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Traditional and novel aspects of the metabolic actions of growth hormone

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ABSTRACT

Growth hormone has been known to be diabetogenic for almost a century and it's diabetogenic properties fostered consideration of excessive and abnormal GH secretion as a cause of diabetes, as well as a role in the microvascular complications, especially retinopathy. However, besides inducing insulin resistance, GH also is lipolytic and a major anabolic hormone for nitrogen retention and protein synthesis. These actions are best illustrated at the extremes of GH secretion: Gigantism/acromegaly is characterized by excessive growth, CHO intolerance, hyperplasia of bone, little body fat and prominent muscle development, whereas total deficiency of GH secretion or action is associated with adiposity, poor growth, and poor muscle development. These actions also become apparent during puberty and pregnancy, times when GH secretion is increased and account for the characteristic changes in body composition and tendency to diabetes. More recently, tissue specific deletions of the GH receptor (GHR), have uncovered newer metabolic effects including it's essential role in triglyceride export from the liver when GHR is deleted in the liver, leading to hepatic steatosis and ultimately to hepatic adenoma formation, effects which may explain these findings in obesity, a state of diminished GH secretion and action. In addition deletion of GH action in muscle and fat is associated with specific patterns of disturbed phenotype and metabolic effects in CHO, fat, and protein metabolism affecting the specific tissue and whole body function. This chapter provides an overview of these classic and newer metabolic functions of GH, placing this hormone and its actions in a central role of body fuel economy in health and disease.

1. Introduction

A metabolic role for growth hormone (GH) has been postulated for over 80 years, one of the first being the Nobel laureate Bernardo Houssay, who showed in 1930 that hyperglycemia and other biochemical abnormalities improved after hypophysectomy in experimental-induced diabetes in dogs [1,2]. By contrast, injections of pituitary extracts, and later purified GH, resulted in hyperglycemia and frank diabetes, younger dogs being more resistant to these effects than adult dogs; complications of diabetes such as retinopathy improved after pituitary infarction during labor and delivery in pregnancy (Sheehan's syndrome). In humans, acromegaly was associated with a greater prevalence of diabetes which could be provoked by several days of GH administration [2]. So strong were these associations that it was believed for some time that GH, or other hormonal abnormalities, might be the cause of diabetes and contribute to the complications. Indeed, until the advent of laser therapy in the mid-1970s, the standard therapy for proliferative retinopathy associated with diabetes was pituitary ablation via surgery or implantation of radioactive yttrium into the pituitary fossa [3].

2. Metabolic effects of infused growth hormone

The availability of purified human GH extracted from cadaveric pituitaries, permitted a more detailed investigation of the metabolic effects of GH infused to healthy volunteers [4]. An intravenous injection of 5 mg of GH (now known to be a pharmacological dose), resulted in a rise of free fatty acids (FFAs) and impairment of glucose disposal during an intravenous glucose tolerance test (Fig. 1a); the k value is the slope of glucose disappearance after an intravenous bolus so that the higher the slope, the more rapid the decline in glucose reflecting the effects of insulin. Notably, both the rise in FFA, as well as the diabetic k value take time to develop, and are preceded by an insulin-like effect as evident in the fall of FFA and initially higher K value. An infusion of GH at 2 mg/h for 5 h induced a rise in FFA, and a small rise in glucose after 2 h; oral glucose tolerance became frankly diabetic despite a large increment in insulin secretion, and the fall of FFA in response to the insulin was blunted (Fig. 1b). In other studies it was shown that GH stimulates amino acid uptake in muscle, even in vitro, suggesting a direct effect of GH [5]. Thus, GH is "diabetogenic" inducing insulin resistance and hyperglycemia, lipolytic and protein anabolic. In addition, it stimulates insulin release by enhancing insulin secretion from the pancreas and it stimulates growth of bone directly as well as indirectly via the generation of IGF-I primarily in the liver (Fig. 2). The significance of these effects is noted in patients who have growth hormone excess in infancy–childhood as exaggerated muscle and bone development, little fat and abnormal carbohydrate (CHO) metabolism; and in those with absent GH effects, as in Laron syndrome, with poor growth and poor muscle development with excessive fat deposits. In normal children, the effects of GH are noted during puberty.

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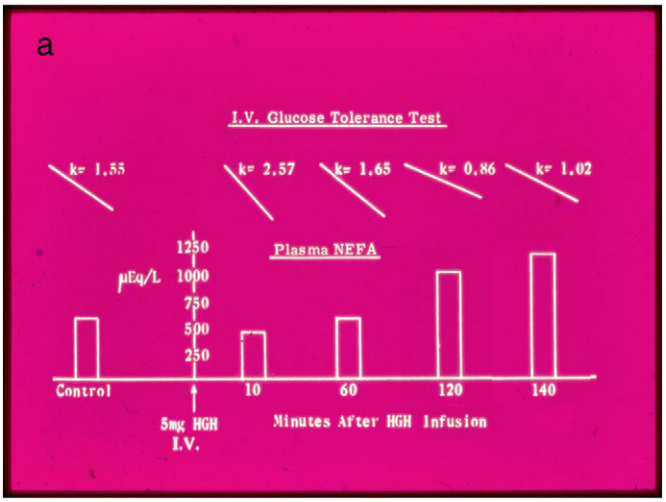

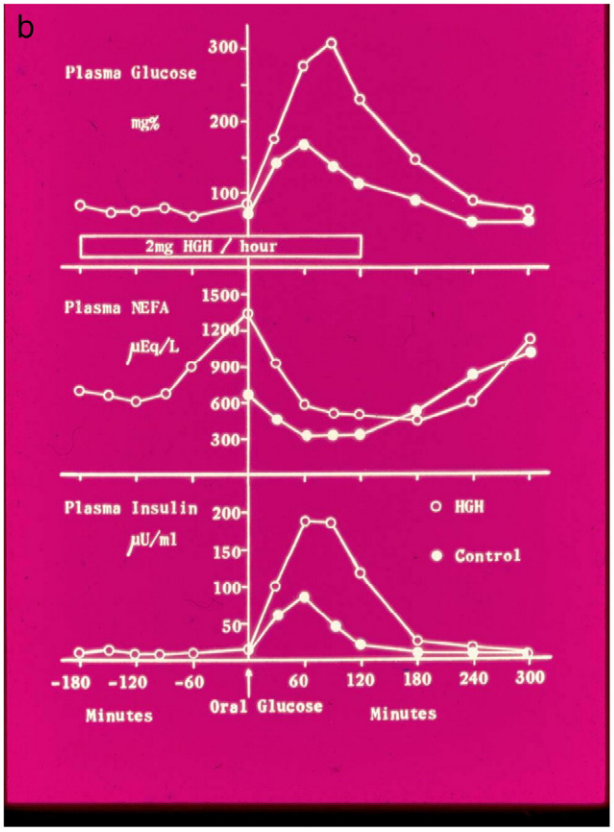

Fig. 1. a. Effects of growth hormone (GH) on intravenous glucose tolerance and non-esterified fatty acids (NEFAs). Note that the k value, an index of insulin-like effects, increases shortly after the glucose bolus and NEFA declines 10 min after the bolus of GH. Thus, initially GH has an "insulin-like effect". The k value steadily declines thereafter and NEFA levels rise, reflecting insulin resistance and lipolysis induced by GH. b. Oral glucose tolerance (OGTT) in the absence (control) and infusion of GH at 2 mg/h for 3 h before and 2 h after the oral glucose load. Note the induction of insulin resistance with frank diabetes despite a threefold increase in insulin. GH induces lipolysis but the uptake of fatty acids is not impaired during the OGTT when insulin is secreted.

3. Carbohydrate metabolism in children during puberty

In normal children undergoing puberty, insulin resistance is manifest as a 2–3 fold increase in the insulin response to an oral glucose tolerance test, whether the dose of glucose is given at a dose of 1.75 g/kg, or "normalized" by giving 55 g/M^2 (Fig. 3). In both of these methods of giving glucose, the fasting glucose concentration, peak glucose and area under the glucose curve remain the same. However, the insulin response is 2–3 fold higher in puberty, irrespective of the amount of administered glucose [6]. Using the technique of the euglycemic glucose clamp, it was shown that the insulin sensitivity index is about twice as high in pre-pubertal as in pubertal children (Fig. 4). When a cohort of prepubertal children was followed longitudinally during puberty, the insulin sensitivity index measured via the euglycemic clamp approach fell by about 50%, whereas the first-phase insulin response, measured via the hyperglycemic clamp approach, doubled [7]. Thus, normal children compensate for insulin resistance during puberty by doubling their insulin response. Of the hormonal changes during puberty, it is not the sex steroids but increased GH secretion at night that is responsible for this change in insulin sensitivity and the resultant need for increased insulin secretion, a situation similar to that of the third trimester of pregnancy. Those who cannot achieve this required increase in insulin secretion, because they have a genetic defect such as MODY, or other defects in insulin secretion including ongoing autoimmune destruction, manifest that they have, or are developing diabetes. This explains why one of the peaks of presentation of diabetes is at puberty, and why gestational diabetes occurs during pregnancy, disappears after the separation of the placenta, and may reappear years later as the defect in insulin secretion becomes worse and cannot compensate for insulin resistance of obesity or other factors.

4. Protein metabolism during puberty

Protein anabolism is markedly increased during puberty as a result of increased GH secretion together with increased insulin secretion, evident from increased rates of protein synthesis in the whole body, as well as the increased extraction of amino acids during infusions of glucose. Thus, during a hyperglycemic clamp, the extraction of the branched chain amino acids leucine, iso-leucine and valine, is greater in pubertal than in pre-pubertal children [8]. Treatment of GH deficient children with GH can restore whole body protein synthesis rates to the same levels as seen in normal age-matched controls, but treatment of such GH deficient children with IGF-I, does not restore normal rates of protein synthesis [9]. Thus, the increased body muscle mass during puberty in males and females, depends on the synergistic effects of GH and insulin, together with the sex steroids, estrogen in females and testosterone in males. The androgenic effects on muscle are greater than those of estrogens, contributing to the greater muscle mass formation in males; estrogens promote greater fat accumulation.

5. Lipid metabolism during puberty

During puberty, rates of total body lipolysis, as reflected in the rates of glycerol turnover, increase by 30%–50%, associated with a 2–3 fold increase in the ratio of oxidation of lipid to the oxidation of glucose. As a result of increased oxidation of fat, caused by increased GH during puberty, fasting free fatty acid (FFA) levels decline. Thus, the effects of GH during puberty favor increased lipid turnover and oxidation, sparing glucose and amino-acids for anabolic growth and lowering fasting FFA. Similar changes also occur when peri-pubertal boys with idiopathic short stature are treated with standard doses of GH at 0.3 mg/kg/week [10]. Four months of such treatment resulted in a significant increase in fat free mass, as well as a decline in total fat mass and percent body fat; insulin as well as IGF-I levels increased, cholesterol and LDL levels declined, whereas HDL, FFA and triglycerides remained unchanged. Thus, treatment with GH for only 4 months in males with idiopathic short stature mimics puberty in significant changes of body composition as well as increasing insulin resistance and higher insulin secretion.

In summary, increased GH secretion during puberty leads to:

- Insulin resistance for carbohydrate metabolism, but not for protein metabolism.