
Endocrine Regulation of Longitudinal Bone Growth

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Abstract

Longitudinal growth is primarily influenced by the GH-IGF-I axis, which is a mixed endocrine-paracrine-autocrine system. Further, classical hormones such as thyroxine, glucocorticosteroids and sex steroids play a role, as well as primarily paracrine systems. In the GH-IGF-I axis, seven disorders can be differentiated: (1) GH deficiency; (2) *GHR* defects; (3) defects in the GH signal transduction pathway; (4) *IGF1* defects; (5) *IGFALS* defects; (6) *IGF1R* defects, and (7) *IGF2* defects. Children with one of the first 3 disorders have near-normal prenatal growth, while children with defects of *IGF1*, *IGF1R* or *IGF2* show prenatal as well as postnatal growth retardation. Hypothyroidism or a thyroid hormone resistance cause growth failure, but the effect of hyperthyroidism on growth is modest. Hypercortisolism causes poor growth, while FGD caused by ACTH insensitivity is associated with tall stature. Increased sex steroids in childhood cause advanced growth but even more skeletal maturation, so that adult height is decreased. Finally, the paracrine-autocrine SHOX-BNP pathway and the related CNP-NPR2 pathway are also involved in growth, as very many other growth factors and their receptors and mediators.

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Most classifications of growth failure are based on the concept that there are disorders of the growth plate itself, usually termed primary growth failure, and of the milieu of the growth plate, usually termed secondary growth failure. The milieu can be abnormal in the sense of deficiencies, such as unavailability of sufficient oxygen, nutrients, and hormones, and in the sense of toxicity, such as increased concentrations of metabolic waste products (e.g. in renal, hepatic and metabolic disorders), toxins, interleukins, and various iatrogenic interventions (e.g. glucocorticosteroids, chemotherapy, irradiation). Psychosocial causes of growth failure, including psychosocial deprivation, anorexia nervosa and depression, are usually also classified under secondary growth failure as a separate category, although there are some indications that the effect of these conditions may be mediated via endocrine mechanisms. The third

category of growth failure is termed 'idiopathic short stature', including familial and nonfamilial short stature.

The most frequently encountered category of secondary growth failure in affluent countries consists of endocrine disorders, including GH deficiency, hypothyroidism, and (more rarely) hypercortisolism (Cushing syndrome). Poor growth in poorly controlled diabetes and insulin resistance (leprechaunism) can also be categorized in this group, although the former can also be considered as an example of increased metabolic waste products. The effects of sex steroids on growth are more complex. Elevated levels of androgens or estrogens in infancy or childhood cause increased growth, but skeletal maturation is even more increased, so that adult height is decreased. On the other hand, a deficiency of sex steroids, such as in hypogonadism, causes a mild growth deceleration in adolescence, but adult height may be increased, with eunuchoidal body proportions, because of late growth plate closure.

While GH deficiency, hypothyroidism and hypercortisolism are endocrine disorders in the classical sense, downstream disorders in the GH-IGF-I axis are examples of the extended concept of endocrinology, encompassing paracrine and autocrine effects besides endocrine effects.

In this review, we shall primarily focus on the role of the various elements of the GH-IGF-I axis, as can be deduced from defects of the various genes involved. The role of thyroxine, glucocorticosteroids and sex steroids, as well as a primarily paracrine system encompassing SHOX/BNP and CNP and its receptor, will be discussed only shortly. We also focus primarily on postnatal growth. The role of the mother, placenta and fetus in endocrine regulation of human fetal growth has been recently reviewed by others [1].

The GH-IGF-I Axis

The GH-IGF-I axis is a complex system, in which various proteins play a role, with endocrine, paracrine and autocrine functions. Since the discovery of IGF-I (originally termed sulphation factor and then somatomedin), several hypotheses have been proposed about the function of this system. The so-called 'Somatomedin hypothesis' has been revised and revisited several times. Evidence generated in recent years suggests that the growth-promoting effects of GH may not be entirely mediated by circulating IGF-I, as was proposed in the original somatomedin hypothesis, and that paracrine/autocrine IGF-I activity may be significantly involved in this process [2].

Pituitary GH secretion, which is regulated by stimulatory (GHRH) and inhibitory (somatostatin) hypothalamic hormones, has a direct as well as indirect action on many tissues. One of the direct actions is to stimulate IGF-I, IGFBP-3 and the ALS, primarily from the liver, but GH also affects transcription of numerous other genes.

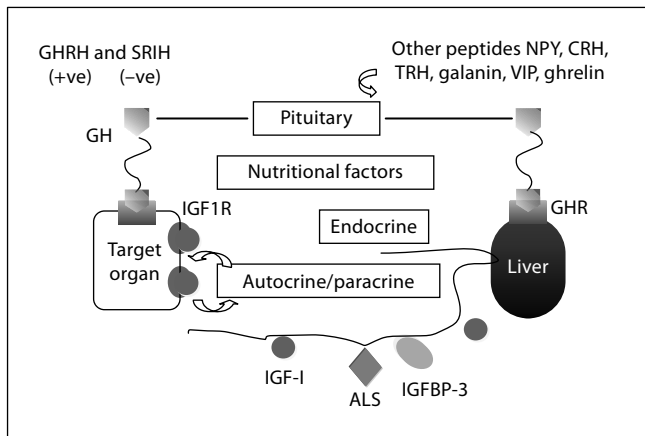


Fig. 1. Schematic representation of the neuroendocrine regulation of growth. Pituitary GH secretion is primarily controlled by two hypothalamic factors: GHRH, which has a stimulatory effect, and SRIH (also called somatostatin), which has an inhibitory effect. However, also other peptides have an effect on GH secretion, such as NPY, CRH, TRH, galanin, VIP and ghrelin. Circulatory GH is bound to receptors present in many tissues, and leads to the transcription of many target genes, including *IGF1*. At the local level, IGF-I has an autocrine and paracrine function. Circulating IGF-I, IGFBP-3 and ALS are primarily derived from the liver, and the major part of circulating IGF-I is bound to GHBP-3 and ALS.

Circulating IGF-I is primarily produced by the liver (under the influence of GH and other factors), and it is accepted that it acts primarily in an endocrine fashion. Most of circulating IGF-I is found as part of the 150-kDa ternary complex also containing its predominant IGF-binding proteins, IGFBP-3 and ALS (fig. 1).

A recent study on bi-transgenic mice carrying in an *Igf1* null background a dormant *Igf1* cDNA placed downstream of a transcriptional ‘stop’ DNA sequence flanked by *loxP* sites (floxed) and also a *cre* transgene driven by a liver-specific promoter showed that the endocrine IGF-I plays a significant role in mouse growth, as its action contributes to approximately 30% of the adult body size and sustains postnatal development, including the reproductive functions of both sexes in the mouse [3].

Traditionally, disorders in this axis have been classified according to the GH status: GH deficiency or GH insensitivity. More recently, some investigators have proposed to give IGF-I a more central role in the classification, and to distinguish secondary IGF deficiency (equal to GH deficiency, or other conditions causing low circulating IGF-I levels), primary IGF deficiency (all congenital forms of GH insensitivity; acquired GH insensitivity, for example because of malnutrition is called ‘secondary’), and IGF resistance.

At present, there are five conditions associated with a low IGF-I in spite of a normal or elevated GH secretion: defects of *GHR*, *STAT5B*, *IKBKB* (*IκB*), *IGF1* and *IGFALS*. The first of these is GH insensitivity syndrome or Laron syndrome caused by

a homozygous defect of the *GHR*. This condition can still be seen as a disturbance in a classical endocrine feedback loop. Defects of the GHR signal transduction pathway (*STAT5B* or *IKBKB* defects) are different because these defects also have an impact on other biological pathways, such as interleukins. The effects of *IGF1* defects cannot be understood in the context of a pure 'classical' endocrine pathway: IGF-I is produced in virtually all cells of the body, and the local effects are more important for growth than the endocrine effects. Here also a time component comes into play: in utero, the IGF-I production is GH independent and mainly dependent of nutrition and insulin, but postnatally the IGF-I production is mainly dependent on GH-secretion, although nutrition and insulin secretion still play a role. Heterozygous defects of *IGF1R* cause a partial insensitivity to IGF-I, which apparently cannot be compensated by increased IGF-I production. The clinical presentation of children with an isolated *IGF2* defect is still uncertain.

We prefer to divide disorders of the GH-IGF-I axis into seven groups: (a) GH deficiency; (b) *GHR* defects; (c) defects in the GH signal transduction pathway; (d) *IGF1* defects; (e) *IGFALS* defects; (f) *IGF1R* defects; (g) *IGF2* defects.

GH Deficiency

The essential role of GH in growth is shown by patients with a total absence of pituitary GH secretion, for example children with a *GHI* gene deletion. Birth weight and length is usually in the normal range, but on average slightly decreased. It is estimated that the adult height loss in such conditions is approximately 4.7 SD (range -3.9 to -6.1 SDS in the four available studies) in patients with spontaneous puberty, and 3 SD if puberty is induced at an advanced age [4]. In cases with untreated hypogonadism, as part of multiple pituitary deficiency, adult height can even be normal or increased, due to extremely late closure of epiphyseal plates. Head circumference is usually normal. The role of GH is further substantiated by the observation that GH administration improves growth rate, and if started early enough and at an appropriate dosage, normalizes adult height [4]. GH deficiency either isolated or as part of multiple pituitary deficiency, can be caused by defects in several genes, which have been recently summarized [5].

GHR Defects

Laron syndrome, also called classical GH insensitivity, is a fully penetrant autosomal recessive disease, first described in 1966. To date, more than 250 patients have been described worldwide with 60 different mutations [6]. Mean birth length has been reported as -1 SDS in the European and Ecuadorian cohorts, but lower in Israeli patients, indicating that in late pregnancy there is already some dependency on GH.

Postnatal growth rate fails immediately after birth, and adult height is 139 and 123 cm for men and women, respectively [6], and head circumference is usually normal, similar to cases with complete GH deficiency [7].

Biochemically, GHBP is undetectable (table 1) or low in patients with extracellular domain mutations or deletions, while it can be normal or even increased in mutations in the part of the gene coding for the anchoring site or the intracellular part of the protein [7, 8]. Circulating IGF-I, IGFBP-3 and ALS are low, and IGFBP-1 and -2 can be increased. For further details on the clinical and biochemical presentation, the reader is referred to Mehta et al. [6]. A summary of the clinical and biochemical characteristics of cases with *GHR*, *STAT5B*, *IKBKB*, *IGF1*, *IGFALS* and *IGF1R* defects is presented in table 1.

Defects in the GH Signal Transduction Pathway

After binding of GH to its receptor, the signal has to be transferred to the cell nucleus to initiate gene transcription of several GH-dependent genes, particularly *IGF1*, *IGFBP3* and *IGFALS*. After GH, which is preformed as a dimer, binds to its receptor, a conformational change occurs, whereby JAK2 is autophosphorylated and activated, in turn leading to phosphorylation of STAT5a and STAT5b molecules. Phosphorylated STAT5 molecules dimerize and translocate to the nucleus, where they bind to DNA and activate target genes [6].

From in vitro investigations on the GH signal transduction pathway and animal studies, it was expected that *STAT5b* defects would lead to GH resistance, and indeed 7 families have been described in which homozygous defects of the *STAT5b* gene were encountered [8, 9]. Patients with homozygous *STAT5b* defects present with severe GH resistance and growth failure (height between -5.6 to -9.9 SDS), but a normal head circumference (-1.4 SDS; table 1). In all cases except one, this is also combined with a severe immune disorder [8], usually leading to pulmonary fibrosis, which is possibly explained by the role of STAT5B as a mediator of IL-2 action and T cell function. Circulating GH can be elevated, but in some cases a normal GH secretion was observed. An elevated serum prolactin has been found in most cases. Preliminary data suggest that a heterozygous defect may lead to a mild decrease in height SDS.

The GH signal transduction pathway is far more complex than a single straight line from GHR to JAK2, STAT5B and gene transcription. There appears to be much cross-talk between various proteins involved in different signal transduction pathways. An example of this is the observation that activating mutations of *PTPN11* (as seen in Noonan syndrome), leading to overactive SHP2, enhances RAS/MAPK signaling, but is associated in some cases with partial GH insensitivity. Similar phenotypes are observed in children with defects in other genes (*SOS1* and *KRAS*) in the RAS/MAPK pathway, which give rise to several syndromes (e.g. Costello syndrome). Height is

Table 1. Clinical and biochemical characteristics of defects of the GH-IGF-I axis

	GHR-/-	STAT5B-/-	Ras-raf+/-	IKBKB+/-	IGFALS-/-	IGF1-/-	IGF1R+/-
Birth size SDS	N or mildly affected	N	N	N	N or low	-5.5 to -2.4	-4 to -1.5
Height SDS	-5.6 to -9.9 SDS	-4.9 to -9.9 SDS	-4 to -1 SDS	-4 SDS	-4.2 to -0.5	-6.9 to -8.5	-5.0 to -2.6
HC SDS	N	N	N or low	N	N or low	-8.0 to -4.0	-4 to -2
Parental height	N	N (1 SD lower than WT)	one parent may be affected	one parent may be affected	N (1 SD lower than WT)	N (1 SD lower than WT)	one parent may be affected
Clinical features	hypoglycemia; frontal bossing; midfacies hypoplasia	immuno-deficiency; pulmonary fibrosis; arthritis	dysmorphisms; pulmonary stenosis; in 40% mild mental handicap	mental retardation; leukocytosis	delayed puberty in 50% of males	mental retardation; deaf; pubertal delay	poor appetite; may be associated with defects of nervous and cardiac system
GHmax	↑↑	↑↑	N	↑↑	N or ↑↑	↑↑	N or ↑↑
IGF-I	↓↓↓	↓↓↓	↓	↓	↓↓↓	undetectable, low, or high	>0 SDS
IGFBP-3	↓↓↓	↓↓↓	N	↓	↓↓↓↓	N	N
ALS	↓↓↓	↓↓↓	↓	?	undetectable	N	N
Other biochemical features	complete GH insensitivity; GHBP often undetectable; PRL N or slightly ↑↑	(almost) complete GH insensitivity; PRL 61–169 ng/ml (N in one case)	partial GH insensitivity (variable)	hyper-IgM syndrome; immuno-deficiency	complete GH insensitivity	insulin resistance	on GH treatment strongly elevated IGF-I

HC = Head circumference; +/- = homozygous; +/- = heterozygous; N = normal; SDS = standard deviation score; WT = wild type; PRL = prolactin.

approximately 30 cm below the population's average [10] (table 1). Preliminary data suggest that haploinsufficiency of *NSD1*, a cause of Sotos syndrome which is associated with tall stature, may lead to suppression of the RAS/MAPK pathway [Visser et al., submitted].

Another gene which may be associated with a combination of GH resistance and immunodeficiency is *IKBKB* (*IκB*). A heterozygous mutation of this gene was found in two unrelated cases with serious immune problems and short stature. We reported that one of these patients had severe short stature and GH resistance