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Biology of the somatotroph axis (after the pituitary)

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Abstract

Normal growth requires that pituitary-secreted growth hormone (GH) bind to its specific receptor and activate a complex signaling cascade, leading to production of insulin-like growth factor-I (IGF-I), which, in turn, activates its own receptor (IGF1R). The GH receptor (GHR) is preformed as a dimer and is transported in a nonligand bound state to the cell surface. Binding of GH to the GHR dimer, results in a conformational change of the dimer, activation of the intracellular Janus Kinase 2 (JAK2) and phosphorylation of signal transducer and activator of transcription (STAT) 5B. Phosphorylated STAT5B dimers are then translocated to the nucleus, where they transcriptionally activate multiple genes, including those for IGF-I, IGF binding protein-3 and the acid-labile subunit (ALS).

Résumé

La croissance normale nécessite que l'hormone de croissance (GH) sécrétée par l'hypophyse se lie à son récepteur spécifique et active une cascade de signalisation complexe, conduisant à la production de l'*insulin-like growth factor-I* (IGF-I) qui, à son tour, active son propre récepteur (IGF1R). Le récepteur à la GH (GHR) est préformé sous forme de dimère et est transporté à la surface de la cellule sous une forme non liée au ligand. La liaison de la GH au dimère du GHR conduit à un changement conformationnel du dimère, à l'activation de la Janus Kinase 2 (JAK2) intracellulaire et à la phosphorylation du « signal transducer and activator of transcription » (STAT) 5B. Les dimères STAT5B phosphorylés sont ensuite transloqués dans le noyau, où ils activent la transcription de plusieurs gènes, dont celui pour l'IGF-I, l'IGF *binding protein-3* et la sous-unité labile acide (ALS).

Keywords

Somatotroph axis; GH; GHR function

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Axe somatotrope; GH; Fonction du récepteur de GH

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Disclosure of interest

The authors declare that they have no competing interest.

Normal growth requires that pituitary-secreted growth hormone (GH) bind to its specific receptor and activate a complex signaling cascade, leading to production of insulin-like growth factor-I (IGF-I), which, in turn, activates its own receptor (IGF1R) [1]. The GHR is synthesized as a 638-amino acid peptide, which is later processed into a mature receptor of 620 amino acids. The extracellular hormone binding domain consists of 246 amino acids, followed by a single membrane-spanning domain and a cytoplasmic domain of 350 amino acids. In humans, the circulating GH-binding protein (GHBP) is derived from the proteolytic cleavage of the extracellular domain of the receptor. The GHR is a member of the class 1 hematopoietic cytokine family. It is highly homologous to the prolactin receptor and shares sequence homology with many of the receptors for interleukins, erythropoietin, leptin, granulocyte-macrophage colony-stimulating factor and interferon.

The GHR is preformed as a dimer and is transported in a nonligand bound state to the cell surface. GH then binds in a sequential manner to the GHR dimer: the first GHR binds to the stronger site 1 of the GH molecule, followed by the second GHR binding to the weaker site 2. Binding of GH results in a conformational change, whereby rotation of the GHRs results in repositioning of the intracellular domains and of Box1-associated Janus Kinase 2 (JAK2), a major GHR-associated kinase [2]. This is critical, as GHR appears to have no intrinsic kinase activity. Co-localization of two JAK2 molecules by the dimerized GHR results in transphosphorylation and activation of one JAK2 by the other and this, in turn, leads to phosphorylation of distal tyrosine residues of GHR that enables SH2 (*Src* homology 2) domain molecules to dock to these sites. Signal transducer and activator of transcription (STAT) 5A and 5B molecules contain SH2 domains and bind to the phosphorylated sites on GHR and are, in turn, themselves phosphorylated, dimerize and translocate to the nucleus, where they bind to DNA and activate target genes.

GH can activate both STAT5A and STAT5B which have overlapping functions [3]. GH is also capable of activating STAT1 and STAT3, but studies in humans with homozygous mutations of *STATB* suggest that essentially all of the growth-promoting actions of GH in humans are mediated through STAT5B. This may differ from the situation in mice, where *Stat5a/b* double null mice are more severely affected than is the case for *Stat5b* null mice, and *Ghr* null mice are the most severely growth retarded. Phosphorylated STAT5A and STAT5B bind STAT5 response elements as dimers or tetramers. STAT5 response elements are located in the second and third intron of the human *IGF1* gene, as well as 73 kb upstream of the initiation site. Activation of JAK-STAT signaling occurs within minutes after GH stimulation, but is transient, due to the tight regulation of the termination of signaling by suppressors of cytokine signaling (SOCS), protein tyrosine phosphatases (PTPs), protein inhibitors of activated states (PIAS) and GHR internalization.

Other GH-activated pathways include mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinase (ERK)-1 and ERK2, the insulin-signaling pathway (by means of insulin receptor substrate [IRS]-1 and IRS-2) and protein kinase C (PKC). While these pathways clearly contribute to the metabolic effects of GH, their role in skeletal growth promotion remains uncertain.

IGF-I is a basic peptide of 70 amino acids, sharing considerable structural homology with IGF-II and approximately 50% homology to insulin [4]. Like insulin, both IGFs have A and B chains connected by disulfide bonds. The connecting (C peptide) region is 12 amino acids long for IGF-I and 8 amino acids for IGF-II. Both IGFs differ from insulin in having C-terminal extensions (D peptides) of 8 and 6 amino acids, respectively. Control of *IGF* gene expression is complex, with variable tissue expression and apparently differential expression in the embryo, fetus, child, adolescent and adult. The human *IGF1* gene is located on the long arm of chromosome 12, while the gene for IGF-II is located on the short arm of chromosome 11, adjacent to the insulin gene.

Despite the structural homology of insulin and the IGFs, the IGFs differ from insulin in that they are transported in serum and in a variety of other biological fluids complexed to a family of six high-affinity binding proteins (IGFBPs) [5]. These IGFBPs extend the half-lives of the bound IGF peptides and regulate their access to tissue receptors. The two major serum IGFBPs, IGFBP-3 and -5, after binding IGF-I or IGF-II, form a ternary complex with an acid-labile subunit (IGFALS), thereby further extending the half-life of the bound IGFs. IGFBP-3 and IGFALS, like IGF-I, are GH-dependent, most likely through the same JAK-STAT pathway that regulates IGF synthesis. The IGFBPs are subject to degradation by a variety of IGFBP proteases, further adding to the complexity of IGF transport and release to receptors.

The growth-promoting actions of IGF-I and IGF-II are mediated through the type I IGF receptor, which, like the homologous insulin receptor, is a heterotetramer composed of two membrane-spanning alpha subunits and two intracellular beta subunits [6]. The alpha subunits contain the binding site for IGF-I or -II and are linked by disulfide bonds. The beta subunits contain a transmembrane domain and a tyrosine kinase domain, which constitutes the presumed signal transduction mechanism. Affinity of this receptor for insulin is approximately 100-fold less than for the IGFs, thereby accounting for the relatively weak mitogenic action of insulin. The type 2 IGF receptor has been found to be identical to the cation-independent mannose-6-phosphate (CIM6P) receptor, a protein involved in the intracellular lysosomal targeting of a variety of acid hydro-lases and other mannosylated proteins. Unlike the type 1 IGF receptor, which binds both IGFs, the type 2 receptor has a substantially reduced affinity for IGF-I and no affinity for insulin. The type 2 receptor does not contain an intrinsic tyrosine kinase domain or any other recognizable signal transduction mechanism and its sole function in regard to the IGF system appears to be that of degrading IGF-II.

Much of our knowledge about the GH-IGF axis and its role in both fetal and postnatal growth has derived from experiments involving targeted disruption of various components of this complex system [7]. Of great interest has been the observation that knockouts of either the GH or GHR genes, while having profound effects on postnatal growth, do not greatly impact growth *in utero*. *Igf1* null mice have birth weights 60% of normal, with further growth retardation postnatally. *Igf2* null mice (or heterozygous mice carrying a paternally derived mutated *Igf2* gene) also have birth weights 60% of normal, but remain about 60% of normal size postnatally. Mice with knockouts of the *igf1* receptor gene (*Igf1r* null mice) are severely growth retarded, with birth weights only 45% of normal and die shortly after birth.

These studies indicate that fetal growth, while profoundly IGF-dependent, is independent of GH action; GH-dependency of growth and IGF production appears to occur around the time of birth.

Such studies have set the stage for detailed genotype: phenotype analysis of human mutations of genes of the GH-IGF axis [8]. While the impact of such mutations generally parallels observations made in mice, subtle differences have been found. While most human conditions are autosomal recessive, careful observations have indicated that, in a number of situations, heterozygosity can result in mild phenotypes. This may result from haploinsufficiency (as in cases of *IGF1R* mutations), dominant negative defects (as in *GHR* and *STAT5B* mutations), imprinting defects (as in *IGF2* mutations) or, simply, mild heterozygous effects (as has been reported for *IGFALS* and *STAT5B*).

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