Metabolic Effects of Growth Hormone in Humans

Niels Møller, Jens Otto Jørgensen, Jens Møller, Lotte Ørskov, Per Ovesen, Ole Schmitz, Jens Sandahl Christiansen, and Hans Ørskov

Growth hormone (GH) has acute actions to stimulate lipolysis and ketogenesis after 2 to 3 hours, effects that may be important in the adaptation to stress and fasting. This is accompanied by a decrease in insulin sensitivity in both liver and muscle. These combined effects may be very deleterious to insulin-dependent diabetic patients, in whom increased GH secretion may precipitate and maintain acute metabolic derangement (ketoacidosis) and be a major initiator of the dawn phenomenon. On the other hand, augmented GH secretion plays a beneficial role in the defense against hypoglycemia, in particular during prolonged hypoglycemia and in patients with impaired ability to secrete other counterregulatory hormones appropriately. It is also certain that GH is a potent anabolic hormone in terms of promoted nitrogen retention, but the extent to which these well-known actions are direct or secondary to hyperinsulinemia, increased activity of insulin-like growth factors (IGFs), or release of protein-conserving lipid intermediates has eluded precise characterization.

OVER THE YEARS, the role of growth hormone (GH) in metabolic regulation has to some extent been dwarfed by the more obvious ability of GH to promote growth. Ironically, it is now emerging that a major part of the growth-promoting potential of GH may be secondary to the less conspicuous metabolic impact of the hormone. Exposure to GH leads to increments in circulating levels of insulin-like growth factor-I (IGF-I), insulin, free fatty acids (FFA), ketone bodies, and often glucose.[1-3] There is mounting evidence that all of these compounds have independent nitrogen-retaining effects, and as such they may be regarded as orchestrators of the inherent anabolic capacity of GH. The individual contribution of each of these factors has not been quantified.

GH secretion is amplified by fasting and stress, whereas meals in general inhibit GH release,[4,5] suggesting that the main effects of GH are expressed in the postabsorptive and fasting states. Under these conditions, IGF-I and insulin levels are low or declining, whereas FFA concentrations are high. This is compatible with the notion that GH-dependent growth and nitrogen retention is critically reliant on mobilization of lipid fuels—in a homeotherm organism with limited carbohydrate stores and without immediate access to food, lipid oxidation must ultimately substitute for all spared protein.

When GH was purified and used in human in vivo studies in the 1950s and 1960s, it quickly became established that administration of large amounts of pituitary GH enhanced lipolysis and, through actions opposing those of insulin, led to hyperglycemia.[6,7] Many of these pioneer studies used very high doses of GH. With modern techniques, the pulsatile nature of GH secretion has now been characterized,[8] and it has been reported that normal man secretes a total of approximately 0.5 mg GH/24 h. The secretion is predominantly pulsatile, and pulses are seen every 2 to 3 hours. In the circulation, a variety of GH derivatives may be detected, a finding with potentially great but so far uncertain significance.[9]

Recently, biosynthetically manufactured GH has become available in plenty, and this, together with the sophistication of techniques for metabolic studies, has revived interest in the significance of GH. The present review will seek to recapitulate some of these recent findings in the field. It will not attempt to deal with the in vitro effects of GH or the metabolic consequences of GH deficiency, the diversity of which is reported elsewhere in this issue.

LIPID METABOLISM

The most striking effect after a single GH pulse is a steep increase in circulating levels of FFA and ketone bodies, reflecting stimulation of lipolysis. Typically, baseline values are doubled and peak values recorded after 2 to 3 hours. Both pulsatile and continuous administration of moderate amounts of GH (70 to 400 μg) to healthy postabsorptive humans lead to a clear dose-dependent stimulation of lipolysis, with increased circulating levels of FFA and glycerol and increased lipid oxidation rates as assessed by indirect calorimetry.[10-12] There is some evidence that the lipolytic sensitivity to GH increases during fasting.[13] An investigation of young healthy subjects showed that the nocturnal mean peak of GH preceded that of FFA by 2 hours,[14] a time lag close to the one found after GH bolus administration, thus supporting the notion that GH acts as a central regulator of circadian oscillations in release and oxidation rates of lipids and other fuel substrates. The idea is further corroborated by studies showing that a lack of nocturnal GH release compromises the physiological overnight surge of lipid fuels,[15] and by studies implying a correlation between nocturnal GH and ketone body concentrations in terms of both time and magnitude.[16]

Insulin-dependent diabetic patients are exposed to high levels of GH, particularly in periods of poor control,[17] and characterization of the role of GH in metabolic regulation in diabetes has accordingly been a prime target in many experimental studies. Insulin-dependent subjects are highly susceptible to the lipolytic, ketogenic, and hyperglycemic effects of GH, since they are deprived of residual β-cell function and hence the ability to generate compensatory

From Medical Department M (Endocrinology and Diabetes) and the Institute of Experimental Research, University of Aarhus, Aarhus, Denmark.

Address reprint requests to Niels Møller, MD, Medical Department M (Endocrinology and Diabetes), Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark.

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hyperinsulinemia. A recent survey has estimated that GH concentrations during poor diabetes control are increased twofold to threefold.[18] Studies conducted by Press et al[19] have unequivocally established the capacity of GH to cause deterioration in metabolic control in type I diabetes. These experiments demonstrated that administration of hourly 100-μg GH pulses after a latency of several hours induced dramatic 100% increases in circulating glucose values together with marked increments in circulating lipid fuels. Notably, the concentration of ketone bodies increased by several hundred percent, underlining the potential of GH excess to initiate and maintain ketosis and subsequently impending acidosis. On the other hand, when a single bolus of 210 μg GH, intended to mimic a pulsatile episode, is given to well-controlled diabetic subjects, transient but marked elevations of lipid substrates are observed, in a manner similar to normal physiology.[20]

Information regarding lipid metabolism in patients with acromegaly is sparse. However, there is explicit evidence that the disease, despite substantial hyperinsulinemia, is characterized by increased levels of circulating lipid intermediates, increased muscle uptake of these intermediates, and an increased rate of lipid oxidation in a magnitude of 40% to 50%.[21] These abnormalities are accompanied by increased rates of total energy expenditure and suppressed rates of glucose oxidation.

On the whole, it may be concluded that the prime effect of GH is stimulation of lipolysis and lipid oxidation. This spares protein and carbohydrate stores from immediate oxidative demands and constitutes a homeostatic mechanism, adding momentum to any incoming protein-conserving signals.

CARBOHYDRATE METABOLISM

The effects of GH on insulin sensitivity have been assessed in some detail, and it has consistently been shown that continuous administration of relatively large amounts (1.5 mg) of GH leads to a substantial impairment of both hepatic and peripheral insulin sensitivity in normal man after 12 hours.[22,23] A more recent study using more moderate amounts of both GH and insulin found that GH impaired hepatic and peripheral insulin sensitivity after approximately 2 hours, that the impairment of peripheral insulin sensitivity largely resided in muscle, and that GH could overwhelm the antilipolytic actions of mild hyperinsulinemia.[24] There is also evidence that GH restrains the increase in glucose flux seen during hyperglycemia, caused by a mass action of glucose.[25] It is presently unclear to what extent alteration of gene expression of glucose transporters and key glucoregulatory enzymes is involved in GH-induced impairment of insulin action. It has been shown that short-term GH exposure blunts the activity of glycogen synthase in striated muscle, but this effect could also relate to augmented lipid metabolites in the circulation.[26]

The extent to which these findings are secondary to increased lipid availability and subsequent "Randle" substrate competition[27] is not known, although it has been shown that co-infusion of GH with nicotinic acid (an antilipolytic agent) abolishes the effects of GH on glucose tolerance.[28]

Postabsorptive glucose metabolism is more subtly affected by GH. Although muscle utilization of glucose is intrinsically low,[29] a further suppression of glucose uptake is typically seen after acute GH exposure.[7,10,11] The increase in lipid oxidation is followed by a proportional decrease in glucose oxidation, total glucose turnover remains unaffected, and—in consequence—nonoxidative glucose turnover increases.[10]

The coexistence of decreased glucose oxidation and suppressed muscle glucose uptake in the presence of unchanged glucose turnover strongly suggests that GH promotes nonoxidative glucose utilization in a nonmuscle compartment of the body. Neither the tissue nor the biochemical pathways involved are known. Stimulated lipogenesis in adipose tissue or liver appears implausible, since ongoing lipogenesis would increase the respiratory exchange ratio as opposed to the observed decrease. Conceivably, GH may increase gluconeogenesis and glucose cycling in, eg, splanchnic tissues/liver, adipose tissue, or skin. Large doses of GH have been reported to suppress postabsorptive, net splanchnic glucose output acutely, compatible with increased glucose uptake,[30] and in vitro experiments have shown increased gluconeogenesis from either alanine or lactate in canine kidney cortex incubated with GH.[31] In addition, studies in acromegalic patients have shown a 50% increase in glucose/glucose-6-phosphate cycling,[32] which could explain a majority of the increased glucose turnover recorded in these patients. It has also been demonstrated that overnight administration of large doses of GH in normal man stimulates gluconeogenesis, as judged by incorporation of labeled carbon dioxide in glucose.[33] Finally, dogs treated with generous amounts of GH for several days had a more than doubled liver glycogen content—from 5 to 11 g/100 g liver.[34]

Although it is to some extent circumstantial, current evidence therefore suggests that the explicit stimulation of lipolysis by GH is accompanied by a proportional decrease in glucose oxidation and an increase in nonoxidative glucose disposal, plausibly in the form of gluconeogenesis and glucose storage.

Apart from these tentative physiological roles, it is now well substantiated that intact GH secretion is crucial in the combat against prolonged hypoglycemia, and it is possible that GH is a main initiator of the nocturnal increase in insulin requirements ("dawn phenomenon") in insulin-dependent patients.[15,35,36]

PROTEIN METABOLISM

The immediate impact of GH on protein metabolism in humans is not well described. The protein-sparing effects of prolonged GH exposure are unequivocal, but most investigations in this area have used high doses of GH for several days, thus inducing "short-term acromegaly."[6,37-39] This invariably leads to stimulation of lipolysis, hyperinsulinemia, and stimulation of IGF-I activity. All of these have potent protein anabolic properties,[40-44] so the distinction

between direct and indirect effects becomes problematic. However, the studies do clearly show that GH causes nitrogen retention, as judged by decreased urinary excretion rates for urea, creatinine, and ammonium. There is additional evidence that massive GH exposure may preferentially stimulate protein synthesis; interestingly, ketone bodies have been reported to stimulate protein synthesis,[44] whereas insulin and IGF-I are believed to restrict breakdown.[40,41] The concept that GH acutely and directly increases synthesis of proteins has received support from forearm-perfusion studies,[45,46] but a recent well-controlled study could not entirely confirm these findings.[47]

The effects of GH on hepatic nitrogen metabolism are also poorly elucidated. Experiments in hypophysectomized rats have indicated that GH may act on the liver to decrease urea synthesis and in parallel increase glutamate release, thereby diminishing hepatorenal clearance of the circulating nitrogen pool.[48] These findings have not been reproduced in short-term studies in humans,[49] but preliminary data suggest that perhaps more prolonged GH exposure may be required for hepatic effects to occur.

CONCLUSIONS

GH has plain and manifest actions to stimulate lipolysis in adipose tissue and subsequently whole-body lipid oxidation. This effect can be regarded as the backbone in a metabolic scenario that allows conservation of protein and carbohydrate. The effects on glucose and protein metabolism are probably more manifold, involving insulin, IGF-I, and FFA. However, it is clear that GH exposure eventually leads to impairment of insulin sensitivity and improvement of nitrogen balance.

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