Review

The Metabolic Effects of Growth Hormone (GH)

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Introduction

In 1910 hypophysectomy was shown to arrest growth (1) and in 1912, Ashner demonstrated that the main action of growth hormone (GH) was to promote longitudinal bone growth (2). Thus GH is essential for body growth but as normal growth occurs over a relatively short time period and GH secretion continues throughout life it is not surprising that GH has many other functions including both acute and chronic effects on metabolism and body composition. GH can produce metabolic effects directly through the GH receptor or indirectly through induction of insulin-like growth factor I (IGF-I). IGF-I can itself act in an endocrine manner circulating in plasma or act in a paracrine/autocrine manner locally at or near its site of production (Fig. 1).

The metabolic effects of GH on carbohydrate and glucose metabolism, fat and lipid metabolism and protein metabolism are discussed in-turn.

Glucose metabolism

In the 1920's Houssay discovered that hypophysectomy reduced the hyperglycemia of diabetes (3). In the 1930's pituitary extracts were shown to be diabetogenic (4). Young demonstrated that the diabetogenic factor in the pituitary co-extracted with the growth promoting activity (5,6) and subsequently short term and long term GH administration was shown to induce transient or permanent diabetes respectively (7). Altszuler et al. (8) showed GH induced diabetes was associated with high circulating levels of insulin and insulin resistance. Sönksen et al. (9) showed that a spectrum of impaired glucose tolerance and diabetes is seen in patients with acromegaly and improved after hypophysectomy. Hepatic glucose production has been shown to be stimulated and in pharmacological doses GH increases plasma glucose concentrations, impairs insulin sensitivity and stimulates insulin secretion (10). Mintz et al. (11) studied endogenous GH secretion and showed impaired glucose tolerance following insulin induced hypoglycemic GH secretion. The dawn phenomenon of relative insulin resistance during the early hours has been associated with the marked nocturnal GH secretion (12). GH hypersecretion in patients with IDDM is thought to contribute to poor diabetic control (13). More recently physiological GH replacement therapy given to adult GH deficient patients has been shown to increase both fasting blood sugars and insulin concentrations (14).

In addition to these "diabetogenic" properties of GH paradoxical transient insulin-like effects on glucose metabolism have also been demonstrated. In vitro GH increases glucose uptake and oxidation in rat muscle, kidney and adipose tissue within 20-60 min of receiving the
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Fig. 1 Possible mechanism of action of growth hormone on metabolism.

Fig. 2 Effect of growth hormone on protein metabolism. 18 adult growth hormone deficient patients were randomised to GH replacement therapy or placebo and whole-body leucine turnover studies performed at baseline and after 2 months treatment. Leucine Ra is a measure of proteolysis (upper graph) and non-oxidative Rd (lower graph) is a measure of protein synthesis. “PLACEBO” = placebo treated group and “GH TREATED” = group given growth hormone replacement therapy.

dose. In normal and hypophysectomised rats (15) a similar acute effect is seen (16) following administration of GH. These insulin-like effects are transient and in the continued presence of GH, tissues become refractory (17), the physiological relevance of such effects are therefore questionable.

**Lipid Metabolism**

In adipose tissue GH also exerts transient insulin-like effects with an initial inhibition of lipolysis and a fall in free fatty acid release (18). The acute antilipolytic effect of GH lasts for only a short time and then lipolysis becomes increased and free fatty acids and ketone levels begin to rise (18,19). It has been shown that GH stimulates ketogenesis and using isolated perfused livers Chernick et al. (19) have shown that the ketogenesis is secondary to the rise in free fatty acid delivery to the liver. Both GH deficient children and GH deficient adults present in a mildly obese state that is reversed by GH replacement therapy (20,21). GH reduces body fat by increasing

Fig. 3 Summary of the metabolic effects of growth hormone.
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hydrolysis of triglycerides releasing free fatty acids and glycerol whilst decreasing free fatty acid re-esterification (22). GH also has effects on cholesterol and lipoprotein metabolism and GH replacement therapy given to adult GH deficient adults has been shown to reduce total and LDL cholesterol (23).

Protein Metabolism

GH is the classical anabolic hormone. It increases both growth and muscle mass in GH deficient children (20). Growth hormone is associated with a decrease in nitrogen excretion and an increase in the number of ribosomes in tissues (24,25). Interestingly Milman et al. (26), failed to increase nitrogen retention with GH in diabetic cats unless insulin was also given. Early studies investigating the effects of GH were performed in hypophysectomised animals and it was shown that hypophysectomy was associated with a loss of body protein and that the administration of anterior pituitary extracts to these animals resulted in an increase in protein content and a reduction in their fat content (6). More recently GH treatment of GH deficient adults has been shown to increase lean body mass (21,27) and thigh muscle mass as measured by cross sectional CT scan (27,28). It is possible for GH to achieve its anabolic effects by either increased protein synthesis or decreased protein breakdown.

Using whole-body leucine turnover studies of adult GH deficient subjects given GH replacement therapy Russell-Jones et al. (14) have shown that GH has a direct effect on protein synthesis and no effect on protein breakdown (Fig. 2). Insulin has also been shown by similar methods to reduce protein breakdown which helps to explain Millman’s observation that insulin in addition to GH was required in diabetic cats to promote nitrogen retention.

In the late 1980’s with the availability of increased amounts of recombinant human GH studies examining the metabolic functions of GH in adults were possible (14,21,23,27,28). The results of such studies have shown unequivocally that GH has a major role in the regulation of metabolism and body composition and should be replaced in deficient subjects of all ages. The metabolic effects of GH are summarized in Fig. 3. GH therefore has an important influence on metabolism and body composition throughout life.

References

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