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Models of GH deficiency in animal studies

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Growth hormone (GH) is a peptide hormone released from pituitary somatotrope cells that promotes growth, cell division and regeneration by acting directly through the GH receptor (GHR), or indirectly via hepatic insulin-like growth factor 1 (IGF1) production. GH deficiency (GHD) can cause severe consequences, such as growth failure, changes in body composition and altered insulin sensitivity, depending of the origin, time of onset (childhood or adulthood) or duration of GHD. The highly variable clinical phenotypes of GHD can now be better understood through research on transgenic and naturally-occurring animal models, which are widely employed to investigate the origin, phenotype, and consequences of GHD, and particularly the underlying mechanisms of metabolic disorders associated to GHD. Here, we reviewed the most salient aspects of GH biology, from somatotrope development to GH actions, linked to certain GHD types, as well as the animal models employed to reproduce these GHD-associated alterations.

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Introduction

Growth hormone deficiency (GHD) is a rare disorder characterized by the inadequate secretion of growth hormone (GH) from the anterior pituitary gland [1,2]. GHD is the most common endocrinopathy, with an estimated prevalence of approximately 1 in 4000 during childhood [1,3]. GHD may occur in isolation (isolated GHD, IGHD), or associated with other anterior and posterior pituitary hormone deficiencies (combined pituitary hormones deficiency; CPHD) [4]. IGHD refers to syndromes affecting only the level of plasmatic GH, where production of other hormones is unchanged.

GHD (or IGHD) can be congenital (present from birth) resulting from genetic mutations, or from structural defects in the brain [5–8]; but it can also be acquired later in life, as a result of trauma, infection, radiation therapy, or tumor growth within the brain [9]. A third category encompasses those GHDs with unknown/undiagnosable causes (idiopathic). In particular, childhood-onset GHD may be congenital, acquired, or idiopathic and results in growth retardation, short stature, maturation delays reflected by the delay of lengthening of the bones, and metabolic disorders. On the other hand, adult-onset GHD is most often acquired, resulting from a pituitary tumor or trauma to the brain but may also be idiopathic. It is characterized by several symptoms including reduced energy levels, altered body composition, osteoporosis, reduced muscle strength, dyslipidemia, insulin resistance, and impaired cardiac function [9].

Congenital, child-onset forms of GHD may be associated with brain structure defects (e.g., septo optic dysplasia) or with midline facial defects, or may result from genetic mutations of genes involved in the development of GH-producing cells, or in the regulation of the production and/or secretion of GH. Hence, GHD can result from the alteration of multiple molecular elements involved in the appropriate functioning of the GH/insulin like growth factor 1 (IGF1) axis [5,7,8,10]. Actually, inherited IGHD syndromes can, although rarely, be associated with alterations (deletions and splice site, frame-shift and nonsense mutations) in GH gene expression. In addition, mutations in key genes for somatotrope differentiation (such as PROP1 and POU1F1) are responsible for rare cases of GH deficiency, usually accompanied by other pituitary hormone deficiencies. Additionally, GH resistance (i.e. due to mutations in GH receptor, GHR) and IGF1 deficiency could also lead to GHD-like phenotypes, as they could also cause poor growth and extreme short stature in childhood [11].

In this work, we will review the most relevant aspects of GH biology, from somatotrope development to GH actions, associated to certain types of GHD, as well as the most important animal models (Table 1) employed to investigate the origin, phenotype, consequences and the mechanisms underlying the metabolic disorders associated to GHD (Table 2).

Pituitary and somatotrope cell development

The pituitary gland, often and deservedly referred to as the “master gland”, is a central regulator of growth, reproduction, metabolic, and whole-body endocrine physiology, and conveys signals from the hypothalamus to various, key target organs [12]. The pituitary synthesizes and releases several hormones that modulate the function of peripheral organs to regulate vital processes, such as growth, puberty, metabolism, stress responses, reproduction, and lactation [12]. The gland is situated within the sella turcica, a depression in the sphenoid bone, at the base of the brain [13]. The mature pituitary

Table 1
Mouse models of GHD.

Mouse model	Origin	Inheritance	Model of human disease	References
GHRHKO	GHRH gene KO	AR	IGHD Type IA (IGHD1A)	[31–35,82–88]
GHRHRKO	A/G mutation in GHRHR	AR	IGHD Type IA (IGHD1A)	[15,35,37–46]
Ames dwarf	T/C transition in PROP1	AR	CPHD Type 2 (CPHD2)	[47–58]
Snell dwarf	G/T transversion in POU1F1	AR, AD	CPHD Type 1 (CPHD21)	[62–69]
AOiGHD	GH-positive cells KO	–	Acquired GHD	[29,70,72–75]
Egr2KO	Egr2-positive cells KO	–	Acquired GHD	[79]

AR means autosomal recessive; AD means autosomal dominant.