Effects of growth hormone on lipid metabolism in humans

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Abstract

The most immediate effect of growth hormone (GH) administration in humans is a significant increase in free fatty acids after 1–2 h, reflecting stimulation of lipolysis and ketogenesis. This stimulation represents an important physiological adaptation to stress and fasting. When the capacity of GH to increase lipolysis is blocked, the protein-retaining and insulin-antagonistic effects of GH on glucose metabolism are either abolished or weakened dramatically, compatible with a key role for lipolysis in orchestrating the metabolic actions of GH.

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1. Introduction

Over the past 50 years, the role of growth hormone (GH) in metabolic regulation has, to some extent, been dwarfed by the more conspicuous ability of GH to promote growth. Ironically, it is now becoming increasingly clear that much of the growth-promoting potential of GH is secondary to the metabolic impact of the hormone. Exposure to GH leads to increases in circulating levels of free fatty acids (FFA), ketone bodies, insulin-like growth factor I (IGF-I), insulin and glucose [1–3]. Accumulating evidence suggests that all of these compounds have independent nitrogen-retaining effects and may be viewed as orchestrators of the inherent anabolic capacity of GH. Fasting and stress amplify GH secretion; whereas meals, in general, inhibit GH release [4,5], suggesting that the main impact of GH is evident in the postabsorptive and fasting states. Under these conditions, IGF-I and insulin levels are low or are in decline, whereas FFA concentrations are high. This could mean that GH-dependent growth and nitrogen retention is critically reliant on mobilisation of lipid fuels. In a homeothermic organism with very limited carbohydrate stores and without immediate access to food, lipid oxidation must serve as an energy source to spare protein.

When pituitary GH was purified and manufactured for use in humans 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 hyperglycaemia [6,7]. Many of these pioneer studies employed very high doses of GH. Utilising modern assays, the pulsatile nature of GH secretion has now been characterised [8], and it has been found that healthy humans secrete a total of roughly 0.5 mg per 24 h. The secretion is predominantly pulsatile. In the circulation, a variety of molecular forms of GH may be detected – a finding with potentially great, but hitherto uncertain significance [9].

Over the past 20 years, biosynthetically manufactured GH has become widely available, and this, along with the greater sophistication of techniques for metabolic studies, has revived interest in the significance of GH. This article recapitulates current knowledge about the role of GH in the regulation of human in vivo lipid metabolism.

2. Lipid metabolism

The most striking effect after a single GH pulsation is a steep increase in the circulating levels of FFA and ketone bodies, reflecting stimulation of lipolysis. Typically, baseline values are doubled and peak values are recorded after 2–3 h [11]. Both pulsatile and continuous
administration of moderate amounts of GH between 70
and 400 μg to healthy, postabsorptive humans leads to a
clear dose-dependent stimulation of lipolysis, increased
circulating levels of FFA and glycerol and increased li-
pid oxidation rates, as assessed by indirect calorimetry
[10–12]. Furthermore, studies utilising isotope dilution
techniques have shown that whole-body palmitate fluxes
increase following pulsatile GH exposure [13].

There is some evidence that the lipolytic sensitivity to
GH increases during fasting [14]. An investigation of
young, healthy subjects reported that the nocturnal
mean peak of GH preceded that of FFA by 2 h [15] – a
time lag very close to the one found after GH bolus
administration. These results support the notion that
GH acts as a central regulator of circadian oscillations
in the release and oxidation of lipids and other fuel
substrates. The idea is further corroborated by studies
showing that lack of nocturnal GH release compromises
the physiological overnight surge of lipid fuels [16] and
by studies implying a correlation between nocturnal GH
and ketone body concentrations in terms of time and
magnitude [17].

Insulin-dependent diabetic patients are exposed to
high levels of GH, particularly during periods of poor
control [18], and characterisation of the role of GH in
metabolic regulation in diabetes has accordingly been
a prime target for many experimental designs. Insulin-
dependent subjects are highly susceptible to the lipolytic,
ketogenic and hyperglycaemic effects of GH, since they
are deprived of residual beta cell function and hence, of
the ability to generate compensatory hyperinsulinaemia.
A recent survey has estimated that GH concentrations
in patients with poor diabetes control are increased two-
to three-fold [19].

Studies conducted by Press et al. [20] have established
the capacity of GH to cause deterioration of metabolic
control in type 1 diabetes. These experiments demon-
strated 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 increases in circulating lipid fuels. Notably, the
concentration of ketone bodies – which are organic ac-
ids and give rise to ketoacidosis – rose by several hun-
dred percent, emphasizing the potential of GH excess to
initiate and maintain ketosis and subsequent acidosis.
On the other hand, when a single bolus of 210 μg GH,
intended to mimic a pulsatile episode, was given to well
controlled diabetic subjects, transient but marked ele-
vations of lipid substrates were observed, occurring in a
manner proportional to normal physiology [21].

Information regarding lipid metabolism in patients
with acromegaly is sparse. There are, however, explicit
suggestions that the disease is characterised by increased
levels of circulating lipid intermediates, increased muscle
uptake of these intermediates and a 40–50% magnitude
increase in the rate of lipid oxidation [22]. These ab-
normalities are accompanied by increased rates of total
energy expenditure and suppressed rates of glucose
oxidation.

Few studies have addressed the issue of how GH
affects regional lipolysis. Employing microdialysis
catheter technique, we recently found that the increase
in local glycerol released in the process of lipolysis was
higher in abdominal adipose tissue compared with
femoral tissue [23], thus supporting the notion that GH
preferentially stimulates upper body lipolysis.

In vitro studies have indicated that the lipolytic ac-
tions of GH may involve stimulation of gene expression
after binding of the GH receptor with JAK2 tyrosine
kinase and subsequent activation of the complex [24].
The entire cascade of interactions responsible for in-
tracellular signalling is not known in detail, but it ap-
ppears to include activation of adenyl cyclase and
stimulation of cAMP production, triggering the hor-
mone-sensitive lipase [25].

On the whole, it may be argued that the prime effect
of GH per se is stimulation of lipolysis and lipid oxida-
tion. This alleviates protein and carbohydrate stores
from immediate oxidative demands, and constitutes a
homeostatic mechanism, adding momentum to protein-
conserving signals.

2.1. Interactions between carbohydrate and lipid metab-
olism

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 led to a substantial impairment
of both hepatic and peripheral insulin sensitivity in
healthy humans after 12 h [26,27]. Following adminis-
tration of more moderate amounts of both GH and
insulin, it was observed that: GH impaired hepatic and
peripheral insulin sensitivity after approximately 2 h;
impairment of peripheral insulin sensitivity largely re-
sided in muscle; and GH had the potency to offset the
antilipolytic actions of light hyperinsulinaemia [28].
There is also evidence that GH moderates the increase in
glucose instability seen during hyperinsulinaemia caused
by “mass action” of glucose [29]. It has been shown that
short-term GH exposure blunts the activity of glycogen
synthase in striated muscle, but this effect could be
secondary to augmented lipid circulation [30].

The above findings may largely be caused by in-
creased lipid availability and subsequent “Randle
substrate competition [31]. It has been shown that co-
fusion of GH with nicotinic acid (an antilipolytic
agent) abolishes the effects of GH on glucose tolerance
[32]. In a more recent study, we observed that admin-
istration of a nicotinic acid derivative to inhibit lipolysis
greatly reduced the ability of GH to decrease insulin
sensitivity [33].
GH more subtly affects postabsorptive glucose metabolism. Although muscle utilisation of glucose is intrinsically low [34], 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, as a consequence, non-oxidative glucose turnover increases [11].

Although circumstantial, current evidence suggests that the explicit stimulation of lipolysis by GH is accompanied by a proportional decrease in glucose oxidation and an increase in non-oxidative glucose disposal, possibly in the form of gluconeogenesis and glucose storage (glycogen), which are two components of non-oxidative glucose disposal.

2.2. Interactions between protein and lipid metabolism

It is well established that GH has protein-retaining effects in humans. Administration of GH leads to decreases in urinary urea excretion, urea fluxes and urea production rates and increases in protein synthesis [35–41]. It is particularly noteworthy that when endogenous GH action is partially blocked under conditions of fasting, urea production rates rise by more than 50%, strongly affirming the importance of GH as a protein-conserving agent during fasting [42].

Since GH exposure invariably increases lipolysis and since lipid intermediates have protein-sparing properties, we tested the hypothesis that the nitrogen-retaining capacity of GH relies on lipolysis stimulation. In this study, preliminary data suggest that blocking lipolysis with a nicotinic acid derivative dramatically increases urea and protein losses and abolishes the ability of GH to induce urea and protein retention (Norrelund et al., unpublished). Thus, it is very conceivable that stimulation of lipolysis is the most important protein-conserving mechanism of GH.

3. GH, lipids and body composition

GH deficiency is associated with increased fat mass, particularly deposition of visceral fat, which is known to be a prominent risk factor for the development of cardiovascular morbidity and mortality [43,44]. A number of studies have shown that GH treatment reduces fat mass [43,44]. Evidently, part of this effect may be secondary to the lipolytic actions of GH. As previously noted, it is likely that GH preferentially stimulates upper body lipolysis [23]. Another mechanism whereby GH may affect fat mass is by modulation of adipose tissue lipogenesis. Indeed, some studies have shown that GH specifically inhibits lipoprotein lipase activity in adipose tissue [45,46]. Whether this translates into any significant reduction in FFA deposition in adipose tissue is presently unclear.

4. Conclusion

In conclusion, GH has potent and explicit actions to stimulate lipolysis, giving rise to increased concentrations of FFA and ketone bodies in the circulation. The ability of GH to spare glucose and protein seems to a large extent to depend on stimulation of lipolysis.

References


