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Review

Physiology and pathophysiology of growth hormone-binding protein: Methodological and clinical aspects

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Abstract

Circulating GH is partly bound to a high-affinity binding protein (GHBP), which in humans is derived from cleavage of the extracellular domain of the GH receptor. The precise biological function GHBP is unknown, although a regulation of GH bioactivity appears plausible. GHBP levels are determined by GH secretory status, body composition, age, and sex hormones, but the cause–effect relationships remain unclarified. In addition to the possible in vivo significance of GHBP, the interaction between GH and GHBP has methodological implications for both GH and GHBP assays. The present review concentrates on methodological aspects of GHBP measurements, GHBP levels in certain clinical conditions with a special emphasis on disturbances in the GH-IGF axis, and discusses the possible relationship between plasma GHBP and GH receptor status in peripheral tissues.

Keywords: Growth hormone; Binding protein; Assay; Body composition; Receptor

1. Introduction

1.1. The growth hormone receptor

Growth hormone (GH) actions are exerted by activation of the GH receptor, which is a 620 amino-acid protein, consisting of a 246 residue extracellular domain, a single 24 amino-acid transmembrane helix, and a 350 amino-acid intracellular domain. This receptor belongs to the GH/prolactin hematopoietic cytokine receptor family (Class I family of cytokine receptors) characterized by a unique transmembrane domain and absence of intrinsic tyrosine kinase. Activation of the receptor occurs by ligand-induced homodimerization, which is a sequential process, implying binding of GH through binding site one to an extracellular domain of the receptor followed by binding of the same GH molecule through binding site 2 to another extracellular domain [1,2]. This process results in functional dimerization of the two receptors, which subsequently induces a conformational change with initialization of the intracellular signalling cascade (see Fig. 1): phosphorylation of JAK2 and GHR leads to phosphorylation of a host of other signalling proteins of which the signal transducers and activators of transcription or STATS are the most important (reviewed in [3 and 4]). It has been suggested that the receptor exists in a non-functional dimer prior to binding of GH [5,6]. Activation of the STATs also leads to the formation of inhibitors of signalling referred to as suppressors of cytokine signalling and cytokine-inducible SH2-domain-containing protein (SOCS and CIS), that participate in a negative feedback loop to regulate cytokine signalling (reviewed in [7]).

Another characteristic of some Class I cytokine receptors (receptors for GH, leptin, interleukin-4,5,7,9, granulocyte colony-stimulating factor, leukaemia inhibitory factor, ciliary neurotrophic factor) is the *presence of the extracellular domains in a circulating form* (see

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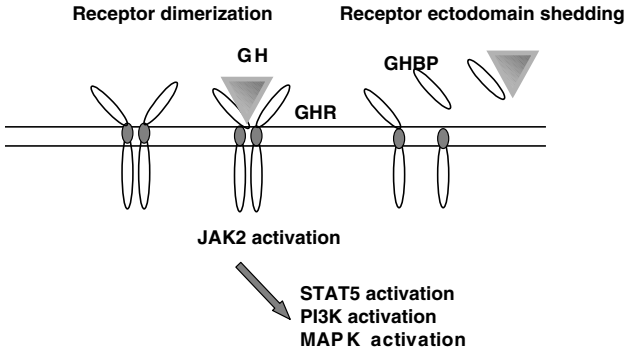

Fig. 1. Growth hormone receptor (GHR) dimerization: binding of one GH molecule through distinct binding sites (1 and 2) to two GHRs. After functional dimerization of two GH receptors, the signalling cascade is initiated by activation of the cytoplasmatic tyrosine kinase JAK2, which subsequently activates transcription factors, which among others comprises STAT5, PI3K and MAPK. GHBP is proteolytically shedded from the extracellular domain of the receptor. The membrane-bound tumor-necrosis-factor-α converting enzyme (TACE) is an important GHBP sheddase, but the regulation of GHBP shedding is not clarified. With physiological levels of GH and GHBP in the circulation, GH is bound through binding site 1 to GHBP in a 1:1 relationship.

below). These soluble forms can function as agonists or antagonists. The soluble GH receptor is designated growth hormone-binding protein (GHBP). The levels of GH, GHR turnover, post-receptor regulation of GHR, and plasma GHBP levels thus determine the biological effects of GH.

The human gene coding for the GHR is localized on chromosome 5. Exons 3–7 and part of exon 2 code for the extracellular domain, exon 8 for the transmembrane domain, and exons 9 and 10 for the intracellular domain [8]. With respect to the intracellular domain-encoding region of the GHR mRNA three isoforms have been described: the most abundant form, the full-length GHR; an alternatively spliced form identical in sequence to GHR, except for a 26-bp deletion in exon 9, leading to a truncation of 97.5% of the intracellular domain (GHR-(1–279)) [9,10]; a second truncated form produced by complete skipping of exon 9 leading to a 277 amino-acid GHR (GHR-(1–277) with only 7 residues in the intracellular domain. The presence of the two latter isoforms inhibits the function of the full-length receptor in vitro [9–13]. As estimated by RT-PCR, the full-length receptor accounts for more than 90% in liver, fat, and muscle. Levels of mRNA for GHR-(1–279) constitute approximately 7–10% in fat and muscle, and only 4% in the liver [14]. Messenger-RNA for GHR-(1–277) constituted only 0.5% of total GHR transcripts in liver and less than 0.1% in muscle and fat.

The truncated GHR-(1–279) has been demonstrated in humans, rabbits, rats and mice [9,15,16]. An increased ability of GHBP production from this receptor as compared to the full-length receptor has been described in humans and rabbits, whereas in the rat and mouse GHBP is not produced from this receptor [15].

With respect to the extracellular domain-encoding region of the GHR mRNA, two isoforms exist: exon 3-retaining (E3(+)) mRNA giving rise to the full-length receptor and exon-3-deleted (E3(−)) mRNA [17]. From the latter a polypeptide lacking 22 amino-acids close to the N-terminus is translated. So far, data indicates that the E3(−) isoform results from a genomic 2.7 bp deletion including exon 3 [18–20], rather than from alternative splicing. Two reports conflict, however, with this finding, since E3(+) genomic DNA was demonstrated in individuals expressing only E3(−) transcripts [21,22]. Expression of E3(−) is not tissue-specifically or developmentally regulated [23,24]. Biopsies from different tissues in the same individuals have shown individual-specific regulation with identical expression pattern in different tissues [25,26], so previous reports of distinct tissue-specificity for distribution of exon 3-retaining and exon 3-excluding isoforms of the hGHR mRNA [17,27]might instead reflect individual-specific expression. Three different distributions of GHRs then exist in tissues according to the genotyping: homozygous E3(+)GHR, homozygous E3(−)GHR, or heterozygous E3(+)/E3(−)GHR. The distribution in the general population for the E3(+)GHR and E3(−)GHR genotypes has been estimated to reflect allele frequencies of 75% and 25%, respectively [18]. Both the E3(+) and the E3(−) receptors give rise to circulating GHBP, which reflects the GHR exon 3 genotype [23,28]. Whether different physiological characteristics are attributed to the receptors/GHBPs is not fully clarified. Recently an increased responsiveness to GH treatment in cases of homodimers and heterodimers of E3(−)GHR was described in GH deficient children [29], however, the mechanism behind this finding is unclear, since the receptors display identical GH-binding properties [30].

1.2. GH-binding proteins (high-affinity, low-affinity)

1.2.1. Growth hormone receptor shedding

From the extracellular domain of the GH receptor the circulating GH-binding protein is produced by proteolytical cleavage through a process known as receptor ectodomain shedding. This high-affinity binding protein was first described in 1986 in human serum [31,32]. In rabbit serum a binding protein displaying the same characteristics was described [33,34]. It was shown to have the same terminal amino-acid sequence as the growth hormone receptor in the liver, indicating that the binding protein corresponded to the extracellular hormone-binding domain of the liver receptor. Recently, the metzincin metalloproteinase tumour necrosis factor-α converting enzyme (TACE), has been identified as an important enzyme for inducing shedding of GH-binding protein [35,36]. It was shown that fibroblasts from TACE