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The Pathophysiology Of Daily Growth Hormone Versus Long-Acting Growth Hormone: A Review

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Abstract

Long-acting growth hormone analogues with lower injection frequency may aid in reducing treatment non-adherence and, as a result, potentially improve therapeutic efficacy. LAGH analogues can be taken on a weekly, biweekly, or monthly basis. There are conceptual reasons to believe that LAGH analogues are weaker compared to daily recombinant human (rh)GH administration. The physiologic secretory pattern of GH is episodic and pulsatile, with several peaks throughout the day and a higher number in the second half of the night while sleeping. Questions have been voiced that elevated and non-pulsatile GH exposure may downregulate or desensitize GH receptor signaling. Hence, it is critical to investigate the pathophysiology of both hormones' actions, including their growth enhancing effects as well as their role in hyperglycemia (the commonest side effect of growth hormone administration). GH can stimulate chondrocyte proliferation, type II collagen synthesis, and extracellular matrix formation via the phosphorylated STAT3 protein. The degree of activation by daily GH and LAGH must be compared. This type of research could shed light on the pathogenicity of daily versus long-acting growth hormone.

I. INTRODUCTION

The anterior pituitary gland synthesizes and secretes human growth hormone (GH), a 22 kDa protein. Ghrelin and hypothalamic GH-releasing hormone (GHRH) enhance GH production and release, which is inhibited by somatostatin and has a negative feedback loop through insulin-like growth factor (IGF)-I [1]. GH release is episodic, with numerous secretory peaks. The majority of spontaneous peaks occur while sleeping, but age, gender, concurrent and chronic disorders, and diet and lifestyle status also play a role. [1, 2].

GH is required for linear growth during childhood and adolescence. Insulin like growth factor-I (IGF-1), which is primarily produced in the liver, is governed by GH, and the two work together to promote osteoblastic activity [1]. GH has a large physiologic impact throughout one's life [2]. Through its anabolic, lipolytic, and ant natriuretic actions, it enhances muscle mass and bone formation, decreases fat mass, and tends to increase total body water. GH stimulates metabolic activity, leading to an increase in resting energy expenditure, fatty acid oxidation, and protein synthesis [3]. Furthermore, converts peripheral thyroxine (T4) to triiodothyronine (T3) and the production of cortisol to non-active cortisol increases. GH also causes hyperinsulinemia by increasing insulin resistance.

Since a new equilibrium was reached during the first years of hormone replacement, the lipolytic effect, and thus the influence on body composition, is most noticeable. Growth retardation, an abnormal body composition with more body fat than lean mass, and reduced physical capability and quality of life are all symptoms of GH insufficiency in children. Treatment with GH in children with growth hormone deficiency (GDH) has been well

established for 20-30 years, and has been shown in multiple trials to advertise linear development and improve metabolic activity [4]. In fact, GH replacement presently lasts far beyond adulthood and even senescence.

Growth hormone deficiency (GHD) in children (CGHD) and adults has been proven to benefit from recombinant human growth hormone (rhGH) therapy provided as daily subcutaneous injections (AGHD). Making the accurate diagnosis, delivering the optimum amount of rhGH, and maintaining patient adherence and perseverance with treatment are all important factors in the efficacy of rhGH therapy[5,6]. Device restrictions, annoyance of required dose frequency, lack of apparent benefit, insurance concerns, and expenses are all obstacles to daily rhGH therapy adherence and persistence[7,8].Poor adherence to rhGH medicine lowered effectiveness in both adolescents and adults, and recent studies predict that roughly 30% of patients adhere to daily rhGH therapy (missing just one dosage per week) [9]. Adherence is particularly poor among teenagers, which may reflect why children's near-adult height scores continue to fall short of the mid-parental target height and the community mean[10,11]. Long-acting growth hormone (LAGH) preparations with lower injection frequency are expected to make patient adherence easier, resulting in longer endurance and maybe better health outcomes.

It has been proposed that a LAGH analogue with a reduced injection frequency may aid in reducing treatment non-adherence and, as a result, perhaps improve treatment outcomes. Many pharmaceutical companies have invested substantial resources in developing LAGH analogues that include a variety of innovative technologies to prolong GH action, potentially allowing for weekly [12], bi-weekly [13-15], or monthly administration [16,17]. There are conceptual reasons to believe that LAGH analogues are inferior than daily rhGH treatment. The physiologic secretory pattern of GH is cyclical and pulsatile, with multiple peaks throughout the day and a larger proportion in the latter half of the night when sleeping. Concerns that elevated and non-pulsatile GH exposure might downregulate or desensitize GH receptor signaling were dispelled when Laursen et al. found that participants who received continuous subcutaneous GH infusions for 6 months maintained normal blood IGF-I levels and did not produce any noticeable symptoms of acromegaly [18].

II. GROWTH HORMONE SIGNALING PATHWAY

When GH binds to its receptor, it triggers the JAK2 tyrosine kinase associated with the GH receptor. JAK2 phosphorylates tyrosines within the GH receptor as well as within itself. These phosphorylated tyrosine's could then attract signaling proteins to the cellular membranes GH receptor-JAK2 complexes. Proteins recruited to GH receptor-JAK2 complexes and phosphorylated by JAK2 include the transcription factors STATS 1, 3, 5a, and 5b that regulate GH sensitive genes including genes encoding c-Fos and IGF-1; IRS 1 and 2 which recruit PI3K and lead to activation of Akt and other proteins; Shc adapter proteins that initiate the Shc/grb2/SOS/Ras/Raf/MEK pathway leading to activation of Erks 1 and 2; SIRPα1 that recruits a tyrosine phosphatase that appears to be a negative regulator of JAK2 activity; and SH2B1, a scaffold protein that enhances GH-induced changes in the cytoskeleton leading to enhanced motility of cells, including macrophages. These pathways work together, presumably with other signaling proteins, to lead to a variety of responses to GH, including body growth, regulation of metabolism, and the ever-emerging actions of GH throughout the body.

III. FUTURE RESEARCH PERSPECTIVES

It may be planned to conduct an experimental study to compare the effects of daily recombinant human growth hormone (rhGH) and long-acting growth hormone analogue (LAGH) on chondrocytes in terms of cell proliferation (as measured by the CCK-8 assay), GH signaling pathway, JAK2 STAT3, STAT5, protein expressions of matrix metallo proteinase 13 (MMP-13), and phosphorylated signal

transducer and activator of transcription. It is possible to compare the DNA synthesis of articular chondrocytes with changes in proto-oncogene c-myc, IGF-1, and IGFBP mRNA expression across time in cultured articular chondrocytes. The expression of GLUT-1 and gluconeogenesis enzymes as mRNA and protein in chondrocytes may provide insight into the hyperglycemic consequences of daily versus long-acting growth hormone.

IV. ENDPOINT MEASURES

Expressions of IGF-1,IGFBP,JAK2-STAT3,STAT5

Expressions of collagen type II, matrix metallo proteinase 13 (MMP-13)

Expressions of GLUT and enzymes of gluconeogenesis

V. EXPECTED OUTCOME AND CONCLUSION

In order to determine the pathogenic mechanisms of hyperglycemia brought on by both analogues of growth hormone, the research may be able to correlate the pathophysiology of daily GH to long acting GH in terms of their signal transduction pathways, expression of several proteins involved in chondrocyte proliferation, and expression of GLUT and enzymes of gluconeogenesis.

The signalling pathway analysis may indicate that daily GH is more important for growth regulation than long-acting analogues of GH. The examination of the expression of glucose transporters generated by both types of growth hormones may shed insight on the cause and severity of this side effect since hyperglycemia is the most frequent adverse reaction to GH therapy.

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