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Metabolic Actions of Growth Hormone in Man

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Abstract. GH continues to be produced after the cessation of childhood growth and is the most abundant pituitary hormone in the adult pituitary. There is strong evidence that GH continues to exert significant biological effects on body metabolism in adult humans. The actions of GH may be direct or indirectly mediated by IGF-1. The direct actions of GH impart major effects on glucose, lipid and sodium homeostasis. GH administration causes hyperinsulinaemia and impairs the ability of insulin to suppress hepatic glucose production and to stimulate glucose uptake and oxidation. GH enhances fat utilisation by stimulating lipolysis and fat oxidation. The significance of these effects is reflected in the finding of increased adiposity in GH deficiency (GHD) and reduced fat mass in acromegaly. GH causes sodium retention which occurs in part through activation of the renin-angiotensin system. Extracellular water volume is diminished in GHD and increased in relation to the extent of GH excess in acromegaly. Lean body mass is reduced in GHD and restored by GH treatment. The anabolic actions of GH are mediated by IGF-1. Studies of whole body protein metabolism show that this occurs through the stimulation of protein synthesis, reduction in protein oxidation but not inhibition of protein breakdown. GH plays an important role in the regulation of substrate metabolism and body composition in man.

Key words: GH, IGF-1, Body composition, Metabolism, Sodium

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THE WELL established ability of GH to stimulate childhood growth reflects the summation of complex effects of the hormone on a range of metabolic and cellular functions. GH continues to be produced after cessation of growth, and remains the most abundant pituitary hormone, suggesting that it continues to exert important metabolic functions in adult life. Indeed, it has been long recognised that short term administration of pituitary extracted human GH (hGH) to adults causes significant effects on glucose, lipid, protein and mineral (e.g. sodium, potassium, phosphate, calcium) metabolism. However, a better understanding of the physiological significance of these effects in adult life has been hampered by limited supplies of hGH and the concern that pituitary preparations of the hormone may have been variably contaminated by unknown bio-active substances. The recent availability of unlimited supplies of recombinant hGH, together with advances in *in-vivo* metabolic techniques have allowed investigators to carefully appraise the physiological action of the hormone in adult life. In this paper we will review data from recent studies that have demonstrated an important role for GH in regulating body composition and energy metabolism. These recent studies using recombinant hGH have also confirmed observations originally made 30 years ago, that GH causes sodium and fluid retention, thereby negating earlier suspicion that these effects may have arisen from bioactive contaminants. This action of GH has remained as intriguing as when first observed. In this article, we will also review recent studies addressing the underlying mechanisms involved and the possible role that GH may have on sodium and fluid homeostasis.

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Body Composition

Novak *et al.* [1] were among the first to report that hGH treatment causes a significant change in body composition in children with hypopituitarism. They observed that the stimulation of body growth in four GH deficient children, over an 18 month period was accompanied by a progressive decrease in total body fat and an increase in total body water and composite body density. These two latter indices are indirect measures of lean body mass. When hGH was stopped for twelve months, body fat increased and composite body density decreased.

The changes in body composition in GH deficient children after stopping hGH treatment have since been confirmed by Rutherford *et al.* [2] using CT scanning. These patients also showed a significant decrease in muscle strength. Several investigators have recently reported that adults with GH deficiency have abnormal body composition characterised by an increase in fat mass and decrease in lean body mass [3–5]. Perhaps the most dramatic demonstration of GH effects on body composition comes from studies in GH deficient adults receiving hGH treatment. Many studies are in agreement in reporting a significant increase in lean body mass and a corresponding reduction in fat mass despite differences in the duration of treatment and the dosage of hGH used [6–11]

In a detailed analysis using CT scanning, Bengtsson *et al.* [9] have shown that the reduction in fat mass is region specific, with the greatest reductions occurring centrally and lesser changes occurring in the limbs. These findings confirm and extend the earlier observation of Salomon *et al.* [8] that hGH treatment reduces waist to hip ratio. GH deficient adults display disproportionate increase in central abdominal fat. There is strong evidence linking obesity and in particular central obesity as a risk factor for diabetes and cardiovascular disease [12, 13]. Indeed, adult patients with GH deficiency have biochemical abnormalities that are linked to increased risk of cardiovascular disease. These patients have increased levels of total and LDL cholesterol [14] and a higher prevalence of impaired glucose tolerance [15]. They have also been found to have a greater prevalence of atheromatous plaques in carotid and femoral vessels [16] and a two fold increase in cardiovascular mortality compared to the general population [17].

Evidence that GH has major effects on body composition is provided by studies of patients with acromegaly. Bengtsson *et al.* [18] have reported that total body water and body potassium, indices of body cell mass are higher and fat mass lower, than predicted. Using dual energy x-ray absorptiometry, we have compared body composition in 20 subjects with acromegaly to 20 normal subjects matched for age, sex, height and weight [19]. Acromegalic patients have a greater proportion of lean tissue mass and a corresponding smaller mass of fat both of which are altered reciprocally with octreotide treatment.

Substrate Metabolism

It is likely that the changes in body composition following hGH treatment arise in part from the significant effects of GH on substrate and energy metabolism. It has been long recognised that GH has significant effects on fat, glucose and protein metabolism. A number of short term metabolic studies have shown that GH increases lipolysis and fat oxidation, reduces glucose oxidation and impairs insulin action. Moller *et al.* [20] have shown that the GH effects on fat and glucose oxidation occur within 3 to 4 h of the commencement of a GH infusion. As well as reducing glucose oxidation, GH also lowers protein oxidation. Using steady state leucine turnover techniques coupled with indirect calorimetry, Horber *et al.* [21] have demonstrated that treatment with GH for seven days reduces protein oxidation by 60 and 70 % in the fed or fasted state, and increases fat oxidation about two fold. In addition to reducing protein oxidation, GH stimulates protein synthesis. In the same study, the authors also showed that the same dose of hGH was able to prevent proteolysis induced by a supra-physiological dose of glucocorticoids [22]. It is likely that the protein sparing effect of GH together with its effects on stimulating protein synthesis, contribute to the increase in lean body mass during treatment.

To investigate the chronic effects of GH, we have undertaken a cross-sectional comparison of energy and substrate metabolism in acromegalic patients and normal subjects pair-matched for age, sex, weight and height [23]. Patients with acromegaly displayed insulin resistance as reflected by

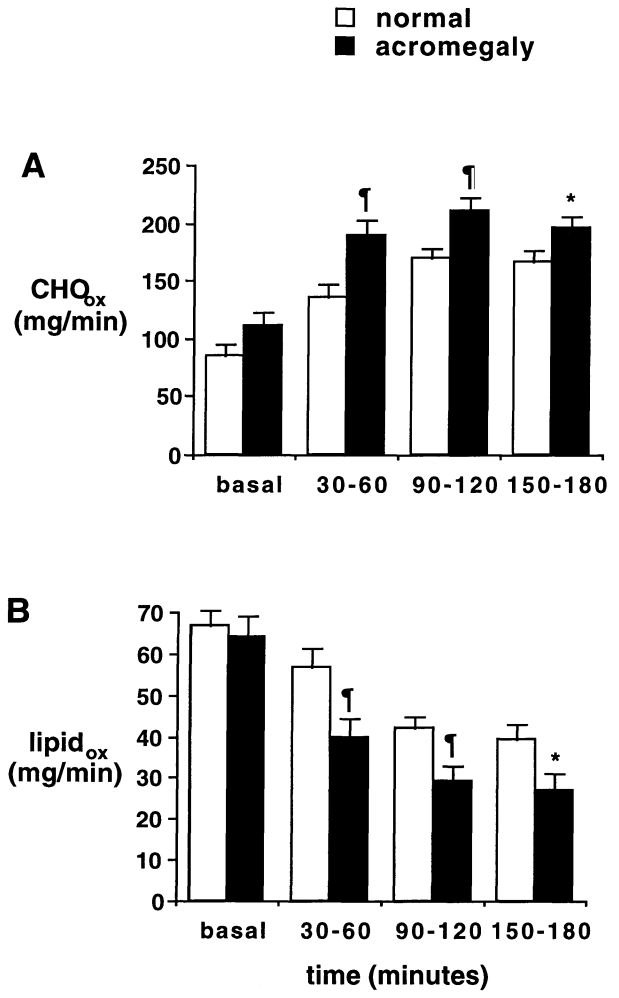

Fig. 1. (A) Carbohydrate oxidation (CHO_{ox}; mean ± SEM) and (B) lipid oxidation ($lipid_{ox}$) in the basal state and during the OGTT in 20 acromegalic patients and 20 pair-matched normal subjects (*P<0.05; ¶P<0.01; acromegaly *vs.* normal) [23].

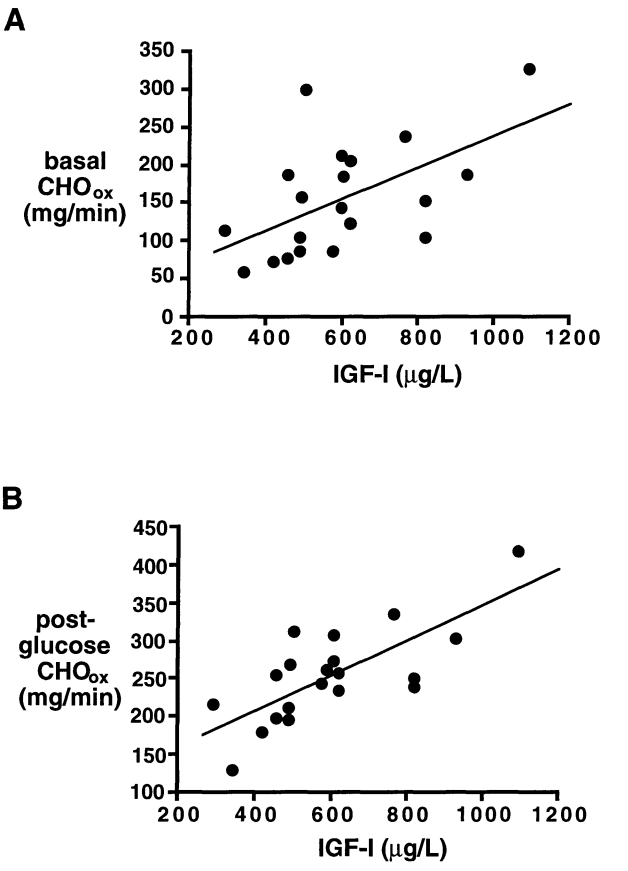

Fig. 2. Scattergram plot of (A) basal (r=0.56; P=0.01) and (B) post-glucose carbohydrate oxidation (CHO_{ox}; r=0.79; P=0.0001) and IGF-I in 20 acromegalic patients [23].

higher glucose and insulin levels in the basal and post-glucose states. In acromegaly, energy metabolism was characterised by a trend towards higher carbohydrate oxidation in the basal state and a greater rate of carbohydrate oxidation following oral glucose. Conversely, lipid oxidation was suppressed by oral glucose to a significantly greater degree in acromegaly (Fig. 1). The findings of increased carbohydrate oxidation and decreased lipid oxidation were unexpected and opposite to that observed after short-term GH administration. IGF-I but not glucose and/or insulin was significantly related to basal and post-glucose carbohydrate oxidation (Fig. 2).

These observations strongly suggest a significant role of IGF-I in glucose metabolism and this notion is supported by recent experimental work. Studies with recombinant IGF-I in man have shown that this growth factor stimulates glucose disposal and increases carbohydrate oxidation [24]. Lewitt *et al.* have provided strong evidence *in-vivo* that IGF-I and its related binding proteins play a significant role in glucose homeostasis [25]. It is believed that the IGF binding proteins, IGFBP-1 and IGFBP-3 largely attenuate the action of IGF-I [26]. The acute variations in binding protein levels could act to modulate insulin-like activity due to uncomplexed IGF-I particularly when IGFBP-1 is acutely suppressed after nutrient loading as was found in the present study.

Although, short-term GH administration increases lipid oxidation, IGF-I levels do not rise to a peak

until 5 days of GH therapy [27]. It is possible that time dependent changes in the pattern of substrate oxidation could occur with the progressive rise in IGF-I. Evidence is provided by a recent study in which co-administration of GH and IGF-I resulted in a lesser rise in serum glucose compared to that observed with GH alone [28]. Thus, the insulin-like effect of IGF-I that stimulates carbohydrate oxidation may evolve slowly with time, in the setting of chronic GH excess, to increase carbohydrate oxidation even in the presence of elevated GH levels. The reason why the effects of IGF-I on substrate oxidation predominant over GH is unclear, but could be explained in part by recent *in-vitro* data demonstrating that IGF-I can decrease GH receptor expression in peripheral tissues and in doing so may reduce peripheral tissue responsiveness to GH [29]. The data from acromegaly indicate that the chronic effects of GH excess on substrate oxidation differ from the short term effects of GH administration and that IGF-I may be an important regulator of substrate oxidation in acromegaly.

Energy Expenditure

One aspect of GH action which has not received detailed study is its regulatory role in energy expenditure. Ikkos *et al.* [30] reported over 30 years ago that basal metabolic rate was greater in patients with acromegaly. It is not clear whether the observed increase in basal energy expenditure is due entirely to a greater mass of lean tissue or to the metabolic effects of enhanced GH secretion independent of lean body mass. Evidence that GH increases basal metabolic rate comes from the recent study by Salomon *et al.* [8] who reported that GH treatment increased resting energy expenditure by an amount that could not be explained by the corresponding increase in lean body mass. The changes were most marked at one month and showed a gradual decline towards normal by 6 months.

We have recently compared basal metabolic rate in acromegalic and matched normal subjects and analysed the data in relation to lean body mass obtained by dual energy x-ray absorptiometry [19]. It was found that basal energy expenditure was significantly increased in acromegaly as was lean body mass. Since lean body mass as determined by dual energy x-ray absorptiometry comprises extracellular water (ECW) and body cell mass (BCM), quantification of ECW allows BCM to be derived. ECW was determined by sodium dilution. The results revealed that the increase in lean body mass could be entirely accounted for by the increase in ECW (Fig. 3). Thus, body cell mass was not increased in acromegaly and could not explain the increase in resting energy expenditure. Serum IGF-1 was significantly related to resting energy expenditure. The mechanisms behind the effect of GH on energy expenditure may relate to increased glucose turnover [31], protein synthesis [22] or increased conversion of T_4 to T_3 [27]. The collective data strongly suggest that GH, like thyroid hormone, should be considered a regulator of basal metabolic rate. The data also suggest that GH may reduce fat mass through effects on energy balance in addition to stimulation of lipolysis.

Sodium Homeostasis

The early accounts of the biological effects of hGH, derived from pituitary extracts, on normal volunteers or GH deficient subjects demonstrated that hGH administration caused fluid retention and weight gain [32, 33]. A number of recent studies of recombinant hGH administration to normal or GH deficient subjects have documented sodium

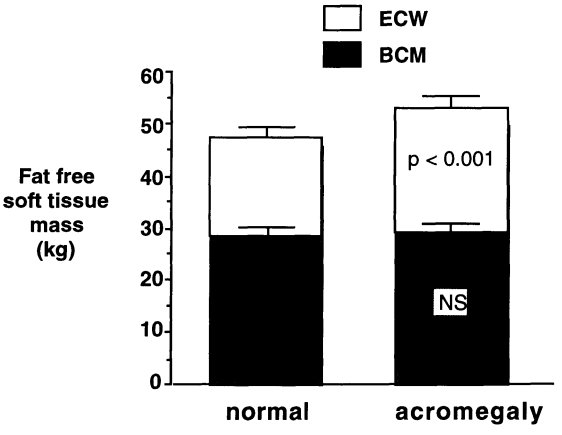

Fig. 3. Lean tissue mass in normal and acromegalic subjects. Lean tissue mass as measured by dual X-ray absorptiometry comprises extracellular water (ECW) and body cell mass (BCM). ECW is estimated by isotopic sodium dilution from which BCM can be derived [19]. NS=not significant.

retention, manifest directly as reduction in urinary sodium [34] and increased extracellular fluid volume [35] or indirectly as oedema, weight gain and rarely hypertension [6, 8, 9]. Further evidence of a role by GH on sodium homeostasis is the finding that ECW is altered in disorders of GH secretion. The reduction in lean body mass in GH deficient adults is due in part to proportionate reduction in ECW [4]. ECW is expanded in acromegaly in relation to the extent of GH hypersecretion [36]. The expanded ECW compartment contributes almost entirely to the increase in lean body mass in acromegaly [19].

The mechanism(s) by which GH induces sodium retention are not well understood. There is evidence that the anti-natriuretic effects are mediated indirectly through modification of the action of other sodium regulating hormones as well as through direct renal effects of GH. The availability of recombinant hGH and more recently of IGF-1 have allowed these issues to be specifically examined.

The acute effects of recombinant hGH on sodium balance and the activity of the renin-angiotensin system was investigated in normal volunteers administered recombinant hGH, at a dose of 0.2 U/kg/day over a 5 day period [34]. This resulted in weight gain, and significant reductions in urinary sodium and urine volume without associated changes in urinary osmolality. Plasma renin activity (PRA) and plasma aldosterone increased, reaching a peak at days 3 to 5 of treatment. Serum potassium, osmolality, and vasopressin (AVP) concentrations did not change significantly before or after hGH administration. Moller *et al.* [35] recently assessed the effects of 0.2 U/kg day GH on the renin-angiotensin system following 14 days of treatment in a placebo controlled blinded study. They found a slight rise in plasma aldosterone concentrations that approached statistical significance. These investigators made the interesting observation that atrial natriuretic peptide (ANP) levels were significantly lower in the GH-treated than in the placebo group, despite an increase in extracellular fluid volume. Suppression of ANP secretion may be one possible mechanism contributing to sodium retention and increased extracellular fluid volume during hGH treatment.

The findings from both of the above studies can be questioned since they were undertaken in normal subjects administered 0.2 U/kg.d of GH which is a dose approximating 5 times the daily production rate. To determine the physiological significance and mechanisms of GH effects on sodium homeostasis, we performed a double-blind, placebo-controlled, cross-over trial comparing the effects of placebo, physiological (0.04 U/kg.d) and supraphysiological (0.08 U/kg.d) replacement doses of GH in a group of adults with organic GH deficiency [37]. The physiological dose increased mean IGF-I values to within the normal range whereas the supraphysiological dose caused supranormal mean IGF-I values, suggesting that the selected doses of 0.04 and 0.08 U/kg.d were appropriate. GH treatment caused a dose-dependent increase in exchangeable sodium, extracellular fluid volume and body weight (Fig. 4). Angiotensinogen levels and PRA were increased

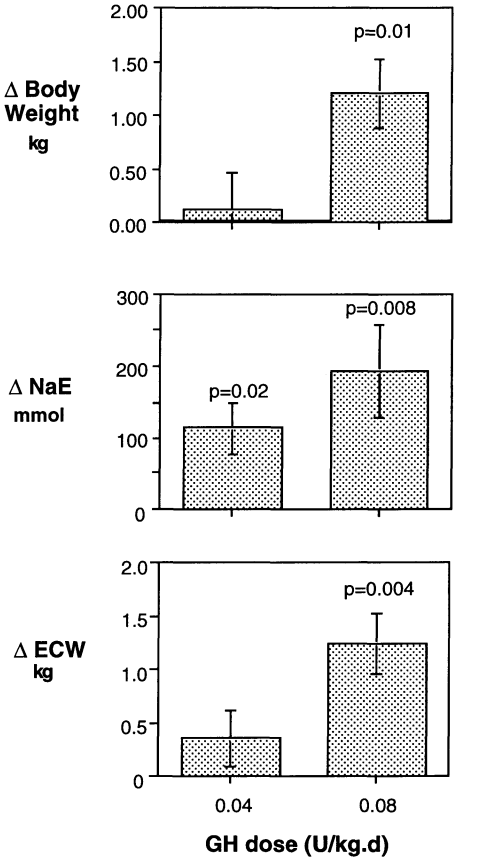

Fig. 4. Changes in body weight, exchangeable sodium (NaE) and extracellular water (ECW) in GH deficient adults after 7 days administration of 0.04 and 0.08 U/kg.d GH in comparison to placebo [37].

in a dose-independent fashion, but there was no significant effect of GH treatment on angiotensin II, aldosterone, or ANP. The results show that the antinatriuretic action of GH is physiologic and dose-dependent. The mechanism of sodium and fluid retention is not primarily due to complete activation of the renin-angiotensin system or to inhibition of ANP release, but more likely to a direct renal tubular effect. Indeed, the observation that GH induced sodium retention could occur in the absence of adrenal glands indicated that this action can occur independent of mineralocorticoid mediation [33]. The possibility that GH has direct tubular effects has been reinforced by the identification of GH receptors in isolated renal proximal tubule basolateral plasma membranes [38].

Conclusion

There is unequivocal evidence that GH subserves important metabolic functions and regulates body composition in adult life. Recent advances in *in-vivo* metabolic techniques have provided insight into the mechanisms involved. Current data suggest that this involves coordinated effects on substrate utilisation, protein synthesis and energy balance. Sodium retention is a physiologic property of GH. GH effects on sodium and fluid homeostasis are probably an intrinsic part of its more global action in regulating body growth and composition since salt and water are integral constituents of all body compartments.

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