

Review

Growth hormone and insulin-like growth factor-1 (IGF-1) and their influence on cognitive aging

William E. Sonntag^{a,b,c,*}, Melinda Ramsey^a, Christy S. Carter^c

^a *Department of Physiology and Pharmacology, Wake Forest University Health Sciences,
1 Medical Center Blvd., Winston-Salem, NC 27157-1083, USA*

^b *Roena Kulynych Center for Memory and Cognition Research, Wake Forest University Health Sciences,
1 Medical Center Blvd., Winston-Salem, NC 27157-1083, USA*

^c *Sticht Center on Aging, Wake Forest University Health Sciences, 1 Medical Center Blvd.,
Winston-Salem, NC 27157-1083, USA*

Received 13 January 2005; accepted 22 February 2005

Abstract

The concept that growth hormone and IGF-1 are required for normal development of the mammalian body and, more recently the brain, is supported by a vast experimental literature. IGF-1 crosses the blood–brain barrier and in recent years, much attention has focused on age-related decreases in serum growth hormone and IGF-1 as potential mechanisms that may influence cognitive function in the elderly. However, interventional studies are needed to establish a definite link between these hormones and function of the aging brain. In rodents, long-term growth hormone/IGF-1 replacement improves learning and memory in aged rats. While the exact mechanism underlying these cognitive improvements is unknown, growth hormone and IGF-1 replacement to aged animals increases neurogenesis, vascular density, and glucose utilization, and alters NMDA receptor subunit composition in brain areas that are implicated in learning and memory. While these observations offer valuable insight into the influence of growth hormone and IGF-1 on neuronal events in the aged mammal, additional functional studies are required to link these changes to cognitive improvements.

© 2005 Elsevier Ireland Ltd. All rights reserved.

Keywords: Growth hormone; NMDA receptor; Blood–brain barrier; IGF-1; Aging

1. Introduction

Growth hormone and its anabolic mediator, insulin-like growth factor-1 (IGF-1), have long been recognized for their critical roles in mammalian growth and development.

* Corresponding author. Tel.: +1 336 716 8605; fax: +1 336 716 8501.
E-mail address: wsonntag@wfubmc.edu (W.E. Sonntag).

However, these hormones affect numerous organ systems and participate in diverse processes such as wound healing and glucose homeostasis. Numerous studies have focused on the potential roles of growth hormone and IGF-1 in brain development, neurogenesis, and neuroprotection. Only recently, however, have scientists explored the possible benefits of growth hormone and IGF-1 to the aging brain. This chapter is focused on the potential mechanisms by which upregulation of the growth hormone/IGF-1 axis improves learning and memory in aged rodents and humans.

2. The growth hormone/IGF-1 axis

Pure bovine growth hormone was first isolated from the pituitary gland by Li et al. (1945) and was subsequently shown to stimulate fatty acid metabolism and amino acid uptake, as well as DNA, RNA and protein synthesis (Corpas et al., 1993; Finkelstein et al., 1972). These actions contribute to its regulatory role in cell division and tissue growth, and, with the exception of fatty acid metabolism, occur via the anabolic mediator insulin-like growth factor-1 (IGF-1). In humans, growth hormone is released in pulsatile bursts from the pituitary gland with the majority of secretion occurring nocturnally in association with slow-wave sleep (Corpas et al., 1993; Born et al., 1988; Tannenbaum and Martin, 1976). Similar pulses are observed in rodents, except that high-amplitude secretory pulses occur every 3.5 h in males (Tannenbaum and Martin, 1976) and hourly in females (Saunders et al., 1976). Regulation of these pulses involves at least two hormones released by the hypothalamus: growth hormone-releasing hormone (GHRH) which increases growth hormone release (Brazeau et al., 1973) and somatostatin, which inhibits its release (Lanzi et al., 1994). It is generally believed that somatostatin tone is dominant during trough periods, whereas when somatostatin is suppressed, growth hormone is released in response to secretion of GHRH (Tannenbaum and Martin, 1976). The dynamic interactions between these hormones are responsible for high amplitude, pulsatile growth hormone secretion. Although the precise function of this ultradian pattern remains unknown, the pulsatile nature of growth hormone release has been confirmed in every species examined to date and appears to be essential to optimize biological potency of the hormone. Both growth hormone and IGF-1 inhibit growth hormone release in a typical negative feedback manner either at the level of the pituitary or indirectly via stimulation of somatostatin and inhibition of GHRH release from the hypothalamus (Berelowitz et al., 1981).

Upon release from the anterior pituitary, growth hormone binds with high affinity to the growth hormone receptor found in tissues throughout the body (Fig. 1). Plasma growth hormone is carried by a growth hormone binding protein which is homologous to the cleaved extracellular domain of the growth hormone receptor (Zhou et al., 1997). Activation of the growth hormone receptor initiates the JAK-STAT signal transduction pathway commonly utilized by cytokine receptors (Roupas and Herington, 1989). Many other intracellular proteins are subsequently phosphorylated, including protein kinase C (PKC), mitogen-activated protein kinase (MAPK), insulin receptor substrate (IRS) proteins, and the signal transducers and activators of transcription (STAT) proteins (Gent et al., 2003). The result of growth hormone receptor activation is an increase in *c-fos*, *c-jun*, serine phosphatase inhibitor-1, IGF-1 gene expression, and finally, IGF-1 synthesis and

Download English Version:

<https://daneshyari.com/en/article/10736659>

Download Persian Version:

<https://daneshyari.com/article/10736659>

[Daneshyari.com](https://daneshyari.com)