Journal of Integrative Neuroscience

J. Integr. Neurosci. **2024**; 23(2): 32
https://doi.org/10.31083/j.jin2302032

Review

Impact of Growth Hormone on Microglial and Astrocytic Function

Mariana R. Tavares[1], Frederick Wasinski[2], Martin Metzger[1], Jose Donato Jr.[1,*]

[1]Department of Physiology and Biophysics, Instituto de Ciencias Biomedicas, Universidade de Sao Paulo, Sao Paulo, SP 05508-000, Brazil
[2]Department of Neurology and Neurosurgery, Universidade Federal de Sao Paulo, Sao Paulo, SP 04039-032, Brazil
*Correspondence: jdonato@icb.usp.br (Jose Donato Jr.)
Academic Editor: Gernot Riedel
Submitted: 6 June 2023 Revised: 13 July 2023 Accepted: 21 July 2023 Published: 18 February 2024

Abstract

The role of growth hormone (GH) in the central nervous system (CNS) involves neuroprotection, neuroregeneration, formation of axonal projections, control of cognition, and regulation of metabolism. As GH induces insulin-like growth factor-1 (IGF-1) expression in many tissues, differentiating the specific functions of GH and IGF-1 in the organism is a significant challenge. The actions of GH and IGF-1 in neurons have been more extensively studied than their functions in nonneuronal cells (e.g., microglial cells). Glial cells are fundamentally important to CNS function. Microglia, astrocytes, oligodendrocytes, and tanycytes are essential to the survival, differentiation, and proliferation of neurons. As the interaction of the GH/IGF-1 axis with glial cells merits further exploration, our objective for this review was to summarize and discuss the available literature regarding the genuine effects of GH on glial cells, seeking to differentiate them from the role played by IGF-1 action whenever possible.

Keywords: microglia; astrocyte; oligodendrocyte; tanycyte; GH; IGF-1; neuroinflammation

1. Introduction

The somatotrophic axis is an important regulator of growth and cellular metabolism in mammals [1]. Somatotrophs are the most abundant endocrine cells present in the anterior pituitary gland [2], and they are responsible for the production of growth hormone (GH). GH regulates growth, development, metabolism, and body composition. Furthermore, GH induces the expression of insulin-like growth factor-1 (IGF-1) in many tissues [1]. GH action on the liver, via its receptor (GHR), is responsible for controlling circulating IGF-1 levels [3,4]. Deletion of the gene encoding the GHR in the liver decreases circulating IGF-1 levels by more than 90% [5]. IGF-1 can act as a downstream mediator of the effects of GH, so it is often challenging to differentiate the direct actions of each hormone separately.

GH secretion is regulated by different neuropeptides secreted by hypothalamic neurons. In this regard, growth hormone-releasing hormone (GHRH) stimulates GH secretion, while somatostatin (SST) inhibits its secretion [1,6]. In addition, ghrelin, a hormone mainly produced in the stomach, also stimulates pituitary GH secretion [7]. GH secretion by the anterior pituitary is the main secretory pathway; however, GH mRNA is expressed in many extrapituitary tissues, including in the central nervous system (CNS) [8,9].

There are several GH-responsive neuronal populations distributed across distinct brain areas [10,11]. Thus, in addition to the effects of GH on peripheral tissues, there is growing evidence indicating that GH also regulates several brain functions. Previous studies have demonstrated that GH displays neurotropic effects since GHR signaling is required for the formation of neuron axonal projections from the arcuate nucleus of the hypothalamus (ARH) to postsynaptic targets [12,13]. Moreover, central GH action controls some aspects of metabolism [14,15]. For example, GHR signaling in different hypothalamic neurons can control food intake [16–18], hepatic insulin sensitivity, peripheral lipid metabolism [19], and the counterregulatory response to hypoglycemia [17].

GH also has neuroprotective and neuroregenerative actions. Local GH expression is associated with neuroprotection and cell survival in response to neural damage [20]. GH treatment reduces cerebellar damage after hypoxia in chicken embryos by inhibiting apoptosis and oxidative stress and regulating cytokine expression [21]. Additionally, the central action of GH is relevant for some cognitive aspects, such as learning, memory formation [22], and stress resilience [23]. GH also modulates fear memory formation in the amygdala [24,25]. Nevertheless, IGF-1 also presents similar effects, regulating cognitive functions and presenting neuroprotective effects [26,27]. Therefore, it is challenging to separate the effects of GH in the CNS from IGF-1-mediated effects, although some progress has been achieved in this regard [22,26]. Furthermore, it is important to highlight that most of the research regarding the central effects of GH is focused on neurons, and far less is known about its role in nonneuronal (glial) cells.

The role of neuroglia is complex due to the diverse types of glial cells involved and their fundamental importance for the functioning of the nervous system. Recent research has shed light on the manifold functions of these cells in various neurological and psychiatric conditions. They provide neurotrophic signals to neurons that are important

for cell survival, differentiation, and proliferation [28]. Microglia, astrocytes, tanycytes, and oligodendrocytes are just some examples of neuroglial cells [29].

The interaction between glial cells and the GH/IGF-1 axis still needs to be further untangled, considering that these cells are potentially responsive to both GH and IGF-1 [30]. In this vein, GH and IGF-1 can have important effects on glial cells, especially in the early stages of development, by regulating plasticity and the activity of these cells, possibly via the production of pro-inflammatory cytokines [31,32]. Therefore, this review summarizes and discusses the available literature regarding the possible effects of GH on glial cells, seeking to differentiate them from the role played by IGF-1 action whenever possible.

2. GH and Microglia/Astrocytes

Microglial cells are considered the immune cells of the CNS. Microglial cells are activated in response to infections or brain damage, and they are essential for recognizing pathogens and inducing an inflammatory response, releasing cytokines, chemokines, and trophic factors, as well as participating in phagocytosis [29]. Under physiological conditions, microglial cells also play a role in brain homeostasis. Microglial action is essential for the generation and maintenance of neural cells, promotion of neuronal survival, regulation of synapses, myelination, clearance of cells, and cognitive aspects, such as learning and memory formation [29,33].

Astrocytes are the most abundant glial cell type. They possess a specific cytoarchitecture that allows them to perceive and respond to several stimuli from the periphery. In the CNS, astrocytes are responsible for many homeostatic effects, such as the formation and maintenance of the blood–brain barrier (BBB), regulation of synapses, supply of nutrients and oxygen to the brain, energy storage, defense against oxidative stress, and tissue repair [29,34]. Astrocytes are important for inflammatory and immune responses, responding to abnormal events in the CNS. Reactive astrocytes are cells that respond to different stressors (e.g., injury, disease, or infection) by undergoing morphological, molecular, and functional remodeling [35].

Initial reports have indicated that the effects of GH on astrocytes seem to be indirect and mediated by IGF-1. Astrocytes present high expression of the IGF-1 receptor (IGF1R) [36], and its activation is relevant for brain development and maturation [37,38]. IGF-1 stimulates astrocyte proliferation *in vitro* [39] and *in vivo* [38] via IGF1R. IGF-1 also regulates astrocyte number [40,41], increasing connexin43 expression and gap junctions in this cell type [42].

The difficulty in separating the roles of GH and IGF-1 is evident in transgenic mice oversecreting GH, as these mice present increased serum levels of both GH and IGF-1. Transgenic mice oversecreting bovine GH (bGH mice) display astrocytic hypertrophy and increased expression of glial fibrillary acidic protein (GFAP), a well-established marker of astrocytes [43]. These are normal processes in aged wild-type mice but indicate accelerated brain aging in bGH mice. Additionally, our group recently showed that bGH mice exhibit increased hypothalamic mRNA expression of important markers of inflammation and reactive microglia, such as GFAP, Iba1, and F4/80 [44]. Since bGH mice show increased levels of both GH and IGF-1, this mouse model is insufficient to determine which hormone is associated with these changes [43].

Conversely, dwarf GHR knockout mice ($GHR^{-/-}$) show decreased GFAP-positive cells in the cortex, indicating a reduction in the number and size of astrocytes. However, despite the impairment of GHR signaling, $GHR^{-/-}$ mice are also IGF-1 deficient, so it is impossible to distinguish the specific roles of GH and IGF-1 using this mouse model [40]. In this regard, we also found that dwarf GH- and IGF1-deficient $Ghrhr^{lit/lit}$ mice show decreased mRNA expression of nestin, GFAP, Iba1, F4/80, and TNF-α in the hypothalamus [44]. This effect requires GHR signaling, as ablation of GHR in nestin-derived cells decreases the levels of F4/80, GFAP, and vimentin (tanycyte marker) mRNA in the hypothalamus [44].

Additional evidence highlights the direct effects of GH on neuroglial cells. GH treatment in rats for 1 week increased the hypothalamic and hippocampal expression of GFAP. This effect was independent of IGF-1 because serum levels of IGF-1 were not different between GH-treated and control rats [45]. We investigated hypothalamic gene expression in mice carrying a hepatocyte-specific GHR deletion ($Albumin^{\Delta GHR}$ mice). $Albumin^{\Delta GHR}$ mice show increased GH serum levels, whereas circulating IGF-1 levels are drastically reduced. We found upregulated hypothalamic expression of Sox10 (oligodendrocyte marker), Iba1, and GFAP in this model. Therefore, GHR signaling can control, at least in the hypothalamus, the expression of important markers of reactive microglia and astrocytes, independent of IGF-1 levels [44].

2.1 GH, Neuroinflammation, and Aging

GH is involved in age- and obesity-induced neuroinflammation in the hypothalamus [12,46]. Eighteen-month-old Ames dwarf male mice (model of GH deficiency) present reduced staining for GFAP in the ARH compared with littermate controls, indicating lower hypothalamic inflammation. This effect is possibly associated with their increased lifespan. Nevertheless, early-life treatment with GH was able to restore GFAP-positive cells in old Ames mice, reaching the same levels observed in wild-type mice [12], evidencing the participation of the GH/IGF-1 axis during development in aging-related neuroinflammatory processes. High-fat diet (HFD)-induced obesity is associated with hypothalamic inflammation and gliosis, and it seems that GH plays a role in this condition. Baquedano *et al.* [46] found that $GHR^{-/-}$ mice present lower expression of markers of gliosis (Iba-1) and inflammation (GFAP) in the

hypothalamus after 7 weeks on an HFD. GHR$^{-/-}$ mice also display reduced proinflammatory cytokine production, despite presenting higher body fat gain. However, it is important to mention that the neuroinflammation induced by overnutrition depends on many factors, such as the genetic background of the animal, composition of the diet, and the time the animals were exposed to the diet. In the context of GH, developmental events are also determinants of diet-induced neuroinflammation, as GH is involved in the differentiation and proliferation of astroglial cells at early stages of development.

These findings reinforce the idea that decreases in GH secretion contribute to a slower/delayed aging process. Accordingly, GH is usually negatively associated with longevity [47] and maintenance of cognitive function with age [48,49] (Fig. 1). The attenuated neuroinflammation seen in animals with GH deficiency can improve cognitive function, possibly via increased insulin sensitivity, which is also strongly associated with longevity. GH is known to induce insulin resistance. Neuroinflammation, especially in the hypothalamus, also induces insulin resistance. Thus, enhanced insulin sensitivity should be considered one of the mechanisms involved in longevity in mice presenting low GH secretion or GH action (e.g., GHR$^{-/-}$ mice) [50,51].

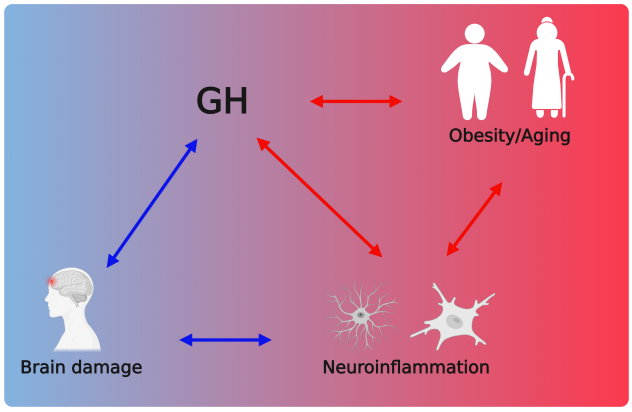

Fig. 1. Schematic summarizing the roles of GH in neuroinflammation. The secretion of GH is influenced by conditions such as obesity and aging, which are directly involved in neuroinflammation, leading to pro-aging effects. Conversely, in situations of brain damage, GH has a beneficial role in supporting neuroglial cells and consequently favoring recovery. Arrows indicate direct influences between situations. GH, growth hormone.

2.2 Brain Injury

Since GH is involved in neuroinflammation, it may also have an essential role in brain injury. Glial cells are extensively activated under neuroinflammation to induce the expression of cytokines, hormones, growth factors, and neurotrophins. In this process, GH can induce not only the expression of growth factors (e.g., IGF-1) but also neurotrophins (e.g., brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT3)) [20,52]. Therefore, GH can act as a neurotrophic factor, and consequently, it has the potential to improve recovery [53].

Microglia and astrocytes express GHR, and following brain injury, GHR expression is upregulated in these cells as well as in damaged neurons [30,54–56]. Scheepens *et al.* [57] found that after brain lesion in rats, immunoreactivity for GH increases in injured regions, including the cerebral cortex. Furthermore, intracerebroventricular (i.c.v.) treatment with GH immediately after the damage reduced neuronal loss in the cortex, hippocampus, and thalamus. This effect seems to be independent of IGF-1. Reinforcing these data, it was reported that after cortical injury in rats, *Gfap* and *Ghr* gene expression was increased in the cerebral cortex, and the population of GHR-positive cells colocalized with reactive astrocytes [54].

GHR binding protein (GHR/BP) immunoreactivity is upregulated in juvenile rats upon brain damage, with an initial rise in the blood vessels a few hours after injury. A second increase in GHR/BP immunoreactivity is observed 3 days postinjury in activated microglial cells present in damaged regions either in the cerebral cortex, hippocampus, or thalamus. This result suggests that GH is involved in wound repair and regeneration after brain injury [55]. Nonetheless, upon the same brain damage protocol, the expression of IGF-1 mRNA was enhanced in microglia in the same areas as GHR/BP immunoreactivity was increased. Therefore, GHR signaling possibly induces IGF-1 expression in these cells. Additional studies are needed to verify the specific contribution of GH and IGF-1 to the functions of microglial cells during brain damage [58].

Another study demonstrated that IGF-1 expression is increased in a subpopulation of reactive astrocytes along the lesioned area [59], suggesting an impact of IGF-1 on neuroinflammation and neuroregeneration. In this regard, IGF-1 protects astrocytes against oxidative stress [60] and reduces the astrocytic inflammatory response under lipopolysaccharide-induced inflammation in the cerebral cortex of rats [61]. IGF-1 overexpression also protects hippocampal neurons and improves cognitive function after brain damage in mice [62]. During ischemia, the lack of circulating GH and IGF-1 in dwarf rats reduces astrocytic infiltration [63]. Given that reactive astrocyte infiltration is an important process in neural repair, GH/IGF-1 action becomes relevant in these specific situations.

Martínez-Moreno *et al.* [64] recently proposed an anti-inflammatory effect of GH in a rat model of spinal cord injury. Chronic treatment with GH was correlated with recovery by the downregulation of proinflammatory cytokines and glial markers in the lesioned local area.

Altogether (see Fig. 1 and Table 1, Ref. [10,35–38,40–43,49–71]), upon brain damage, GH directly contributes to the CNS response to inflammatory processes as well as tis-

Table 1. Summary of the effects of the GH/IGF1 axis on neuroglial cells.

Target cells	Mediator	Effect	References
Astrocytes/Oligodendrocytes/Tanycytes	IGF-1	Proliferation	[35,36,58,70,71]
Astrocytes	IGF-1	Cell number	[37,38]
Astrocytes	GH/IGF-1	Hypertrophy	[40]
Astrocytes/Microglia	GH	mRNA expression of inflammatory markers	[41,42]
Astrocytes/Microglia	GH/IGF-1	Aging- and overnutrition neuroinflammation	[10,43]
Astrocytes/Microglia	GH	Neurotrophic factor	[49–51]
Astrocytes/Microglia	GH/IGF-1	Neurotrophic factor	[52,57]
Astrocytes/Microglia	IGF-1	Neurotrophic factor	[53–56]
Oligodendrocytes	IGF-1	Differentiation	[59,60]
Oligodendrocytes	IGF-1	Myelogenesis	[61–64]
Oligodendrocytes	IGF-1	Remyelination	[65,66]
Oligodendrocytes	GH	Myelogenesis	[67–69]

IGF-1, insulin-like growth factor-1; GH, growth hormone.

sue regeneration and wound repair, with IGF-1 possibly being a local effector recruited by GHR signaling to perform these functions. Interestingly, the activity of the GH/IGF-1 axis seems to have ambiguous effects. Thus, GH favors pro-aging effects in relation to neuroinflammation under normal and obesity conditions, whereas the activation of this axis appears to be beneficial in brain repair after damage or injury.

3. GH and Oligodendrocytes

Oligodendrocytes are a subgroup of glial cells that are mainly responsible for the synthesis of the myelin sheath in the CNS. The myelin sheath is an isolating layer that helps to increase the speed of transmission of nerve impulses along axons. Damage to the myelin sheath is critically involved in the pathogenesis of several neurological diseases and neuropsychiatric disorders [28].

IGF-1 can increase the proliferation of oligodendrocytes in the dentate gyrus of the hippocampus [65] and regulates the differentiation of these cells [66,67]. Additionally, strong evidence indicates a role of IGF-1 in myelination, particularly in regulating the development of myelogenesis [68,69,71–73]. IGF-1 is also important for remyelination upon injury [70,74], playing an essential role in neurologic diseases that involve demyelination.

Nevertheless, evidence regarding the individual role of GH in oligodendrocytes is scarce. Studies published decades ago suggested that GH deficiency causes hypomyelination [71,75,76], probably due to decreased oligodendrocyte proliferation. However, data in the literature are conflicting, since another study showed normal myelination in a dwarf mouse model [77].

In conclusion, although there is robust evidence indicating a role of IGF-1 in the proliferation and differentiation of oligodendrocytes and consequently in myelination, the specific function of GH in these cells still needs to be clarified.

4. GH and Tanycytes

Tanycytes are a subtype of glial cells found at the floor and ventrolateral walls of the third ventricle of the hypothalamus near the ARH. These cells share some features with astrocytes and microglial cells, but also display distinct characteristics. There are four subpopulations of tanycytes described: α_1, α_2, β_1, and β_2. These subdivisions allow differentiation of the morphology, location, projections, and functions of these cells. For example, β-tanycytes present barrier properties, whereas this characteristic is absent in α-tanycytes. They also have distinct mechanisms to transport molecules, among other functions [78].

Tanycytes are part of the median eminence (ME) barrier, together with endothelial cells. In this strategically placed structure, tanycytes are essential for maintaining a healthy brain environment, acting as a filter and preventing exposure of cerebrospinal fluid (CSF) and neurons to the blood and potentially toxic molecules. In the ME, tanycytes can also modulate important hypothalamic functions, such as metabolism and reproduction [79].

I.c.v. injection of IGF-1 increases the proliferation of tanycytes in the hypothalamus of rats [80]. Some tanycytes can act as neuronal progenitors in the postnatal hypothalamus [81], so IGF-1 acts through tanycytes to promote adult neurogenesis. Conversely, IGF-1 knockout in hypothalamic stem or progenitor cells increases α-tanycyte self-renewal, protecting them from age-induced damage and leading to enhanced neuronal production [82]. Therefore, the role of IGF-1 in influencing the proliferation and self-renewal of tanycytes deserves more attention, as it seems to regulate adult hypothalamic neurogenesis.

Connexin43 is the most abundant connexin isoform expressed in hypothalamic tanycytes of rats and possibly contributes to the majority of gap junction function of α-tanycytes [83]. In addition, the communication between tanycytes and parenchymal neurons is impaired by the absence of connexin43 in mice [83]. The physiologic role of tanycytic connexin43 is closely related to the communica-

tion of metabolic status to hypothalamic neurons, transport of metabolites (i.e., nutrients, hormones) from the peripheral blood to the CSF, and regulation of hypothalamic functions [83]. The specific role of GH in regulating tanycytic functions is still obscure. However, it was demonstrated that exogenous GH was capable of increasing connexin43 expression in the hypothalamus of rats, suggesting that GH may play a role in gap junction formation, enhancing the communication between glial cells and hypothalamic neurons [84].

Furthermore, upon cortical injury, the barrier proprieties in mice undergo late alterations, such as increased permeability of the third ventricle. This is associated with decreased GH serum levels, which also alters the morphology of tanycytes, revealing the role of these cells in different neuroendocrine neurons controlling the anterior pituitary [85]. The capacity of GH to influence barrier properties deserves further exploration, as it indicates that GH may influence hypothalamic functions through tanycytic actions.

5. Conclusions

The findings reported in this review suggest that GH and its receptor play a role in nerve cell development and maintenance, synaptic plasticity, and regulation of cognitive processes. Furthermore, we have described the isolated effects of GH in nonneural cells of the CNS, such as microglial cells/astrocytes and tanycytes.

In this review, we describe that the effects of GH in the brain extend far beyond its neuroendocrine actions, including neuroprotective effects, which can help to protect the brain from damage and degeneration, neurotrophic factor action, and support of microglial and astrocyte functions. This may be particularly relevant in the aging brain, as GH levels tend to decline with age and may contribute to age-related cognitive decline (Fig. 1). Regarding oligodendrocytes, we noted the role of IGF-1 in differentiation, proliferation, and myelination, whereas GH action in these cells still needs to be clarified. Additionally, we also highlight the role of GH in the expression of connexin43, which can modulate barrier properties and tanycyte communication with hypothalamic neurons.

In conclusion, the GH axis plays an important role in supporting neuroglial cells. However, we also highlighted several mechanisms that remain to be elucidated, such as the specific role of GH in oligodendrocyte myelination and tanycytic functions.

Author Contributions

MRT and FW conducted a literature review, wrote the manuscript and designed the figures and tables. MM conducted a literature review and assisted in writing. JDJ was responsible for the conceptualization, supervision and reviewing the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research was funded by Fundacao de Amparo a Pesquisa do Estado de Sao Paulo (FAPESP/Brazil, grants number: 2019/07005-4 to F.W.; 2020/10102-9 to M.R.T.; 2020/01318-8 to J.D.J.; 2017/16473-6 to M.M.) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq/Brazil; to J.D.J.).

Conflict of Interest

The authors declare no conflict of interest statement. Jose Donato Jr. is serving as one of the Editorial Board members of this journal. We declare that Jose Donato Jr. had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Gernot Riedel.

References

[1] Al-Samerria S, Radovick S. The Role of Insulin-like Growth Factor-1 (IGF-1) in the Control of Neuroendocrine Regulation of Growth. Cells. 2021; 10: 2664.

[2] Ruf-Zamojski F, Zhang Z, Zamojski M, Smith GR, Mendelev N, Liu H, *et al*. Single nucleus multi-omics regulatory landscape of the murine pituitary. Nature Communications. 2021; 12: 2677.

[3] Devesa J, Almengló C, Devesa P. Multiple Effects of Growth Hormone in the Body: Is it Really the Hormone for Growth? Clinical Medicine Insights. Endocrinology and Diabetes. 2016; 9: 47–71.

[4] List EO, Berryman DE, Funk K, Jara A, Kelder B, Wang F, *et al*. Liver-specific GH receptor gene-disrupted (LiGHRKO) mice have decreased endocrine IGF-I, increased local IGF-I, and altered body size, body composition, and adipokine profiles. Endocrinology. 2014; 155: 1793–1805.

[5] Fan Y, Menon RK, Cohen P, Hwang D, Clemens T, DiGirolamo DJ, *et al*. Liver-specific deletion of the growth hormone receptor reveals essential role of growth hormone signaling in hepatic lipid metabolism. The Journal of Biological Chemistry. 2009; 284: 19937–19944.

[6] Murray PG, Higham CE, Clayton PE. 60 YEARS OF NEUROENDOCRINOLOGY: The hypothalamo-GH axis: the past 60 years. The Journal of Endocrinology. 2015; 226: T123–T140.

[7] Zhao TJ, Liang G, Li RL, Xie X, Sleeman MW, Murphy AJ, *et al*. Ghrelin O-acyltransferase (GOAT) is essential for growth hormone-mediated survival of calorie-restricted mice. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107: 7467–7472.

[8] Harvey S. Extrapituitary growth hormone. Endocrine. 2010; 38: 335–359.

[9] Lu M, Flanagan JU, Langley RJ, Hay MP, Perry JK. Targeting

growth hormone function: strategies and therapeutic applications. Signal Transduction and Targeted Therapy. 2019; 4: 3.
[10] Furigo IC, Metzger M, Teixeira PDS, Soares CRJ, Donato J, Jr. Distribution of growth hormone-responsive cells in the mouse brain. Brain Structure & Function. 2017; 222: 341–363.
[11] Kastrup Y, Le Grevès M, Nyberg F, Blomqvist A. Distribution of growth hormone receptor mRNA in the brain stem and spinal cord of the rat. Neuroscience. 2005; 130: 419–425.
[12] Sadagurski M, Landeryou T, Cady G, Kopchick JJ, List EO, Berryman DE, *et al*. Growth hormone modulates hypothalamic inflammation in long-lived pituitary dwarf mice. Aging Cell. 2015; 14: 1045–1054.
[13] Wasinski F, Furigo IC, Teixeira PDS, Ramos-Lobo AM, Peroni CN, Bartolini P, *et al*. Growth Hormone Receptor Deletion Reduces the Density of Axonal Projections from Hypothalamic Arcuate Nucleus Neurons. Neuroscience. 2020; 434: 136–147.
[14] Donato J, Jr, Wasinski F, Furigo IC, Metzger M, Frazão R. Central Regulation of Metabolism by Growth Hormone. Cells. 2021; 10: 129.
[15] Tavares MR, Frazao R, Donato J. Understanding the role of growth hormone in situations of metabolic stress. The Journal of Endocrinology. 2022; 256: e220159.
[16] Bohlooly-Y M, Olsson B, Bruder CEG, Lindén D, Sjögren K, Bjursell M, *et al*. Growth hormone overexpression in the central nervous system results in hyperphagia-induced obesity associated with insulin resistance and dyslipidemia. Diabetes. 2005; 54: 51–62.
[17] Furigo IC, Teixeira PDS, de Souza GO, Couto GCL, Romero GG, Perelló M, *et al*. Growth hormone regulates neuroendocrine responses to weight loss via AgRP neurons. Nature Communications. 2019; 10: 662.
[18] Zhong C, Song Y, Wang Y, Zhang T, Duan M, Li Y, *et al*. Increased food intake in growth hormone-transgenic common carp (Cyprinus carpio L.) may be mediated by upregulating Agouti-related protein (AgRP). General and Comparative Endocrinology. 2013; 192: 81–88.
[19] Cady G, Landeryou T, Garratt M, Kopchick JJ, Qi N, Garcia-Galiano D, *et al*. Hypothalamic growth hormone receptor (GHR) controls hepatic glucose production in nutrient-sensing leptin receptor (LepRb) expressing neurons. Molecular Metabolism. 2017; 6: 393–405.
[20] Olivares-Hernández JD, Carranza M, Balderas-Márquez JE, Epardo D, Baltazar-Lara R, Ávila-Mendoza J, *et al*. Neuroprotective and Regenerative Effects of Growth Hormone (GH) in the Embryonic Chicken Cerebral Pallium Exposed to Hypoxic-Ischemic (HI) Injury. International Journal of Molecular Sciences. 2022; 23: 9054.
[21] Baltazar-Lara R, Zenil JM, Carranza M, Ávila-Mendoza J, Martínez-Moreno CG, Arámburo C, *et al*. Growth Hormone (GH) Crosses the Blood-Brain Barrier (BBB) and Induces Neuroprotective Effects in the Embryonic Chicken Cerebellum after a Hypoxic Injury. International Journal of Molecular Sciences. 2022; 23: 11546.
[22] Furigo IC, Melo HM, Lyra E Silva NM, Ramos-Lobo AM, Teixeira PDS, Buonfiglio DC, *et al*. Brain STAT5 signaling modulates learning and memory formation. Brain Structure & Function. 2018; 223: 2229–2241.
[23] Vander Weele CM, Saenz C, Yao J, Correia SS, Goosens KA. Restoration of hippocampal growth hormone reverses stress-induced hippocampal impairment. Frontiers in Behavioral Neuroscience. 2013; 7: 66.
[24] Gisabella B, Farah S, Peng X, Burgos-Robles A, Lim SH, Goosens KA. Growth hormone biases amygdala network activation after fear learning. Translational Psychiatry. 2016; 6: e960.
[25] Meyer RM, Burgos-Robles A, Liu E, Correia SS, Goosens KA. A ghrelin-growth hormone axis drives stress-induced vulnerability to enhanced fear. Molecular Psychiatry. 2014; 19: 1284–1294.
[26] Le Grevès M, Le Grevès P, Nyberg F. Age-related effects of IGF-1 on the NMDA-, GH- and IGF-1-receptor mRNA transcripts in the rat hippocampus. Brain Research Bulletin. 2005; 65: 369–374.
[27] Saatman KE, Contreras PC, Smith DH, Raghupathi R, McDermott KL, Fernandez SC, *et al*. Insulin-like growth factor-1 (IGF-1) improves both neurological motor and cognitive outcome following experimental brain injury. Experimental Neurology. 1997; 147: 418–427.
[28] Bianchi VE, Locatelli V, Rizzi L. Neurotrophic and Neuroregenerative Effects of GH/IGF1. International Journal of Molecular Sciences. 2017; 18: 2441.
[29] Quincozes-Santos A, Santos CL, de Souza Almeida RR, da Silva A, Thomaz NK, Costa NLF, *et al*. Gliotoxicity and Gioprotection: the Dual Role of Glial Cells. Molecular Neurobiology. 2021; 58: 6577–6592.
[30] Lobie PE, García-Aragón J, Lincoln DT, Barnard R, Wilcox JN, Waters MJ. Localization and ontogeny of growth hormone receptor gene expression in the central nervous system. Brain Research. Developmental Brain Research. 1993; 74: 225–233.
[31] Åberg D. Role of the growth hormone/insulin-like growth factor 1 axis in neurogenesis. Endocrine Development. 2010; 17: 63–76.
[32] Chowen JA, Garcia-Segura LM. Microglia, neurodegeneration and loss of neuroendocrine control. Progress in Neurobiology. 2020; 184: 101720.
[33] Trapp BD, Wujek JR, Criste GA, Jalabi W, Yin X, Kidd GJ, *et al*. Evidence for synaptic stripping by cortical microglia. Glia. 2007; 55: 360–368.
[34] Bélanger M, Allaman I, Magistretti PJ. Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metabolism. 2011; 14: 724–738.
[35] Escartin C, Galea E, Lakatos A, O'Callaghan JP, Petzold GC, Serrano-Pozo A, *et al*. Reactive astrocyte nomenclature, definitions, and future directions. Nature Neuroscience. 2021; 24: 312–325.
[36] Shemer J, Raizada MK, Masters BA, Ota A, LeRoith D. Insulin-like growth factor I receptors in neuronal and glial cells. Characterization and biological effects in primary culture. The Journal of Biological Chemistry. 1987; 262: 7693–7699.
[37] Dyer AH, Vahdatpour C, Sanfeliu A, Tropea D. The role of Insulin-Like Growth Factor 1 (IGF-1) in brain development, maturation and neuroplasticity. Neuroscience. 2016; 325: 89–99.
[38] Ni W, Rajkumar K, Nagy JI, Murphy LJ. Impaired brain development and reduced astrocyte response to injury in transgenic mice expressing IGF binding protein-1. Brain Research. 1997; 769: 97–107.
[39] Ajo R, Cacicedo L, Navarro C, Sánchez-Franco F. Growth hormone action on proliferation and differentiation of cerebral cortical cells from fetal rat. Endocrinology. 2003; 144: 1086–1097.
[40] Ransome MI, Goldshmit Y, Bartlett PF, Waters MJ, Turnley AM. Comparative analysis of CNS populations in knockout mice with altered growth hormone responsiveness. The European Journal of Neuroscience. 2004; 19: 2069–2079.
[41] Ye P, Popken GJ, Kemper A, McCarthy K, Popko B, D'Ercole AJ. Astrocyte-specific overexpression of insulin-like growth factor-I promotes brain overgrowth and glial fibrillary acidic protein expression. Journal of Neuroscience Research. 2004; 78: 472–484.
[42] Aberg ND, Blomstrand F, Aberg MAI, Björklund U, Carlsson B, Carlsson-Skwirut C, *et al*. Insulin-like growth factor-I increases astrocyte intercellular gap junctional communication and connexin43 expression in vitro. Journal of Neuroscience Research.

2003; 74: 12–22.
[43] Miller DB, Bartke A, O'Callaghan JP. Increased glial fibrillary acidic protein (GFAP) levels in the brains of transgenic mice expressing the bovine growth hormone (bGH) gene. Experimental Gerontology. 1995; 30: 383–400.
[44] Wasinski F, Tavares MR, Gusmao DO, List EO, Kopchick JJ, Alves GA, *et al*. Central growth hormone action regulates neuroglial and proinflammatory markers in the hypothalamus of male mice. Neuroscience Letters. 2023; 806: 137236.
[45] Baquedano E, Chowen JA, Argente J, Frago LM. Differential effects of GH and GH-releasing peptide-6 on astrocytes. The Journal of Endocrinology. 2013; 218: 263–274.
[46] Baquedano E, Ruiz-Lopez AM, Sustarsic EG, Herpy J, List EO, Chowen JA, *et al*. The absence of GH signaling affects the susceptibility to high-fat diet-induced hypothalamic inflammation in male mice. Endocrinology. 2014; 155: 4856–4867.
[47] Bartke A. Growth hormone and aging. Reviews in Endocrine & Metabolic Disorders. 2021; 22: 71–80.
[48] Basu A, McFarlane HG, Kopchick JJ. Spatial learning and memory in male mice with altered growth hormone action. Hormones and Behavior. 2017; 93: 18–30.
[49] Kinney BA, Coschigano KT, Kopchick JJ, Steger RW, Bartke A. Evidence that age-induced decline in memory retention is delayed in growth hormone resistant GH-R-KO (Laron) mice. Physiology & Behavior. 2001; 72: 653–660.
[50] Basu R, Qian Y, Kopchick JJ. MECHANISMS IN ENDOCRINOLOGY: Lessons from growth hormone receptor gene-disrupted mice: are there benefits of endocrine defects? European Journal of Endocrinology. 2018; 178: R155–R181.
[51] Masternak MM, Panici JA, Bonkowski MS, Hughes LF, Bartke A. Insulin sensitivity as a key mediator of growth hormone actions on longevity. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2009; 64: 516–521.
[52] Martinez-Moreno CG, Fleming T, Carranza M, Ávila-Mendoza J, Luna M, Harvey S, *et al*. Growth hormone protects against kainate excitotoxicity and induces BDNF and NT3 expression in chicken neuroretinal cells. Experimental Eye Research. 2018; 166: 1–12.
[53] Díaz-Galindo MDC, Calderón-Vallejo D, Olvera-Sandoval C, Quintanar JL. Therapeutic approaches of trophic factors in animal models and in patients with spinal cord injury. Growth Factors. 2020; 38: 1–15.
[54] Lavrnja I, Ajdzanovic V, Trifunovic S, Savic D, Milosevic V, Stojiljkovic M, *et al*. Cortical ablation induces time-dependent changes in rat pituitary somatotrophs and upregulates growth hormone receptor expression in the injured cortex. Journal of Neuroscience Research. 2014; 92: 1338–1349.
[55] Scheepens A, Sirimanne E, Beilharz E, Breier BH, Waters MJ, Gluckman PD, *et al*. Alterations in the neural growth hormone axis following hypoxic-ischemic brain injury. Brain Research. Molecular Brain Research. 1999; 68: 88–100.
[56] Möderscheim TAE, Christophidis LJ, Williams CE, Scheepens A. Distinct neuronal growth hormone receptor ligand specificity in the rat brain. Brain Research. 2007; 1137: 29–34.
[57] Scheepens A, Sirimanne ES, Breier BH, Clark RG, Gluckman PD, Williams CE. Growth hormone as a neuronal rescue factor during recovery from CNS injury. Neuroscience. 2001; 104: 677–687.
[58] Beilharz EJ, Russo VC, Butler G, Baker NL, Connor B, Sirimanne ES, *et al*. Co-ordinated and cellular specific induction of the components of the IGF/IGFBP axis in the rat brain following hypoxic-ischemic injury. Brain Research. Molecular Brain Research. 1998; 59: 119–134.
[59] Garcia-Estrada J, Garcia-Segura LM, Torres-Aleman I. Expression of insulin-like growth factor I by astrocytes in response to injury. Brain Research. 1992; 592: 343–347.
[60] Genis L, Dávila D, Fernandez S, Pozo-Rodrigálvarez A, Martínez-Murillo R, Torres-Aleman I. Astrocytes require insulin-like growth factor I to protect neurons against oxidative injury. F1000Research. 2014; 3: 28.
[61] Bellini MJ, Hereñú CB, Goya RG, Garcia-Segura LM. Insulin-like growth factor-I gene delivery to astrocytes reduces their inflammatory response to lipopolysaccharide. Journal of Neuroinflammation. 2011; 8: 21.
[62] Madathil SK, Carlson SW, Brelsfoard JM, Ye P, D'Ercole AJ, Saatman KE. Astrocyte-Specific Overexpression of Insulin-Like Growth Factor-1 Protects Hippocampal Neurons and Reduces Behavioral Deficits following Traumatic Brain Injury in Mice. PLoS ONE. 2013; 8: e67204.
[63] Yan H, Mitschelen M, Toth P, Ashpole NM, Farley JA, Hodges EL, *et al*. Endothelin-1-induced focal cerebral ischemia in the growth hormone/IGF-1 deficient Lewis Dwarf rat. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2014; 69: 1353–1362.
[64] Martínez-Moreno CG, Calderón-Vallejo D, Díaz-Galindo C, Hernández-Jasso I, Olivares-Hernández JD, Ávila-Mendoza J, *et al*. Gonadotropin-releasing hormone and growth hormone act as anti-inflammatory factors improving sensory recovery in female rats with thoracic spinal cord injury. Frontiers in Neuroscience. 2023; 17: 1164044.
[65] Aberg ND, Brywe KG, Isgaard J. Aspects of growth hormone and insulin-like growth factor-I related to neuroprotection, regeneration, and functional plasticity in the adult brain. TheScientificWorldJournal. 2006; 6: 53–80.
[66] Hsieh J, Aimone JB, Kaspar BK, Kuwabara T, Nakashima K, Gage FH. IGF-I instructs multipotent adult neural progenitor cells to become oligodendrocytes. The Journal of Cell Biology. 2004; 164: 111–122.
[67] Shi B, Ding J, Liu Y, Zhuang X, Zhuang X, Chen X, *et al*. ERK1/2 pathway-mediated differentiation of IGF-1-transfected spinal cord-derived neural stem cells into oligodendrocytes. PLoS ONE. 2014; 9: e106038.
[68] Carson MJ, Behringer RR, Brinster RL, McMorris FA. Insulin-like growth factor I increases brain growth and central nervous system myelination in transgenic mice. Neuron. 1993; 10: 729–740.
[69] Freude S, Leeser U, Müller M, Hettich MM, Udelhoven M, Schilbach K, *et al*. IRS-2 branch of IGF-1 receptor signaling is essential for appropriate timing of myelination. Journal of Neurochemistry. 2008; 107: 907–917.
[70] Mason JL, Xuan S, Dragatsis I, Efstratiadis A, Goldman JE. Insulin-like growth factor (IGF) signaling through type 1 IGF receptor plays an important role in remyelination. The Journal of Neuroscience. 2003; 23: 7710–7718.
[71] Morisawa K, Sugisaki T, Kanamatsu T, Aoki T, Noguchi T. Factors contributing to cerebral hypomyelination in the growth hormone-deficient little mouse. Neurochemical Research. 1989; 14: 173–177.
[72] Ye P, Carson J, D'Ercole AJ. In vivo actions of insulin-like growth factor-I (IGF-I) on brain myelination: studies of IGF-I and IGF binding protein-1 (IGFBP-1) transgenic mice. The Journal of Neuroscience. 1995; 15: 7344–7356.
[73] Ye P, Li L, Richards RG, DiAugustine RP, D'Ercole AJ. Myelination is altered in insulin-like growth factor-I null mutant mice. The Journal of Neuroscience. 2002; 22: 6041–6051.
[74] Hlavica M, Delparente A, Good A, Good N, Plattner PS, Seyedsadr MS, *et al*. Intrathecal insulin-like growth factor 1 but not insulin enhances myelin repair in young and aged rats. Neuroscience Letters. 2017; 648: 41–46.
[75] Noguchi T. Retarded cerebral growth of hormone-deficient mice. Comparative Biochemistry and Physiology. C, Comparative Pharmacology and Toxicology. 1991; 98: 239–248.

[76] Noguchi T, Sugisaki T, Nishikawa N, Tsukada Y. Restoration of microcephalic cerebrum with hypomyelination in the growth hormone-deficient mouse (lit): stimulatory effects of GH restricted to the first 20 days of postnatal life. Neurochemical Research. 1988; 13: 249–252.
[77] Lehman DM, Hale DE, Cody JT, Harrison JM, Leach RJ. Molecular, morphometric and functional analyses demonstrate that the growth hormone deficient little mouse is not hypomyelinated. Brain Research. Developmental Brain Research. 1999; 116: 191–199.
[78] Rodríguez EM, Blázquez JL, Pastor FE, Peláez B, Peña P, Peruzzo B, *et al*. Hypothalamic tanycytes: a key component of brain-endocrine interaction. International Review of Cytology. 2005; 247: 89–164.
[79] García-Cáceres C, Balland E, Prevot V, Luquet S, Woods SC, Koch M, *et al*. Role of astrocytes, microglia, and tanycytes in brain control of systemic metabolism. Nature Neuroscience. 2019; 22: 7–14.
[80] Pérez-Martín M, Cifuentes M, Grondona JM, López-Avalos MD, Gómez-Pinedo U, García-Verdugo JM, *et al*. IGF-I stimulates neurogenesis in the hypothalamus of adult rats. The European Journal of Neuroscience. 2010; 31: 1533–1548.
[81] Xu Y, Tamamaki N, Noda T, Kimura K, Itokazu Y, Matsumoto N, *et al*. Neurogenesis in the ependymal layer of the adult rat 3rd ventricle. Experimental Neurology. 2005; 192: 251–264.
[82] Chaker Z, George C, Petrovska M, Caron JB, Lacube P, Caillé I, *et al*. Hypothalamic neurogenesis persists in the aging brain and is controlled by energy-sensing IGF-I pathway. Neurobiology of Aging. 2016; 41: 64–72.
[83] Recabal A, Elizondo-Vega R, Philippot C, Salgado M, López S, Palma A, *et al*. Connexin-43 Gap Junctions Are Responsible for the Hypothalamic Tanycyte-Coupled Network. Frontiers in Cellular Neuroscience. 2018; 12: 406.
[84] Aberg ND, Carlsson B, Rosengren L, Oscarsson J, Isaksson OG, Rönnbäck L, *et al*. Growth hormone increases connexin-43 expression in the cerebral cortex and hypothalamus. Endocrinology. 2000; 141: 3879–3886.
[85] Osterstock G, El Yandouzi T, Romanò N, Carmignac D, Langlet F, Coutry N, *et al*. Sustained alterations of hypothalamic tanycytes during posttraumatic hypopituitarism in male mice. Endocrinology. 2014; 155: 1887–1898.