Growth Hormone & IGF Research 24 (2014) 47–53

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Review

Extrapituitary growth hormone synthesis in humans

Diana Cristina Pérez-Ibave [a], Iram Pablo Rodríguez-Sánchez [a], María de Lourdes Garza-Rodríguez [a], Hugo Alberto Barrera-Saldaña [a,b,*]

[a] Department of Biochemistry and Molecular Medicine, School of Medicine, Autonomous University of Nuevo León, Monterrey 64630, Mexico
[b] Vitaxentrum, Blvd. Puerta del Sol 1005, Colinas de San Jerónimo, Monterrey, Nuevo León, 64460 Mexico

ARTICLE INFO

Article history:
Received 14 August 2013
Received in revised form 27 January 2014
Accepted 27 January 2014
Available online 12 February 2014

Keywords:
Growth hormone (GH)
Growth hormone receptor (GHR)
Insulin growth factor 1 (IGF-1)
Chorionic somatomammotropin hormone (CSH)
Growth hormone releasing hormone (GHRH)

ABSTRACT

The gene for pituitary growth hormone (*GH-N*) in man belongs to a multigene *locus* located at chromosome 17q24.2, which also harbors four additional genes: one for a placental variant of *GH-N* (named *GH-V*) and three of chorionic somatommamotropin (*CSH*) type. Their tandem arrangement from 5′ to 3′ is: *GH-N*, *CSH-L*, *CSH-1*, *GH-V* and *CSH-2*. GH-N is mainly expressed in the pituitary from birth throughout life, while the remaining genes are expressed in the placenta of pregnant women. Pituitary somatotrophs secrete GH into the bloodstream to act at receptor sites in most tissues. GH participates in the regulation of several complex physiological processes, including growth and metabolism. Recently, the presence of GH has been described in several extrapituitary sites, such as neural, ocular, reproductive, immune, cardiovascular, muscular, dermal and skeletal tissues. It has been proposed that GH has an autocrine action in these tissues. While the body of evidence for its presence is constantly growing, research of its possible function and implications lag behind. In this review we highlight the evidence of extrapituitary synthesis of GH in humans.

Contents

* Corresponding author at: Departamento de Bioquímica y Medicina Molecular, Facultad de Medicina de la Universidad Autónoma de Nuevo León, Av. Madero y Dr. Aguirre Pequeño, Col. Mitras Centro, Monterrey, Nuevo León 64460, Mexico. Tel.: +52 81 83294173x2591; fax: +52 81 83337747.
E-mail address: habarrera@gmail.com (H.A. Barrera-Saldaña).

http://dx.doi.org/10.1016/j.ghir.2014.01.005
1096-6374

1. Introduction

1.1. Molecular biology of GH locus:

The growth hormone (*GH*) gene is part of a multigene family that in humans is located in the long arm of chromosome 17 at band 24.2 [1]. The *locus* encompasses about 50 kb and harbors five genes: two of *GH* (*GH* normal or *GH-N* and *GH* variant or *GH-V*) and three of chorionic somatommamotropin (*CSH-L*, *CSH-1* and *CSH-2*) [2]. The most 5′ gene is *GH-N*, which encodes a 191 amino acid (22 kDa) protein [3] and is expressed primarily in the somatotrophs of the anterior pituitary gland. After its release into the circulation, it acts at distant target sites regulating postnatal growth and metabolism [4]. The gene's primary transcript is differentially spliced and a 45-nucleotide shorter mRNA variant gives rise to a 20 kDa GH-N isoform, ten times less abundant than the main isoform [2]. Transcription of the pituitary *GH-N* gene is dependent on the pituitary transcription factor Pit-1, which binds at two adjacent regions of the *GH-N* gene promoter region and induces expression of this gene in somatotrophs. Pit-1 is not restricted to GH-pituitary secreting cells; since some extrapituitary tissues express *Pit-1* mRNA, these can reflect extrapituitary sites of GH production [2,5,6].

During pregnancy the *GH-N* gene of the mother's pituitary gland is turned off, while the remaining four genes in the locus are expressed in the syncytiotrophoblast of the placenta. *CSH-1* and *CSH-2* encode an identical mature 22 kDa hormone [7], while *CSH-L* is considered a pseudogene due to a mutation in its second intron that precludes normal splicing [8]. Finally, the main product of *GH-V* is also a 22 kDa protein, but it has been proven to give rise to 20 kDa, 24 kDa, 25 kDa, and 26 kDa isoforms [8] (see Fig. 1). The actions of GH-N are mediated by binding to its receptor (GHR) and activating downstream signaling cascades. A single GH molecule binds to two GHR molecules and induces GHR dimerization that ultimately results in the various biological effects of GH. The actions of GH include postnatal longitudinal growth and protein, lipid, and carbohydrate metabolism.

Many but not all effects of GH are mediated via somatomedin (insulin like growth factor-1 [IGF-1]). Multiple factors other than GH contribute to the expression of serum IGF-1, including nutritional state, liver function, serum protease activity, IGF-1 binding proteins, and sex hormones [9]. GH release regulatory factors include GH releasing hormone (GHRH), somatostatin, GH releasing peptide (ghrelin), and IGF-1.

1.2.1. Placenta

During pregnancy, GH-N synthesis in the pituitary of the mother is suppressed, while that of GH-V in the syncytiotrophoblast layer of the human placenta is activated. In the maternal circulation from 12 to 20 weeks up to term, fetus placental GH-V gradually replaces maternal pituitary GH-N, which becomes undetectable. The CSH protein, which is the product of *CSH-1* and *CHS-2*, is secreted into both the maternal and fetal circulation after the sixth week of pregnancy [10,11]. The pattern of *GH-V*/*CSH* mRNA expression in term placenta consists of *CSH* mRNA representing 95%, and *GH-V* mRNA 5% of the total *GH*/*CSH* RNA [12]. However, a wide variation of RNA expression levels of *CSH* genes from placenta to placenta has been observed [13].

GH-V and CSH act in concert in the mother to stimulate IGF-1 production and modulate intermediary metabolism, resulting in an increase in the availability of glucose and amino acids to the fetus. In the fetus, CSH acts via lactogenic receptor (prolactin receptor) and possibly a unique CSH receptor to modulate embryonic development, regulate intermediary metabolism, and stimulate the production of IGFs (IGF-1 and IGF-2), insulin, adrenocortical hormones, and pulmonary surfactant. GH-N, which is synthesized by the fetal pituitary, has little or no physiological action in the fetus until late in pregnancy due to the lack of functional GH receptors on fetal tissues. While circulating GH concentrations are high in fetal life, skeletal growth is only slightly reduced by GH deficiency in uterus. This has been explained by the relatively low binding of GH to fetal hepatic tissue, suggesting a lack of GHR [14]. GH-V, which is also a potent somatogenic hormone, is not released in the fetus circulation [10,15]. While several isoforms have been described for GH-V in the placenta [2,16], the functions of these isoforms are still unknown [2].

1.2. Extrapituitary GH in human

The concept that GH-N synthesis occurs only in the pituitary gland has been changing in the last quarter century, due to the emergence of evidence of its presence in numerous extrapituitary tissues as

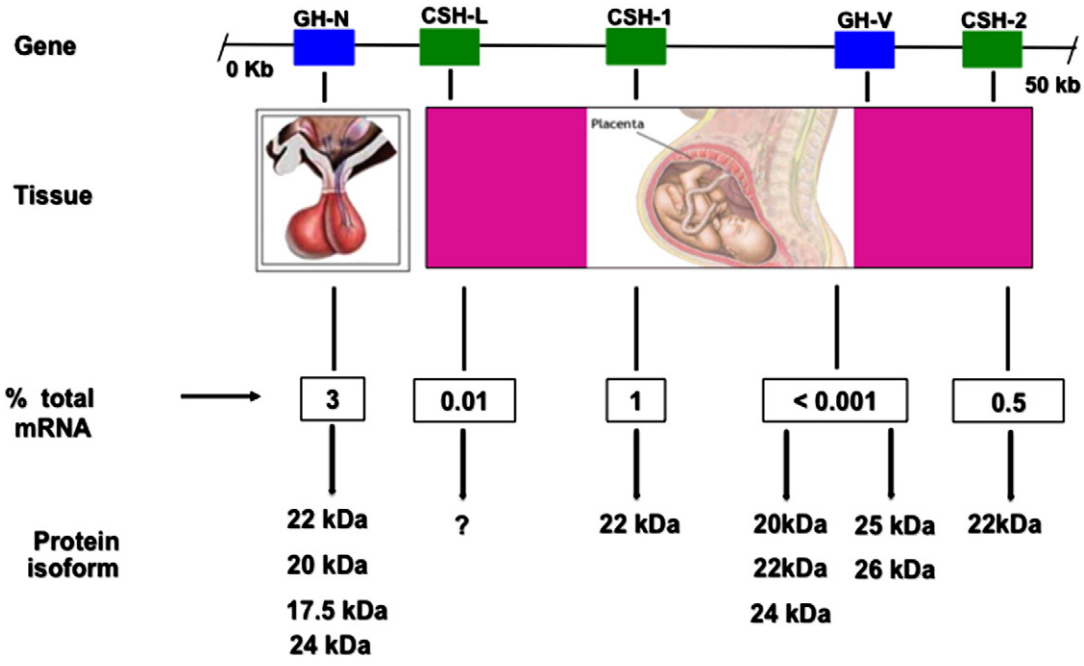

Fig. 1. The human GH *locus*. *Locus* structure, tissue site of expression, levels of mRNAs, and protein isoforms resulting from the gene members of the GH multigene family are shown.