The Role of Insulin-like Growth Factor-1

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The anterior pituitary also referred to as the adenohypophysis, originates from the oral ectoderm during embryonic development. It is enclosed by a network of blood capillaries originating from the hypothalamus, as a part of the hypophyseal portal system, responsible for transporting hormones from the hypothalamus to the anterior pituitary and from the anterior pituitary to the circulatory system. Hence, the hypophyseal portal system prevents hypothalamic hormones from entering directly into the circulation..

Keywords: IGF-1 singalling ; growth hormone ; GHRH ; energy expenditure ; adipose tissues physiology

1. Introduction

The neuroendocrine system (NES) is composed of a mixture of specialized cells, which are mainly neuro-peptidergic neurons, located in four hypothalamic nuclei, and capable of secreting neurohormones directly into the bloodstream through the hypophyseal portal blood system [1]. The NES in mammals plays a major role in regulating body growth and reproduction as well as metabolic activity. The hypothalamus, located in the lower region of the diencephalon, is considered the primary source for regulation of the axis producing neural hormones targeting pituitary cells to support multiple biological and physiological activities [2]. Growth Hormone (GH) is a master regulator hormone produced in somatotroph cells and plays a major role in somatic development. The counter-regulatory effects of hypothalamic growth hormone-releasing hormone (GHRH) and somatostatin (SST) primarily regulate GH expression and release, respectively [3]. Additional regulatory mechanisms have been identified, including the peripheral signal, insulin-like growth factor 1 (IGF-1), which is the topic of this entry.

IGF-1 feedback regulation of GH production has been demonstrated by pharmacologic interventions and in genetically modified mouse models [3][4]. IGF-1 is a polypeptide hormone mainly produced in the hepatocytes and exerts its effect through high-affinity binding to the IGF-1R, located on the cell surface of target tissues [5]. IGF-1 affects a wide variety of biological activities such as somatic cell development, cell differentiation, cortical neuronal activity, regulation of brain development, and is involved, directly and indirectly, in longevity [6][7][8][9][10][11]. Interestingly, IGF-1 has a very potent physiological effect in vivo; however, its effects in vitro are relatively weak unless other hormones or growth factors are present [5]. This mechanism is important to examine and correlate the IGF-1 biological effect in the appropriate tissue and at any specific point in time [5]. Several laboratories, including ours, have identified the key roles of IGF-1 as a major negative regulator of GH production, resulting in a modulation of the growth-related effects of GH [10][12]. Models designed to study IGF-1 modulation of GH synthesis and secretion are associated with a disruption in either downstream signaling or embryologic development of the GH/IGF axis. This review discusses the role of IGF-1 in regulating the GH-axis in somatic growth and metabolic homeostasis. We will present genetically modified mouse models with deletion of the IGF-1 receptor (IGF-1R) in hypothalamic GHRH neurons and somatotrophs that reveal novel mechanisms controlling adipose tissues physiology and energy expenditure.

2. The Hypothalamus and Pituitary Gland Axis

The hypothalamic-pituitary axis is a complex, yet, well-defined entity that integrates neuronal and hormonal signals to maintain mammalian growth and somatic development [13]. The hypothalamus is a key regulatory tissue integrating the nervous and the endocrine system to support biological and physiological activities that include reproduction, somatic development, energy balance, and metabolic homeostasis [14][15]. The hypothalamus is strategically located in the lower part of the diencephalon of the brain receiving differentiating signals from other brain areas and, as a consequence, is responsive to environmental signals [14][15]. The hypothalamus communicates with the pituitary gland through two main pathways. First, the neurosecretory cells synthesize hormones, such as oxytocin (OT) and vasopressin or antidiuretic hormone (ADH), that are transported directly to the posterior pituitary gland by axons. Hormones that control the anterior pituitary gland are synthesized and stored in the neuroendocrine cells in the hypothalamus and transported to the anterior

lobe through the hypophyseal portal system [7]. The pituitary gland, located at the base of the brain in the sella turcica, is connected to the hypothalamus by the pituitary stalk (infundibulum) [15]. The pituitary gland has two main regions, the anterior pituitary, and the posterior pituitary, responsible for synthesizing nine hormones that govern essential physiological activities.

The anterior pituitary also referred to as the adenohypophysis, originates from the oral ectoderm during embryonic development [16]. It is enclosed by a network of blood capillaries originating from the hypothalamus, as a part of the hypophyseal portal system, responsible for transporting hormones from the hypothalamus to the anterior pituitary and from the anterior pituitary to the circulatory system. Hence, the hypophyseal portal system prevents hypothalamic hormones from entering directly into the circulation. [13]. The seven hormones produced from the anterior pituitary gland: GH, prolactin (PRL), thyroid-stimulating hormone (TSH), melanin-stimulating hormones (MSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) [16]. The hormones produced from the anterior pituitary are referred to as trophic hormones because they exert their biological activities on the other endocrine tissues. Anterior pituitary hormone production is tightly controlled by the regulatory hormones produced from the hypothalamus, which may be stimulatory or inhibitory [3][17][18].

The posterior pituitary lobe originates from neuro-epithelia cells and is therefore referred to as the neurohypophysis. It is anatomically and structurally differentiated from the anterior lobe of the pituitary gland [19]. The posterior lobe consists of neuro-glial cells and nerve fibers extending from the hypothalamus and is considered an extension of the brain [13]. The two hormones secreted by the posterior lobe of the pituitary gland, OT and ADH, are produced by neurosecretory cells in the hypothalamus and transported through the cell axons to be stored in the posterior lobe, from which they are secreted into the circulation system by neuronal signals from the hypothalamus [19].

3. IGF-1 and the IGF-1 Receptor

In 1978 Rinderknecht and colleagues at the University of Zurich isolated circulating factors with insulin-like activities, which could be distinguished from insulin by their lack of cross-reactivity with insulin antibodies. Their growth-promoting activity was demonstrated when chemically defined media was supplemented with these factors at low concentrations in vitro. These substances were termed IGF-1 and 2 based on their structural homology with insulin [20]. The same group provided the primary structure and the amino acid sequences of the IGFs.

IGF-1 is a polypeptide hormone with high structural homology with insulin and binds with high affinity to the IGF-1R, activating both the mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinases PI3K signaling pathways in target tissue [6][21]. IGF-1 is mainly produced from liver hepatocytes, and its production and release are primarily controlled by GH [5]. IGF-1 is also expressed in nearly every tissue in the body and plays a pivotal role in regulating a wide variety of bioactivities such as cell proliferation, differentiation, and survival [6][7]. GH/IGF-1 levels dramatically decrease with age, suggesting that a reduction in IGF-1 biological activity is associated with age-related changes to the organism [7].

Using multiple experimental methodologies, including in vivo and in vitro models, IGF-1 has been shown to possesses potent bioactivity to induce cell growth and differentiation of targeted tissues [5]. Despite the similarity between IGF-1 and insulin, insulin plays a major in regulating short-term anabolic activities such as mediating glucose homeostasis and lipid and protein synthesis, while IGF-1 primarily mediates long-term action including cell fate and survival [5]. IGF-1 exerts it is biological activities by binding to the IGF-1R on target tissues [18]. The IGF-1R is a tetrameric glycoprotein-tyrosine kinase receptor, consisting of two extracellular α subunits and two intracellular β subunits that facilitate downstream signals transduction [22][23]. The binding of the IGF-1 ligand to the receptor on the cell surface leads to the activation of two major pathways (MAP) kinase and the PI3 kinase to regulate the IGF-1 response on target tissues [24][25]. In addition, several isoforms of IGF-1 bind to acid-labile subunits (ALS) to mediate ligand/receptor complex formation [26]. IGF-1 has a very short half-life. Therefore, its biological activities are regulated in a spatiotemporal manner to control IGF- 1/IGF-1R levels in the circulation [27][28][29]. Insulin-like growth factor-binding proteins (IGF-1BPs), described initially as free serum carriers, are abundantly expressed in most tissues and play a major role in mediating the biological activities of IGF-1 through autocrine/paracrine modes of action [27]. IGF-1BPs have been shown to inhibit the action of IGF-1. However, several recent studies have demonstrated an up-regulatory mode of action by unclear mechanisms [27][28]. Despite the high structural homology of IGF-1 with insulin, the IGF-1BPs bind exclusively to IGF-1 [27]. Recently, several members of the IGF-1BP family have been shown to regulate other physiological activities in an IGF-independent mechanism including, interaction with other proteins in the extracellular and intracellular space, and mediate the interactions of other growth factor pathways such as transforming growth factor-beta (TGFβ) and epidermal growth factor (EGF) [27]. In humans, more than 99 % of circulating IGF-1 is found to be combined with IGF-1BPs with a relatively prolonged half-life (15 h) compared to unbounded IGFs (10–12 min) [30][31].

A prior study in rodents has shown that food restriction during the early postnatal period (lactation) caused permanent growth retardation and later metabolic changes correlated with lower serum IGF-1 levels compared to the normally fed pups [32]. In the normally fed pups, IGF-1 preferentially stimulates GHRH-neurons growth through two main pathways, PI3K/AKT and ERK/MEK, with a higher contribution of the PI3K/AKT pathway [33]. GHRH-neurons harvested from underfed pups showed a reduction in the GHRH growth, inhibition of axon elongation, which causes lower innervation of the median eminence by the GHRH axon and becomes insensitive to the growth-promoting effects of IGF-1 compared to the age-matched normally fed pups. This loss of function does not involve changes in IGF-1R and ERK/MEK rather is caused by a defect in the AKT activation pathway [33]. IGF-1 is synthesized and produced by almost all tissues and plays a fundamental role in cell differentiation, cell growth, and development [34][35]. In vivo studies using cell-specific Igf-1 gene knockout mice showed that almost 75% of circulating IGF-1 is produced by the liver, which is responsive to somatotropic GH [36][37]. GH binding to the hepatic GH receptor (GHR) stimulates the production and release of IGF-1 peptides into the circulation [36][38]. IGF-1 exerts its biological effects by binding to the IGF-1R on target tissues [35]. The bioavailability and physiological effects of IGF-1 are regulated by a group of secreted proteins known as IGF-1BPs, which bind with high affinity to IGF-1 to act as transport proteins for circulating IGF-1 [39]. The studies using cell-specific Igf-1 gene knockout mice have demonstrated that locally produced IGF-1 is more effective than systemic IGF-1 in the control of various biological activities, including somatic cell development, cell differentiation, central nervous system (CNS) development, and embryonic development [6][36][40][41]. In addition to the liver, many other organs and tissues produce IGF-1. These non-hepatic derived, autocrine and paracrine forms of IGF-1 bind to IGFBPs with lower affinity than hepatic IGF-1.

4. IGF-1 and IGF-1R Expression in Neuroendocrine Tissues

In rodents, mRNA expression of IGF-1, IGF-2, and IGF-1R was found during early embryonic development and in the adult by in situ hybridization. The IGF-1R gene has a uniform, stable pattern of expression and distribution in all neuroepithelial cell lineages [42]. High levels of IGF-1R and IGF-1 gene expression were observed in the sensory and cerebellar projection of neurons during late postnatal development [42]. In the cerebral cortex and during hippocampal formation, IGF-1 and the IGF-1R are present in specific cell populations; IGF-1R mRNA is highly expressed in the pyramidal cells in Ammon's horn, in granule cells in the dentate gyrus, and pyramidal cells in lamina VI of the cerebral cortex [42]. On the other hand, IGF-1R mRNA is expressed in isolated medium- to large-sized cells randomly distributed throughout the hippocampus and iso-cortex [42]. In addition, the IGF-1R and IGF-2 are highly expressed in the choroid plexus, meninges, and vascular sheaths [42]. In the rat pituitary gland, IGF-1/IGF-1R is expressed in all of the endocrine cells, with the highest levels of protein expression in the corticotrophs, somatotrophs, and gonadotrophs. Low levels of IGF-1R expression are present in the thyrotrophs and lactotrophs [43].

References

1. Alvarez-Bolado, G. Development of neuroendocrine neurons in the mammalian hypothalamus. Cell Tissue Res. 2019, 375, 23–39.
2. Levine, J.E. Chapter 1-An Introduction to Neuroendocrine Systems. In Handbook of Neuroendocrinology; Fink, G., Pfaf f, D.W., Levine, J.E., Eds.; Academic Press: San Diego, CA, USA, 2012.
3. Romero, C.J.; Ng, Y.; Luque, R.M.; Kineman, R.D.; Koch, L.; Bruning, J.C.; Radovick, S. Targeted Deletion of Somatotr oph Insulin-Like Growth Factor-I Signaling in a Cell-Specific Knockout Mouse Model. Mol. Endocrinol. 2010, 24, 1077–1089.
4. Domené, S.; Domené, H.M. Genetic Mutations in the GH/IGF Axis. Pediatr Endocrinol Rev. 2018, 16, 39–62.
5. Hakuno, F.; Takahashi, S.I. IGF1 receptor signaling pathways. J. Mol. Endocrinol. 2018, 61, T69–t86.
6. Vitale, G.; Pellegrino, G.; Vollery, M.; Hofland, L.J. ROLE of IGF-1 System in the Modulation of Longevity: Controversie s and New Insights From a Centenarians' Perspective. Front. Endocrinol. 2019, 10.
7. Junnila, R.K.; List, E.O.; Berryman, D.E.; Murrey, J.W.; Kopchick, J.J. The GH/IGF-1 axis in ageing and longevity. Nat. Rev. Endocrinol. 2013, 9, 366–376.
8. Takahashi, Y. The Role of Growth Hormone and Insulin-Like Growth Factor-I in the Liver. Int. J. Mol. Sci. 2017, 18, 144 7.
9. Wei, M.; Dong, L.; Zhang, H.; Teng, Z.; Wang, X.; Yan, Z.; She, L.; Li, Y.; Wang, X. Review of Insulin-Like Growth Facto r 1 Signaling Pathway and Its Role in Protection against Brain Diseases. Transl. Neurosci. Clin. 2017, 3, 237–245.
10. Wrigley, S.; Arafa, D.; Tropea, D. Insulin-Like Growth Factor 1: At the Crossroads of Brain Development and Aging. Fro nt. Cell. Neurosci. 2017, 11.

11. Maglio, L.E.; Noriega-Prieto, J.A.; Maroto, I.B.; Martin-Cortecero, J.; Muñoz-Callejas, A.; Callejo-Móstoles, M.; Fernánd ez de Sevilla, D. IGF-1 facilitates extinction of conditioned fear. Elife 2021, 10.

12. Gahete, M.D.; Córdoba-Chacón, J.; Lin, Q.; Brüning, J.C.; Kahn, C.R.; Castaño, J.P.; Christian, H.; Luque, R.M.; Kinem an, R.D. Insulin and IGF-I inhibit GH synthesis and release in vitro and in vivo by separate mechanisms. Endocrinology 2013, 154, 2410–2420.

13. Fink, G.; Pfaff, D.W.; Levine, J. Handbook of Neuroendocrinology; Elsevier Science & Technology: San Diego, CA, US A, 2011.

14. Lechan, R.M.; Toni, R. Functional Anatomy of the Hypothalamus and Pituitary. In Endotext; Feingold, K.R., Anawalt, B., Boyce, A., Chrousos, G., de Herder, W.W., Dungan, K., Grossman, A., Hershman, J.M., Hofland, J., Kaltsas, G., et al., Eds.; MDText.com, Inc.: South Dartmouth, MA, USA, 2000.

15. Lechan RM, T.R. Functional Anatomy of the Hypothalamus and Pituitary. 2016. Available online: https://www.ncbi.nlm.ni h.gov/books/NBK279126/ (accessed on 12 June 2021).

16. Pituitary Gland Physiology. In StatPearls, StatPearls Publishing; El Sayed, S.A.; Fahmy, M.W.; Schwartz, J. (Eds.) Stat Pearls Publishing LLC.: Treasure Island, FL, USA, 2020.

17. Gjerstad, J.K.; Lightman, S.L.; Spiga, F. Role of glucocorticoid negative feedback in the regulation of HPA axis pulsatilit y. Stress 2018, 21, 403–416.

18. Hiller-Sturmhöfel, S.; Bartke, A. The endocrine system: An overview. Alcohol Health Res. World 1998, 22, 153–164.

19. Physiology, Pituitary Hormones. In StatPearls; Sadiq, N.M.; Tadi, P. (Eds.) StatPearls Publishing LLC.: Treasure Island, FL, USA, 2020.

20. Rinderknecht, E.; Humbel, R.E. Primary structure of human insulin-like growth factor II. Febs Lett. 1978, 89, 283–286.

21. AsghariHanjani, N.; Vafa, M. The role of IGF-1 in obesity, cardiovascular disease, and cancer. Med. J. Islam Repub Ira n. 2019, 33, 56.

22. Annunziata, M.; Granata, R.; Ghigo, E. The IGF system. Acta Diabetol. 2011, 48, 1–9.

23. Liu, J.P.; Baker, J.; Perkins, A.S.; Robertson, E.J.; Efstratiadis, A. Mice carrying null mutations of the genes encoding in sulin-like growth factor I (Igf-1) and type 1 IGF receptor (Igf1r). Cell 1993, 75, 59–72.

24. Kulik, G.; Klippel, A.; Weber, M.J. Antiapoptotic signalling by the insulin-like growth factor I receptor, phosphatidylinosito l 3-kinase, and Akt. Mol. Cell Biol. 1997, 17, 1595–1606.

25. LeRoith, D. Insulin-like growth factor I receptor signaling--overlapping or redundant pathways? Endocrinology 2000, 14 1, 1287–1288.

26. Baxter, R.C.; Martin, J.L.; Beniac, V.A. High molecular weight insulin-like growth factor binding protein complex. Purifica tion and properties of the acid-labile subunit from human serum. J. Biol. Chem. 1989, 264, 11843–11848.

27. Bach, L.A. IGF-binding proteins. J. Mol. Endocrinol. 2018, 61, T11–t28.

28. Clemmons, D.R. Modifying IGF1 activity: An approach to treat endocrine disorders, atherosclerosis and cancer. Nat. Re views. Drug Discov. 2007, 6, 821–833.

29. Guler, H.P.; Zapf, J.; Schmid, C.; Froesch, E.R. Insulin-like growth factors I and II in healthy man. Estimations of half-liv es and production rates. Acta Endocrinol. 1989, 121, 753–758.

30. Rajaram, S.; Baylink, D.J.; Mohan, S. Insulin-like growth factor-binding proteins in serum and other biological fluids: Re gulation and functions. Endocr. Rev. 1997, 18, 801–831.

31. Firth, S.M.; Baxter, R.C. Cellular Actions of the Insulin-Like Growth Factor Binding Proteins. Endocr. Rev. 2002, 23, 824 –854.

32. Kappeler, L.; De Magalhaes Filho, C.; Leneuve, P.; Xu, J.; Brunel, N.; Chatziantoniou, C.; Le Bouc, Y.; Holzenberger, M. Early postnatal nutrition determines somatotropic function in mice. Endocrinology 2009, 150, 314–323.

33. Decourtye, L.; Mire, E.; Clemessy, M.; Heurtier, V.; Ledent, T.; Robinson, I.C.; Mollard, P.; Epelbaum, J.; Meaney, M.J.; Garel, S.; et al. IGF-1 Induces GHRH Neuronal Axon Elongation during Early Postnatal Life in Mice. Plos One 2017, 1 2, e0170083.

34. Le Roith, D. Seminars in medicine of the Beth Israel Deaconess Medical Center. Insulin-like growth factors. New Engl. J. Med. 1997, 336, 633–640.

35. Delafontaine, P.; Song, Y.-H.; Li, Y. Expression, Regulation, and Function of IGF-1, IGF-1R, and IGF-1 Binding Proteins in Blood Vessels. Arterioscler. Thromb. Vasc. Biol. 2004, 24, 435–444.

36. Lewitt, M.S.; Boyd, G.W. The Role of Insulin-Like Growth Factors and Insulin-Like Growth Factor-Binding Proteins in th e Nervous System. Biochem. Insights 2019, 12, 1178626419842176.
37. Kineman, R.D.; Rio-Moreno, M.d.; Sarmento-Cabral, A. 40 YEARS of IGF1: Understanding the tissue-specific roles of I GF1/IGF1R in regulating metabolism using the Cre/loxP system. J. Mol. Endocrinol. 2018, 61, T187.
38. Jones, J.I.; Clemmons, D.R. Insulin-like growth factors and their binding proteins: Biological actions. Endocr. Rev. 199 5, 16, 3–34.
39. Ding, H.; Wu, T. Insulin-Like Growth Factor Binding Proteins in Autoimmune Diseases. Front. Endocrinol. 2018, 9.
40. Adamo, M.L.; Neuenschwander, S.; LeRoith, D.; Roberts, C.T., Jr. Structure, expression, and regulation of the IGF-I ge ne. Adv. Exp. Med. Biol. 1993, 343, 1–11.
41. Wang, Y.; Bikle, D.D.; Chang, W. Autocrine and Paracrine Actions of IGF-I Signaling in Skeletal Development. Bone Re s. 2013, 1, 249–259.
42. Bondy, C.; Werner, H.; Roberts, C.T.; LeRoith, D. Cellular pattern of type-I insulin-like growth factor receptor gene expr ession during maturation of the rat brain: Comparison with insulin-like growth factors I and II. Neuroscience 1992, 46, 9 09–923.
43. Eppler, E.; Jevdjovic, T.; Maake, C.; Reinecke, M. Insulin-like growth factor I (IGF-I) and its receptor (IGF-1R) in the rat anterior pituitary. Eur. J. Neurosci. 2007, 25, 191–200.
