Impact of Growth Hormone on Microglial and Astrocytic Function

Mariana R. Tavares¹, Frederick Wasinski², Martin Metzger¹, Jose Donato Jr.¹,*

¹Department of Physiology and Biophysics, Instituto de Ciencias Biomedicas, Universidade de Sao Paulo, Sao Paulo, SP 05508-000, Brazil
²Department of Neurology and Neurosurgery, Universidade Federal de Sao Paulo, Sao Paulo, SP 04039-032, Brazil
*Correspondence: jdonato@icb.usp.br (Jose Donato Jr.)

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 tanyocytes 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; tanyocyte; GH; IGF-1; neuroinflammation

1. Introduction

The somatotropic 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 hypophysial 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, tanyocytes, 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 overexpressing GH, as these mice present increased serum levels of both GH and IGF-1. Transgenic mice overexpressing 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<sup>−/−</sup>) 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<sup>−/−</sup> 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<sup>−/−</sup> 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 (tanyocyte 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<sup>AGHR</sup> mice). Albumin<sup>AGHR</sup> 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<sup>−/−</sup> 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, GH 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].

GH 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 increased 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.

Martinez-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-
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 Tanyctyes

Tanyctyes 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 tanyctyes described: α1, α2, β1, and β2. These subdivisions allow differentiation of the morphology, location, projections, and functions of these cells. For example, β-tanyctyes present barrier properties, whereas this characteristic is absent in α-tanyctyes. They also have distinct mechanisms to transport molecules, among other functions [78].

Tanyctyes are part of the median eminence (ME) barrier, together with endothelial cells. In this strategically placed structure, tanyctyes 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, tanyctyes can also modulate important hypothalamic functions, such as metabolism and reproduction [79].

I.c.v. injection of IGF-1 increases the proliferation of tanyctyes in the hypothalamus of rats [80]. Some tanyctyes can act as neuronal progenitors in the postnatal hypothalamus [81], so IGF-1 acts through tanyctyes to promote adult neurogenesis. Conversely, IGF-1 knockout in hypothalamic stem or progenitor cells increases α-tanyctye 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 tanyctyes deserves more attention, as it seems to regulate adult hypothalamic neurogenesis.

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

---

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

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

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

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 tanyocyte communication with hypothalamic neurons.

In conclusion, the GH axis plays an important role in supporting neuralglial cells. However, we also highlighted several mechanisms that remain to be elucidated, such as the specific role of GH in oligodendrocyte myelination and tanyctic 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 Cientifico e Tecnologico (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


[31] Åberg D. Role of the growth hormone/insulin-like growth factor 1 axis in neurogenesis. EndoCRINE Development. 2010; 17: 63–76.


Mason JL, Xuan S, Dragatis I, Efstatiadis 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.


