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GROWTH HORMONE, INSULIN-LIKE GROWTH FACTOR-1 AND THE AGING BRAIN

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Abstract

Growth hormone (GH) and insulin-like growth factor (IGF)-1 regulate the development and function of cells throughout the body. Several clinical diseases that result in a decline in physical and mental function are marked by mutations that disrupt GH or IGF-1 signaling. During the lifespan there is a robust decrease in both GH and IGF-1. Because GH/IGF-1 are master regulators of cellular function, impaired GH and IGF-1 signaling in aging/disease states leads to significant alterations in tissue structure and function, especially within the brain. This review is intended to highlight the effects of the GH and IGF-1 on neuronal structure, function, and plasticity. Furthermore, we address several potential mechanisms through which the age-related reductions in GH and IGF-1 affect cognition. Together, the studies reviewed here highlight the importance of maintaining GH and IGF-1 signaling in order to sustain proper brain function throughout the lifespan.

Introduction

Growth hormone (GH) and insulin-like growth factor (IGF)-1 have a critical role in cell proliferation, stress resistance and survival in many cell types throughout the body. Although there are numerous studies that detail the peripheral effects of GH and IGF-1 deficiency and replacement on tissue function, the effects of these hormones on the brain have received less attention. Within the CNS, there are robust expression GH and IGF-1 receptors (Bondy et al. 1992; Lobie et al. 1993), suggesting that neurons, glia and/or the cerebrovasculature are critical effector tissues for GH/IGF-1 signaling. Considering the numerous potential actions of these hormones, it is not surprising that impairments in GH and IGF-1 signaling are associated with a variety of effects on brain structure and function. In this review, we provide an overview of the effects of circulating and GH and IGF-1 on neuronal structure and function. Previous reviews from our laboratory have explored the effects of these hormones on the cerebrovasculature (Sonntag et al. 2013; Sonntag et al. 2000b).

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Sources of GH and IGF-1 in the CNS and circulation

Growth hormone is secreted in a pulsatile manner by somatotrophs within the anterior pituitary gland in response to GH-releasing hormone and somatostatin secreted from hypothalamic neurons into the hypophyseal portal vessels that connect to the pituitary gland. GH affects a variety of cells throughout the body, including neurons and glial cells within the CNS. Although the mechanism by which GH crosses the blood brain barrier is not fully-understood, previous studies have shown that injection of exogenous GH leads to rapid accumulation of the hormone in the parenchyma of the brain (Pan et al. 2005). The release of GH into the circulation also leads to the production of IGF-1 within the liver, which subsequently enters the bloodstream and readily crosses the blood brain barrier into the CNS (Armstrong et al. 2000; Carro et al. 2000; Reinhardt and Bondy 1994). Studies using Fisher 344 x Brown Norway hybrid rats (F344BN) at different ages ranging from adolescence to advanced age demonstrate that IGF-1 levels in circulation and the cerebrospinal fluid (CSF) both decrease with age (Figure 1A); in fact, there is a positive association between IGF-1 in circulation and the CSF ($R^2 = 0.524$, $p < 0.02$). This correlation is likely explained by uptake through a blood-CSF route (Carro et al. 2000). Circulating IGF-1 has been shown to cross into the brain following activation of the IGF-1 receptor (Yu et al. 2006), as well as through the membrane multicargo transporter megalin/low-density lipoprotein receptor-related protein-2 (LRP2) (Carro et al. 2005). LRP2-mediated transport has contributed to exercise-induced increases in brain IGF-1 levels (Carro et al. 2005) and has been shown to be attenuated by both aging (Carro et al. 2005) and a western style diet (Dietrich et al. 2007). Neuronal activity induced by electrical, sensory or behavioral stimulation, has also been shown to drive IGF-1 transport into the brain through other vascular beds by promoting matrix metalloproteinase-9 activity and cleaving IGFBP3 - allowing free IGF-1 to enter the CNS (Nishijima et al. 2010). Thus, both circulating GH and IGF-1 enter the brain and have the potential to regulate neuronal function.

In addition to growth factors derived from the circulation, neurons, glia and vasculature have the ability to produce growth factors that support surrounding tissues. Although it is unclear whether the brain produces physiologically relevant concentrations of GH, substantial amounts of IGF-1 are synthesized within the brain. When circulating IGF-1 levels are decreased by genetic manipulations or increased by systemic replacement, IGF-1 levels within the brain are modified by approximately 30% respectively (Mitschelen et al. 2011; Yan et al. 2011). Thus, despite the relatively high concentration of IGF-1 in the sera, the majority of IGF-1 within the brain is produced in a paracrine manner (Bondy et al. 1992). Although the importance of circulating IGF-1 for regulating brain function is well-established, the regulation and role of locally produced IGF-1 has received little attention. The importance of this pathway is detailed in the Ames Dwarf model of GH/IGF-1 deficiency. In this model, severe deficits in circulating IGF-1 do not produce cognitive deficits as would normally be expected based on our understanding of the role of IGF-1 in brain function. However, analysis of brain levels of IGF-1 in these animals demonstrates a substantial increase in IGF-1 levels compared to control animals that can only be derived from brain production of IGF-1 (Sun et al. 2005). This study provides important data

suggesting that the production of IGF-1 by the brain is a highly regulated process and is most likely an essential aspect of maintaining normal brain function.

The GH/IGF-1 axis and age

Early in development and during adolescence, high levels of GH/IGF-1 are critical for the growth of somatic cells. Levels of GH and IGF-1 remain low throughout childhood and around adolescence the amplitude of growth hormone pulses increase. The elevated high amplitude GH pulses result in increased concentrations of circulating IGF-1. With increasing age in both humans and rodent models, GH secretion declines resulting in a decrease in circulating IGF-1 (Bando et al. 1991; Corpas et al. 1993; Frutos et al. 2007; Rudman et al. 1981; Sonntag et al. 1990). In fact, the levels of circulating GH are almost negligible in human patients over the age of 60 years (Corpas et al. 1993). Considering that hepatic IGF-1 production is regulated by GH, it is not surprising that IGF-1 levels are decreased with age in humans and animal models of human aging (Muller et al. 2012; Niblock et al. 1998; Smith et al. 1989). In the F344xBN rat for example, IGF-1 protein levels show age-dependent decreases both in the circulation and in the brain (Figure 1A). Coinciding with protein levels, mRNA levels of IGF-1 decrease in the liver as well as brain with age (Figure 1B). Interestingly, transcription of the IGF-1 receptor in the brain increases with age (Figure 1B), suggesting a potential attempt at compensation in receptor levels when IGF-1 decreases. Even though the capacity for uptake of IGF-1 into the CSF after intraperitoneal injection has been shown to increase in aged mice compared to young controls (Muller et al. 2012), we have observed that basal CSF levels of IGF-1 continue to decrease with age (Figure 1A). In addition to a reduction in IGF-1 levels, IGF binding proteins that regulate IGF-1 activity at the cellular level show differential transcriptional alterations with age in the hippocampus (Figure 1C). These data provide clear support for the conclusion that both endocrine and paracrine IGF-1 trophic support for the brain decreases with age.

Childhood-vs. adult-onset GH/IGF-1 deficiency

Despite the dramatic increases in GH and IGF-1 during adolescence, the significance of this increase for development of normal brain function in adults is poorly understood. Despite this lack of information, it is known that GH deficiency at different stages of life results in unique clinical symptoms. For example, GH and IGF-1 deficiency during adolescence results in reduced muscle mass and bone growth and this can be reversed by administration of GH. It is becoming clearer that complete development of adult bone density and muscle mass continues into early adulthood, therefore continuing GH treatment during the “transition years” after adolescence appears to be necessary. In rodent models, reduced levels of GH and IGF-1 during early life result in insulin insufficiency since adequate levels of these hormones are necessary for development of pancreatic beta cells (Carter et al. 2002). In addition, reproductive function (number of offspring, regularity of cycles and the length of the reproductive competent period) is compromised in the presence of GH and IGF-1 deficiency (Sonntag et al. 2005a).

It has been recognized for some time that GH/IGF-1 deficiency in adults is associated with increased cardiovascular risks. GH deficient adults have abnormal lipoprotein profiles (Cuneo et al. 1993), impaired cardiac function (Cuocolo et al. 1996), and impaired insulin tolerance (Johansson et al. 1995), which can be improved by GH treatment. In GH deficient patients, GH replacement has a favorable effect on endothelial t-PA release and fibrinolysis capacity, likely to account for their decreased vascular complications (Miljic et al. 2013). In patients with adult-onset GH deficiency in response to pituitary irradiation, higher cardiovascular risk at baseline was reversed by 10-years of GH replacement (Elbornsson et al. 2013). Similarly, Lewis dwarf rats with early-onset GH/IGF-1 deficiency have a greater incidence of intracranial hemorrhage (Sonntag et al. 2005a). However, GH supplementation specifically during adolescence (followed by adult-onset GH deficiency) did not reduce the overall incidence but was able to significantly delay the onset of hemorrhage contributing to their prolonged lifespan (Sonntag et al. 2005a). Based on these studies, it appears that GH and IGF-1 have an 'organizational' action early during the lifespan that influences cellular function and tissue development and a 'regulatory' function on numerous tissues after development is complete. Unfortunately, no clear scientific investigations have been undertaken to address the significance of the dramatic rise in GH and IGF-1 during adolescence. The effects of adult-onset GH and IGF-1 deficiency have been addressed in several studies but our understanding of the effects of this deficiency on health and the onset of disease is far from complete.

GH/IGF-1 Regulation of Neuronal Development, Structure, and Function

It is well accepted that GH and IGF-1 signaling are critical for proper development and function of many major organ systems. As reviewed in (Aleman and Torres-Aleman 2009), there are numerous studies supporting a critical role for IGF-1 in normal brain development and function. Clinical studies have shown that point mutations in both the IGF-1 and IGF-1R genes result in decreased IGF-1 signaling and lead to microcephaly and mental impairment (Abuzzahab et al. 2003; Bonapace et al. 2003; Gannage-Yared et al. 2013; Juanes et al. 2014; Netchine et al. 2009; Walenkamp et al. 2005; Woods et al. 1996). These patients often exhibit significant delays in psychomotor function and hearing loss (Bonapace et al. 2003; Walenkamp et al. 2005). Studies using animal models also emphasize the importance of IGF-1 signaling for brain development. Homozygous deletion of both IGF-1 and IGF-1R results in >90% lethality (Liu et al. 1998; Liu et al. 1993; Powell-Braxton et al. 1993a; Powell-Braxton et al. 1993b). While this is most likely the consequence of respiratory failure, both IGF-1 and IGF-1R knockout mice exhibit central nervous system deficits compared to control animals. This includes reduced brain size, loss of myelination, and a loss of specific parvalbumin-containing neurons (Beck et al. 1995). The animals also exhibit pronounced histomorphological changes within the nervous system (Liu et al. 1993). Neuron-specific deletion of IGF-1R results in severe microcephaly and behavioral deficits similar to those observed in human patients (Kappeler et al. 2008). Additionally, IGF-1 knock-out mice exhibit hearing loss similar to the changes observed with clinical IGF-1 and IGF-1R mutations (Cediel et al. 2006). Thus, the effects of reduced or absent IGF-1 signaling during development support an important role of these hormones in the development and organization of the central nervous system.

Alterations in GH signaling also lead to developmental deficits within the central nervous system. Similar to IGF-1 deficiency, patients presenting with GH deficiency have been shown to exhibit microcephaly (Dacou-Voutetakis et al. 1974). Furthermore, patients with Laron dwarfism, an autosomal recessive disease characterized by insensitivity to GH, exhibit cognitive deficits that range from mild to severe (Shevah et al. 2005). The severity of the cognitive impairment is correlated with pronounced structural abnormalities within the brain (Shevah et al. 2005). The general conclusion is that the effects of GH deficiency are mediated by a loss of circulating IGF-1. However, the direct actions of GH signaling within mouse models are not as clear as IGF-1. Absolute brain size is reduced in GH receptor knock-out mice (Ransome et al. 2004); yet, when normalized to body weight, this effect is lost (Ransome et al. 2004). When examining histological changes, it is evident that certain areas of the brain, including the hippocampus, are significantly smaller in the GHR knock-out mice compared to wild-type controls (Ransome et al. 2004). Surprisingly, these reductions in hippocampal size have not been reported to impact learning and memory, since the Ames dwarf mice (lacking GH, TSH and prolactin) and the GHR knock-out mice perform as well as wild-type controls in learning tasks that access specific cognitive domains (Kinney et al. 2001a; Kinney et al. 2001b). Interestingly, aged GHR knock-out mice appear to perform better than wild-type controls (Kinney et al. 2001a; Kinney et al. 2001b). Since the GHR knockout mice live longer than controls, one interpretation is that improvements in learning and memory in these animals represent a substantial delay in brain aging (Brown-Borg et al. 1996; Coschigano et al. 2003). Nevertheless, there are critical questions related to the motivational components of the tasks and the specific behavioral tests that have been conducted to assess learning and memory. Whether these studies adequately assess specific cognitive domains that are relevant to humans remains an open question, and further research on this topic is crucial to assess the effects of GH and/or IGF-1 deficiency on aging.

Post-adolescence, GH and IGF-1 remain important regulators of neuronal structure and function. As mentioned, circulating levels of GH and IGF-1 decrease considerably with age (Sonntag et al. 2005b). In fact, GH and IGF-1 levels are reduced by 30–60% in the elderly (Florini et al. 1985; Johanson and Blizzard 1981; Rudman et al. 1981). This decrease is temporally-associated with the appearance of cognitive impairment and supplementation of IGF-1 has been shown to reverse this deficit (Arwert et al. 2006; Deijen et al. 2011; Deijen et al. 1998; Sonntag et al. 2005b; Trejo et al. 2007; van Dam et al. 2000). On a cellular level, when IGF-1 is reduced, neurons exhibit decreased structural complexity and impaired long-term potentiation (Cheng et al. 2003; Glasper et al. 2010; Maher et al. 2006; Scolnick et al. 2008; Trejo et al. 2007). Not surprisingly, exogenous application of IGF-1 leads to increased neuron complexity (multiple spine boutons) within the hippocampus as well as enhanced excitability and long-term potentiation (the molecular correlate of learning) (Bozdagi et al. 2013; Maher et al. 2006; Molina et al. 2013; Shi et al. 2005; Trejo et al. 2007). Moreover, intracerebroventricular replacement of IGF-1 to aged rats to the levels observed in young animals enhances spatial memory performance (Markowska et al. 1998).

Similar to IGF-1, growth hormone-releasing hormone (GHRH) or GH supplementation leads to significant improvements in a variety of learning and memory tasks (Kwak et al. 2009; Le Greves et al. 2006). Injection of GHRH beginning at 9 months of age, which

subsequently restores circulating GH and IGF-1 levels, prevents the age-related decline in cognitive performance (Thornton et al. 2000). In addition, several studies have reinforced the concept that early intervention to restore GH can lead to long-term benefits. Within the Lewis Dwarf rat, early GH supplementation reversed the spatial memory deficits normally exhibited later in life (Nieves-Martinez et al. 2010b). The enhancement of learning and memory with GH is mechanistically similar to that with IGF-1 administration and is likely mediated by an increase in excitability/long-term potentiation, a cellular manifestation of learning and memory (Le Greves et al. 2006; Mahmoud and Grover 2006; Molina et al. 2012; Molina et al. 2013; Park et al. 2010). Finally, GH replacement during adolescence for only 10 weeks followed by adult-onset GH deficiency improved learning and memory at 18 months of age compared to animals that received no supplementation (Nieves-Martinez et al. 2010a). Together, these studies provide multiple lines of evidence that GH and IGF-1 are key regulators of neuronal structure and function throughout an animal's lifespan. Reduced GH and IGF-1 levels during early life can impair proper brain development, thereby leading to cognitive deficits, while a post-developmental loss of GH and/or IGF-1 can alter neuronal structure as well as excitability, thereby impairing learning and memory. Moreover, restoring GH/IGF-1 signaling at specific stages of lifespan can positively affect cognition potentially through specific mechanisms that are yet to be identified.

Mechanisms of IGF-1 action on the aging brain: IGF-1 Regulation of the N-methyl-D-aspartate (NMDA) receptor, synaptic plasticity

Although the specific molecular actions of IGF-1 that contribute to improved cognitive performance in aged animals remain unknown, a series of recent studies provide strong evidence that synaptic morphology and function is regulated by IGF-1. In pyramidal neurons, Shi et al. quantified total synaptic profiles as well as synaptic profiles in multiple spine bouton (MSB) complexes in the CA1 region of the hippocampus and determined the postsynaptic density (PSD) length (Shi et al. 2005). The results indicated a decrease in total synapses between middle and old age but maintenance of PSD length and MSB synapses (Shi et al. 2005). IGF-1 infusion to old animals did not reverse the aging-related decline in total synapses but did increase PSD length and the number of MSB synapses. These changes appear to be morphological correlates of enhanced synaptic efficacy and suggest that aging and IGF-1 affect different, but complementary, aspects of synaptic function in the CA1 region of the hippocampus.

In addition to morphology of the synapse, age-related cognitive decline may be mechanistically associated with a reduction in synaptic function, which has been reported to be essential for neuronal excitability due to altered expression of synaptic proteins, including the NMDA receptor. The NMDA receptor is a key synaptic protein that has been shown to be differentially regulated in aging (as reviewed by (Magnusson 2012; Magnusson et al. 2010)). It is critical for establishing an action potential in neurons and maintaining expression of LTP at the Schaffer collaterals, which are important in hippocampal dependent learning and memory (Collingridge et al. 1983; Kauer et al. 1988; Morris et al. 1986). Based on these results, impairments in the expression and regulation of the NMDA receptor have been proposed to lead to significant alterations in learning and memory. The functional

NMDA receptor is a tetramer composed of different subunits including GluN1, GluN2A-D, or GluN3A-D. Within the hippocampus, the NMDA complex is often composed of two GluN1 subunits and either two GluN2A or two GluN2B subunits (Monyer et al. 1994). Previous results indicate that there are differential age-related changes in GluN1, GluN2A, and GluN2B (as previously reviewed (Magnusson 2012)). While GluN1 has not been reported to decrease, several studies suggest that expression of GluN2B significantly decreases with age (Magnusson et al. 2002; Molina et al. 2012; Sonntag et al. 2000a). Importantly, overexpression of GluN2B rescues the age-related cognitive deficits in aged mice (Brim et al. 2013), suggesting that the loss of the subunit underlies age-related impairments in learning and memory. The age-related changes in GluN2A are not fully understood, as studies have shown conflicting changes in the expression of GluN2A with advanced age (Magnusson et al. 2002; Molina et al. 2012; Sonntag et al. 2000a).

One potential mechanism underlying the age-related changes in NMDA receptor signaling may be the reductions in GH and IGF-1 that occur during aging. Consistent with this concept, our laboratory has previously shown that supplementation of IGF-1 in aged rats can restore the age-related alterations in GluN2A/GluN2B expression (Sonntag et al. 2000a). These findings are further supported by studies that show exogenous GH and IGF-1 increase the expression of the NMDAR subunits (Le Greves et al. 2005; Le Greves et al. 2002; Le Greves et al. 2006). Furthermore, it is possible that GH and IGF-1 regulate signaling pathways that alter NMDAR trafficking and insertion in the membrane (kinesin motor proteins such as KIF17), kinetics of channel opening/availability (kinases such as CaMKII), and protein recycling (endocytic proteins such as clathrin-coated pit protein AP2).

To date, there are no studies that address these potential interactions even though this may be an important component of age-related cognitive decline and part of the mechanisms of action of IGF-1. As a result, further studies are necessary to better understand the specific mechanisms through which aging and GH and/or IGF-1 affect NMDA receptor function.

Concluding remarks

GH and IGF-1 are critical regulators of structure and function within the nervous system. Several deficits in behavior are associated with a reduction in GH and IGF-1 signaling including, but not limited to, impaired cognition. At the cellular level, the loss of GH and IGF-1 leads to impaired neuronal excitability, along with changes in synaptic proteins including the NMDA receptor. Separate roles for GH and IGF-1 on brain function have not been well-established, but evolving data suggest that these hormones may exert unique effects during different stages of the lifespan. While the studies highlighted in this review were essential for establishing the groundwork in understanding the effects of the GH and IGF-1 axis in the brain, there is still much work required to identify the molecular mechanisms that are responsible for the actions of these hormones on brain function.

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Highlights

- Levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) decrease with age.
- Several aspects of neuronal development, structure, and function are regulated by GH/IGF-1.
- Age-related reductions in GH/IGF-1 negatively affect cognition.
- Maintaining GH and IGF-1 signaling may be beneficial for maintaining brain function in aging.

Figure 1. Age-dependent changes in IGF-1 signaling

Average levels of protein (A) and mRNA (B-C) of the IGF-1 signaling proteins at various ages in F344 x BN rats. Data is normalized to the 3 month baseline and represented as mean $\pm$ SEM (n=16–40). * indicates significant difference compared to 3 month control, *p<0.05.