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Early investigations of 20-kDa human placental GH show promise

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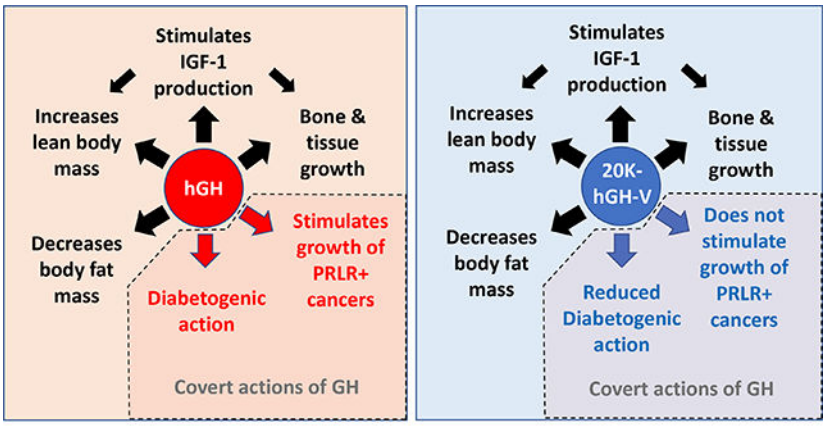
Graphical Abstract



hGH and 20K-hGH-V stimulate IGF-1 production, bone and tissue growth, and regulate body composition, but unlike hGH, 20K-hGH-V lacks diabetogenic action and has reduced ability to stimulate prolactin receptor positive cancers.

Keywords

growth hormone; placental growth hormone; growth hormone variant; growth hormone 2; GH-V; GH-2

Introduction

Growth hormone (GH) is a 22-kDa polypeptide secreted from the anterior pituitary. While it is well known for its role in controlling longitudinal bone growth, GH also acts on multiple tissues either directly or indirectly to control many aspects of metabolism during development and throughout life. For example, GH plays an important role in nutrient partitioning as it alters the synthesis, oxidation, and distribution of carbohydrates, proteins,

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and lipids. To this end, one of the earliest observed actions of GH is a potent anti-insulin/diabetogenic activity. This anti-insulin activity was discovered ~90 years ago by Dr. Bernardo Houssay in a series of experiments for which he was awarded the 1947 Nobel Prize in medicine. In these experiments, Dr. Houssay demonstrated that pituitary gland removal in animals - such as dogs and toads - enhances insulin sensitivity; in contrast, animals injected with high levels of pituitary extracts develop insulin resistance and diabetes [1, 2]. In the 1960s, Rabinowitz and colleagues confirmed that GH has anti-insulin activity in humans by demonstrating that it acutely blocks insulin stimulated glucose uptake [3, 4]. Multiple studies have since reinforced that GH is a diabetogenic agent with anti-insulin activity especially when administered at high doses [5–11].

GH-V

In humans, the GH gene family (Fig.1A) is made up of five related genes that share similar amino acid sequence and protein structure likely evolving from a common ancestor [12]: 1) GH-N (also called GH1 or pituitary GH); 2) GH-V (also referred to as GH2 or placental GH); 3) placental lactogen 1 (also called chorionic somatomammotropin hormone 1); 4) placental lactogen 2 (also called chorionic somatomammotropin hormone 2); and 5) a pseudogene called chorionic somatomammotropin-like hormone. While GH-N is produced mainly in the pituitary, GH-V or placental GH as its name implies, is produced by specialized cells called syncytiotrophoblasts in the placenta. GH-V levels increase during pregnancy and replace pituitary derived GH in circulation. At the amino acid level (Fig.1B and C), GH-V differs from GH-N by 13 of 191 total residues [12, 13]. Like GH-N, the most abundant form of GH-V is the 22-kDa isoform (isoform 1 of 4 total), which has been shown to promote growth as well as maternal insulin resistance. In 1998, a rare 20-kDa isoform (isoform 4) of GH-V was detected in human placenta [14]. Similar to GH-N, the 20-kDa isoform of GH-V is the product of a 45-bp deletion resulting from the use of an alternative or cryptic precursor mRNA acceptor site within exon 3. While the existence of 20-kDa GH-V is known, it is not believed to have any natural biological relevance in humans since it is either not detected or only detected at extremely low levels – accounting for only 0.6% of GH-V mRNA isoform abundance in placenta [15].

20-kDa GH-V lacks diabetogenic activity

Despite a lack of natural utility, a study by Vickers and colleagues in 2009 indicates that 20-kDa GH-V may have potential as a therapeutic drug because it lacks the diabetogenic activity of hGH [16]. Because of this, our laboratory recently tested 20-kDa GH-V in a mouse model of GH deficiency. We showed that 20-kDa GH-V treatment given to young GH deficient mice produces significant increases to circulating IGF-1, femur length, and body length compared to saline treated controls [17]. Furthermore, these increases were similar to GH deficient mice treated with hGH (ie. 22-kDa GH-N), indicating that 20-kDa GH-V has full ability to stimulate IGF-1 and longitudinal bone growth. Since GH is known to increase lean mass and reduce fat mass, we also tested the ability of 20-kDa GH-V to alter body composition in GH deficient mice. We reported that treatment with 20-kDa GH-V, similar to hGH administration, significantly increased lean body mass while decreasing fat mass [17]. These data were in agreement with data from Vickers et al., as 20-kDa GH-V reduced body fat in high fat fed rats similar to those treated with hGH [16]. Importantly,

in our mouse study, analysis of glucose homeostasis revealed that 20-kDa GH-V lacked the diabetogenic activity observed in mice treated with GH. That is, 20-kDa GH-V failed to cause hyperinsulinemia seen in hGH treated mice, and mice treated with 20-kDa GH-V were significantly more sensitive to insulin compared to hGH treated mice [17]. These findings in mice agree with the study in rats [16] as 20-kDa GH-V treatment in non-GH deficient high fat fed rats reduced insulin and C-peptide levels compared to rat receiving GH treatment. Importantly, these data suggest that 20-kDa GH-V may represent improvements to current GH therapies for individuals at risk insulin resistance/metabolic disease.

Does pituitary 20-kDa GH-N also lack diabetogenic activity?

In the 1980's through the early 2000's, studies in animals [18–21] and humans [22] suggested that the short form of pituitary GH, 20-kDa GH-N, may also have decreased diabetogenic activity. Unfortunately, the timing of blood sampling in the lone human study appears to be inappropriate for evaluating a diabetogenic effect (or lack thereof). More specifically, the diabetogenic activity of GH is transient and measures of insulin sensitivity need to be performed within a short window (~1–5 hours) after GH treatment to detect this diabetogenic effect [9, 10]. Because Hayakawa and colleagues [22] tested subjects 24 hours after GH injection, it is not surprising that alterations to glucose homeostasis were not detected. Furthermore, the reports in animal studies [18–21] are in disagreement with other animal studies performed in the same species (dogs and rats) which demonstrate that pituitary 20-kDa GH-N indeed has diabetogenic activity [23, 24]. Therefore, it appears that more studies are needed to help settle this debate about 20-kDa GH-N.

20-kDa GH-V lacks lactogenic activity: implication for PRLR-positive cancers

In addition to lacking diabetogenic activity, two separate laboratories have demonstrated that unlike GH-N, 20-kDa GH-V does not bind the prolactin receptor (PRLR) [13, 16]. This finding has clinical importance since PRLR signaling has been suggested to play a role in progression of certain cancer types including prostate [25, 26], breast [25, 27], ovarian [28, 29] and colon [30]. GH is also implicated in progression in the same cancers as well as others [31–37]. Since hGH binds strongly to PRLR in addition to the GHR, the binding of hGH to PRLR may be responsible for hGH's ability to stimulate growth of these cancers [31, 36, 37]. Because 20-kDa GH-V does not bind to PRLR, we tested its ability to stimulate proliferation of PRLR-positive human cancers compared to that of hGH. Three distinct PRLR positive human cancer cell lines (two breast and one colon cancer cell line) showed a significantly reduced proliferation rate when treated with 20-kDa GH-V compared to hGH. Therefore, these results are in agreement with the theory that GH stimulation of PRLR is partially responsible for proliferation of certain PRLR-positive cancers. Importantly, these data also suggest that 20-kDa GH-V may represent improvements to current GH therapies for individuals at risk for PRLR-positive cancers.

Concluding remarks

Early studies by three separate laboratories (Solomon, Vickers, and our laboratory) indicate that 20-kDa GH-V may have potential use for GH replacement therapy especially in instances where insulin resistance and/or PRLR-positive cancers are a concern. While the clinical relevance of GH's diabetogenic activity and the ability to stimulate PRLR-positive

cancers are controversial and less of a concern in GHD children, treatment in GHD adults is a more appropriate target since metabolic syndrome/diabetes and cancer rates increase with advancing age. As we are in the early stages of evaluating 20-kDa GH-V, more research is needed to better evaluate the benefits and safety of this new therapeutic candidate. However, early studies in cultured cells and in rodents are promising.

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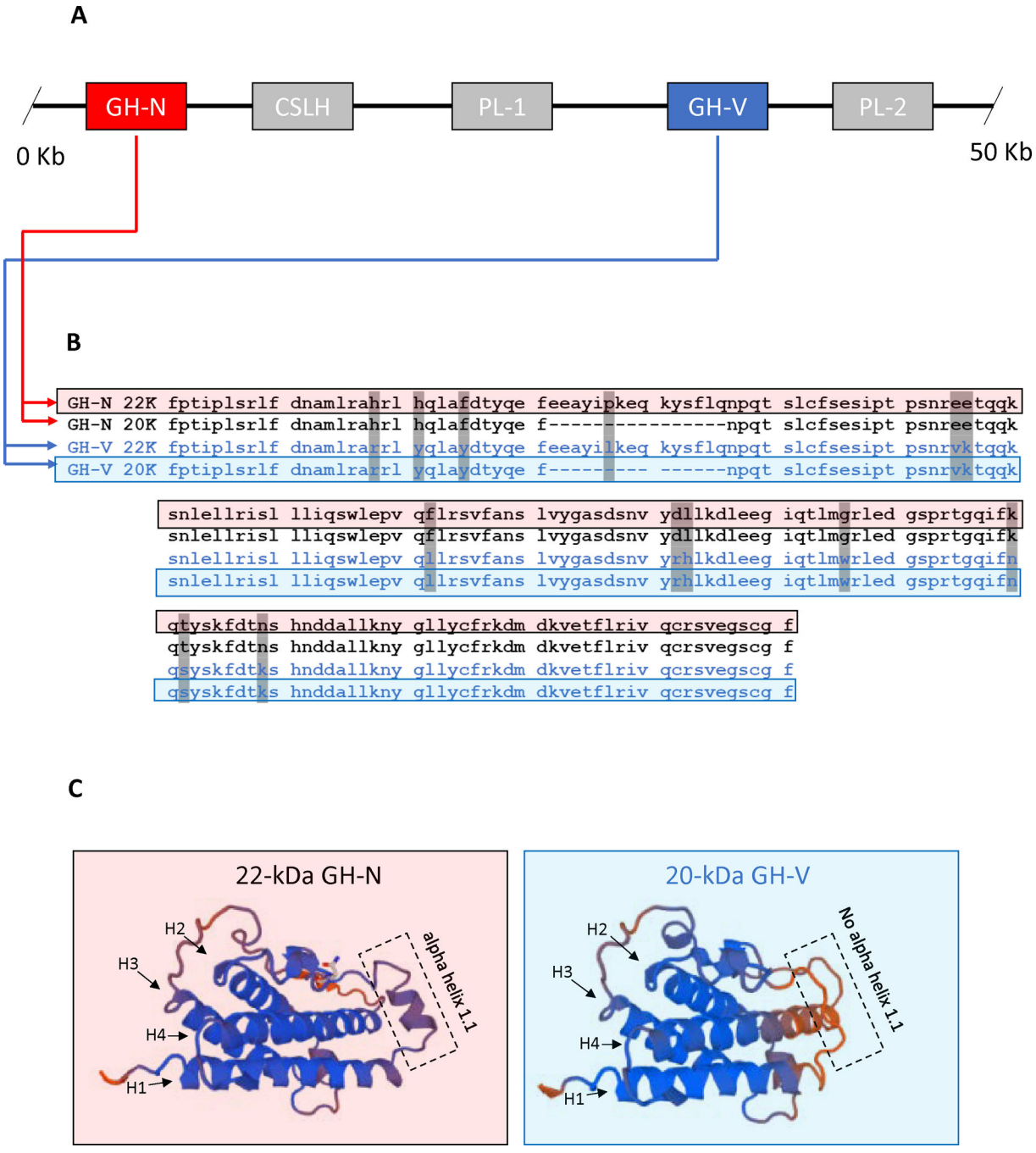

Fig. (1).

Gene family, amino acid comparison, and predicted structure of 22-kDa GH-N and 20-kDa GH-V. (A) The human GH gene family spans a 50 Kb region in chromosome 17. The two GH genes GH-N (red box) and GH-V (blue box) are shown with placental lactogens also shown (grey boxes). (B) Amino acid sequence comparison for the 20 and 22 kDa isoforms of GH-N (black lettering) and GH-V (blue lettering). Grey shading indicates where amino acids differ between GH-N and GH-V. (C) SWISS-MODEL (swissmodel.expasy.org) predicted protein structures of 22-kDa GH-N (left side) and 20-kDa GH-V (right side)

reveals the absence of a small alpha-helix between alpha-helix 1 and alpha-helix 2 for 20-kDa GH-V which may explain the differences in activities reported between these two hormones.