anatomical features of the brain parenchyma were ob-served on MRI scans of these patients. However, when growth hormone was replaced, al-terations in brain morphology and connectivity were evident, as well as a reduction in fatigue and other related symptoms [29,30].

Growth hormone and its effect on bone mass loss induced by mild head trauma

It has been demonstrated that recurrent mild head trauma exerts certain effects on the vol-ume of trabecular bone at different scales depending on the affected skeletal site. In con-trast, cortical bone is unaffected [31]; it is believed that this is due to several mechanisms among which are: the site where bone remodeling takes place, regulatory mechanisms of trabecular and cortical bone formation, the site of the trabecular bone formation and the cortical bone formation [32,33]). Finally, neuroendocrine signals generated by trauma may affect trabecular bone formation and remodeling more than cortical bone formation and remodeling. Findings showed that low-dose growth hormone treatment was useful, as it partially rescued the loss of trabecular bone mass, which had been caused by the combi-nation of trauma and immobility generated by trauma. However, more research in humans is needed to confirm these effects [34].

Roles of GH/IGF-1 in non-severe traumatic brain injury

Normally IGF-1 exerts a neuroprotective and neurorepair mechanism after any brain inju-ry [35]. Rapidly after cranioencephalic trauma GH/IGF-1 levels are elevated, regardless of growth hormone status [36,37]. However, depending on which IGF-1 allele is present in the neurocritical-posttraumatic patient, neuropsychiatric symptoms and feelings of dizzi-ness or lightheadedness may be present or become chronic, so the final outcome of the traumatic injury is variable [38-40].

Alterations in the axis GH/IGF-1 - intestinal microbiota after traumatic brain injury

The rapid expansion in the field of interaction between different systems such as gastroin-testinal, immune, endocrine, neurological in relation to the intestinal microbiota, has led to the conclusion that the microbiota has an influence on any of these systems [41-43]. This leads to the discussion of an axis currently known as the microbiota-gut-brain axis [44,45]. Recent analyses have demonstrated a link between altered gut microbiota and altered neurocognitive, behavioral and neuropathological states [46-50].

Growth hormone deficiency in subarachnoid haemorrhage and cerebral ischemia

Subarachnoid hemorrhage (SAH) is a disease of acute onset and sudden onset consisting of three phases: acute rupture phase, vasospasm phase and recovery phase. The most fre-quent neuroendocrine abnormalities studied in SAH are disorders of the hypothalamic-pituitary-adrenal axis [51,52].

Endocrine disorders were found in 78% of patients with subarachnoid hemorrhage and in those with ischemic stroke. The most common findings were low IGF-1 levels compatible with growth hormone deficiency (45%), followed by hypogonadism (39%), thyroid dys-function (36%) and hypo-reactivity to cortisol (33%) [53].

The pathophysiological mechanisms of endocrine disruption in patients with brain injury following subarachnoid hemorrhage are not clear, however, it is believed that hypothala-mic and pituitary injury secondary to hematoma compression, ischemic injury or elevated intracranial pressure would be a logical explanation for the endocrine disorders generated [53]. Another explanation for these findings is the influence of proinflammatory cytoki-nes, such as IL-6, TNF α, IL-1B, present in acute brain injury processes of various kinds, which may exert inhibitory or stimulatory effects on pituitary and hypothalamic hormones [54].

CONCLUSIONS

Hypopituitarism secondary to brain lesions has not been fully described, it has been ob-served that traumatic brain lesions can deform the brain tissue and subsequently generate biochemical changes; Permanent lesions have been explained due to the alteration in the form and function of blood vessels, finding a compromise in cerebral irrigation, as a con-sequence of this and taking into account the anatomical location, the pituitary is an organ susceptible to ischemic changes, which happens in

brain lesions causing a hormonal loss, mainly of soma-totropin and gonadotropins, in conclusion, there is an alteration in the metabolism of GH.

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