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Metabolic Effects of Acute and Prolonged Growth Hormone Excess in Normal and Insulin-deficient Man

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Summary. The metabolic effects of acute (4 h) and prolonged (24 h) growth hormone excess at pathophysiological concentrations were studied by growth hormone administration to normal subjects with and without somatostatin induced insulin deficiency. Acute growth hormone excess produced mild hyperinsulinaemia, but blood glucose concentrations were unaltered whereas chronic growth hormone excess caused a small (0.5 mmol/l) but significant rise in overnight-fasting blood glucose concentration together with a similar rise in fasting insulin levels (Mean ± SEM 9 ± 1 v 4 ± 1 mU/l, $p < 0.01$). When insulin secretion was suppressed by somatostatin, a hyperglycaemic effect of acute growth hormone excess was unmasked, and the hyperglycaemic effect of chronic growth hormone excess was exaggerated. Acute growth hormone administration without somatostatin had a mild ketogenic action despite stimulated insulin secretion but no change in plasma non-esterified fatty acid or blood glycerol levels was observed. Somatostatin magnified the ketogenic effect of acute growth hormone excess, and unmasked a lipolytic action. Prolonged growth hormone excess had a lipolytic action that was increased by somatostatin, although the ketogenic effect of growth hormone was only seen during somatostatin induced insulin deficiency. The acute hyperglycaemic, lipolytic and ketogenic actions of growth hormone in normal subjects are limited by a compensatory rise in insulin secretion although with chronic exposure hyperglycaemic and lipolytic effects are seen. In insulin-deficient states, however, elevated growth hormone levels could be important in promoting hyperglycaemia and hyperketonaemia.

Key words: Growth hormone, insulin, insulin deficiency, glucagon, blood glucose, ketone bodies, ketogenesis, lipolysis, non-esterified fatty acids

Serum growth hormone concentrations are inappropriately elevated in "juvenile onset" diabetics with the highest levels found in the most poorly controlled subjects [1–4]. Nevertheless the contribution of growth hormone to the metabolic abnormalities of diabetes is uncertain. Previous studies have demonstrated hyperglycaemic, lipolytic and ketogenic actions of growth hormone in normal, diabetic, and hypophysectomised man and animals [5–10]. Many of the growth hormone preparations used in the older studies were contaminated with other peptides and the doses were often pharmacological. More recently the lipolytic and ketogenic effects of growth hormone have been demonstrated in severely insulin-deficient diabetics [11], but few data are available in normal man. In the present study we have investigated the metabolic actions of acute and prolonged growth hormone excess in normal subjects and in subjects rendered partially insulin-deficient by infusion of somatostatin.

Subjects and Methods

Protocol

1. Acute Studies. Six normal subjects, mean age 29 years (range 20–40 years), per cent ideal body weight 104 ± 3 (mean ± SEM), were studied after an overnight (12 h) fast. Dietary carbohydrate intake was more than 300 g daily for at least 48 h before study and no subject was taking any drugs. All had normal liver and renal function tests. Intravenous Venflon (Viggo) cannulae were positioned in both antecubital fossae between 0800 h and 0815 h. Subjects remained recumbent throughout the test. On four separate occasions, with at least one week between infusions, subjects received one of the following continuous intravenous infusion regimes.

(1) NaCl (0.154 mol/l, total volume 30–50 ml) for 240 min;

(2) synthetic linear somatostatin (Ferring), 100 μg/h, in NaCl (0.154 mol/l, 30–50 ml) for 240 min;

(3) human growth hormone (Kabi) 500 μg/h in NaCl (0.154 mol/l, 30–50 ml) for 240 min;

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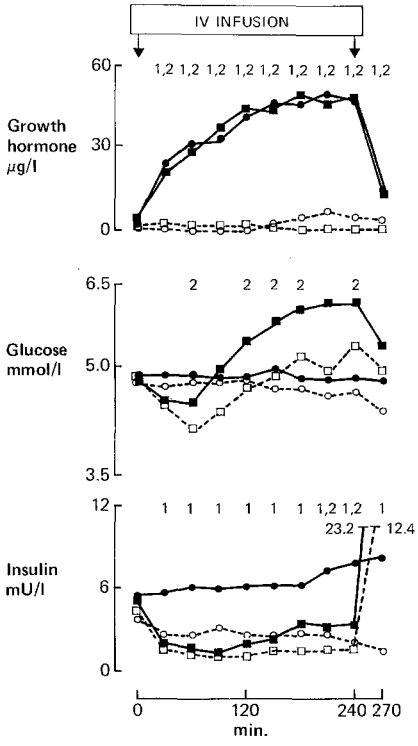

Fig. 1. Serum growth hormone, blood glucose and serum insulin response to intravenous infusion of saline and human growth hormone (500 μg/h) with and without somatostatin (100 μg/h). 1 = values during growth hormone infusion significantly different from saline at 5% level or less. 2 = values during infusion of both growth hormone and somatostatin significantly different from somatostatin alone at 5% level or less. Values are the mean of 6 subjects. O---O saline infusion, ●——● growth hormone infusion, □---□ somatostatin infusion, ■——■ somatostatin plus growth hormone infusion

(4) human growth hormone (500 μg/h) plus somatostatin (100 μg/h) for 240 min.

Two basal blood samples were taken 25 and 30 min after cannulation, and then the continuous intravenous infusion was started. Further blood samples were taken at 30 min intervals for 270 min.

2. Prolonged Studies. Five normal subjects previously studied in the acute experiments also participated in the chronic studies (mean age 27 years, per cent ideal body weight 103 ± 3). Subject preparation and cannulation was as for the acute studies, with infusion studies after an overnight fast. At intervals at least 2 weeks apart, subjects received intramuscular injections of human growth hormone (Kabi), 2 mg, 24 h and 12 h before continuous intravenous infusion of

(1) NaCl (0.154 mol/l, 30–50 ml), for 240 min; or

(2) synthetic linear somatostatin (Ferring), 100 μg/h in NaCl (0.154 mol/l, 30–50 ml) for 240 min.

Blood samples were taken at the same times as for the acute experiments.

In two subjects, blood for growth hormone estimation was taken at 30 min intervals for 12 h after a single 2 mg IM growth hormone injection. Levels peaked at 3.5 h (15 and 19 μg/l) with a return to baseline at 12 h.

Informed consent was obtained from all subjects before the study, which was approved by the Southampton Hospitals Ethical Committee.

Chemical Methods

Blood for glucose, 3-hydroxybutyrate, lactate, pyruvate, glycerol and alanine estimation was taken in ice-cold 5% w/v perchloric acid and assayed by automated fluorimetric enzymatic methods within 24 h [12]. Acetoacetate was measured by an automated spectrophotometric method on the perchlorate samples within 24 h [13]. Plasma nonesterified fatty acids (NEFA) were measured by a radioactive cobalt method [14] and serum triglyceride as glycerol after hydrolysis [15]. Serum growth hormone [16] and insulin [17] were measured by double antibody radioimmunoassay. Blood samples (2.25 ml) for glucagon assay were collected into 0.25 ml aprotonin (2500 I. U.) containing 25 μmole EDTA and plasma glucagon measured by radio-immunoassay [18]. Serum cortisol was measured by competitive protein binding [19].

Statistical analysis was performed using Student's t-test for paired data. Values are given as mean ± SEM.

Results

1. Acute Studies

Hormonal Changes. The effects of saline infusion alone on hormone levels are shown in Figure 1 and Table 1. Growth hormone showed the expected intermittent spontaneous surges in individuals. Insulin levels gradually decreased over the 4 h. Glucagon showed no significant change. Somatostatin infusion resulted in a 50% decrease in circulating serum insulin concentrations ($p < 0.05$, from 90 to 180 min) (Fig. 1) and a 30–40% decrease in plasma glucagon levels (Table 1). Basal serum growth hormone concentrations were unaffected but the spontaneous surges in growth hormone secretion seen during saline infusion were absent. A rebound in secretion of insulin and glucagon was evident after the end of the somatostatin infusion.

Growth hormone infusion produced serum levels of 40–50 μg/l at 4 h. This produced a mild elevation in circulating serum insulin concentrations compared with the saline control (Fig. 1). During growth hormone plus somatostatin infusion a 50% decrease in circulating serum insulin concentrations was seen compared with growth hormone infusion alone. Some escape of insulin secretion occurred after 3 h combined growth hormone and somatostatin administration with insulin levels 40% higher at this stage than during somatostatin infusion alone. Nonetheless, continued suppression was evident from the insulin rebound observed on cessation of the infusion. No effect of growth hormone on plasma glucagon or serum cortisol concentrations was evident at any time (Table 1).

Metabolite Changes. Saline infusion resulted in a gradual fall in glucose concentrations. After an initial decline, significant at 60 and 90 min, somatostatin alone caused a progressive rise in blood glucose levels towards the end of the infusion (blood glucose at 240 min, 5.4 ± 0.3 mmol/l with somatostatin; 4.6 ± 0.2 mmol/l with saline, $p < 0.05$).

Table 1. Serum or plasma hormone and blood metabolite concentrations during intravenous saline, somatostatin and growth hormone infusions

Hormone or metabolite		Lactate mmol/l			Pyruvate mmol/l			Alanine mmol/l			Triglyceride mmol/l			Cortisol nmol/l			Glucagon ng/l		
Time (min)		0	120	240	0	120	240	0	120	240	0	120	240	0	120	240	0	120	240
1. Acute studies																			
Saline	Mean	0.55	0.61	0.56	0.054	0.052	0.049	0.23	0.22	0.21	0.74	0.62	0.58	444	323	256	45	37	38
	SEM	0.03	0.06	0.04	0.004	0.008	0.005	0.01	0.02	0.02	0.20	0.16	0.17	48	47	43	8	11	5
SRIF	Mean	0.59	0.60	0.66	0.060	0.050	0.051	0.25	0.24	0.25	0.60	0.65	0.58	368	212	231	56	33	26[a]
	SEM	0.04	0.02	0.09	0.005	0.004	0.004	0.02	0.01	0.01	0.18	0.23	0.021	64	16	18	9	9	6
hGH	Mean	0.63	0.68	0.62	0.061	0.059	0.048	0.26	0.24	0.20	0.58	0.66	0.70	420	252	201	41	29	43
	SEM	0.04	0.05	0.03	0.005	0.006	0.004	0.02	0.02	0.01	0.15	0.15	0.19	59	38	37	11	7	8
hGH +	Mean	0.75	0.77	0.76	0.070	0.062	0.049	0.29	0.29	0.25	0.59	0.61	0.55	411	153	196	39	27	24[a]
SRIF	SEM	0.09	0.12	0.05	0.008	0.013	0.004	0.02	0.02	0.02	0.15	0.10	0.13	36	27	37	11	6	5
2. Chronic studies																			
Saline	Mean	0.65	0.64	0.58	0.071	0.064	0.057	0.25	0.23	0.22	0.76	0.61	0.58	313	208	197	36	20	17
after hGH	SEM	0.09	0.04	0.03	0.009	0.005	0.004	0.02	0.01	0.02	0.25	0.13	0.10	89	63	35	14	8	9
SRIF	Mean	0.60	0.68	0.66	0.068	0.060	0.061	0.27	0.27	0.27	0.50	0.47	0.48	217	215	199	42	26	7[a]
after hGH	SEM	0.05	0.04	0.05	0.008	0.004	0.009	0.02	0.02	0.02	0.06	0.02	0.09	50	54	45	5	9	3

Saline = IV 0.154 mol/l sodium chloride, 30–50 ml in 4 h
SRIF = IV somatostatin, 100 μg/h for 4 h
hGH = IV human growth hormone, 500 μg/h for 4 h
hGH + SRIF = IV somatostatin 100 μg/h plus IV human growth hormone 500 μg/h for 4 h
Saline after hGH = IV 0.154 mol/l sodium chloride after 2 mg hGH IM 24 h and 12 h earlier
Somatostatin after hGH = IV somatostatin, 100 μg/h, after 2 mg hGH IM 24 h and 12 h earlier
Values given as mean ± SEM
[a] Saline or growth hormone infusion significantly different ($p < 0.05$) from corresponding somatostatin or growth hormone plus somatostatin infusion respectively, by Student's t-test for paired data

Blood glucose concentrations were not altered over the four hour infusion of growth hormone alone. During combined growth hormone and somatostatin infusion blood glucose levels were higher than those seen during somatostatin infusion alone, evident by 60 min and continuing throughout the infusion period (Fig. 1).

Plasma NEFA concentrations were similar during growth hormone, somatostatin and saline infusions but a minor rise in blood glycerol was induced by growth hormone by 240 min (Fig. 2). In contrast combined growth hormone and somatostatin infusion caused a rise in both plasma NEFA and blood glycerol concentrations.

Somatostatin infusion alone resulted in a rise in blood ketone body concentrations, significant compared to saline from 60 min onwards. Similarly blood ketone body concentrations were elevated by growth hormone from 150 min onwards compared with the saline control. Combined growth hormone and somatostatin infusion exaggerated this ketone body rise (Fig. 2)

Blood concentrations of the gluconeogenic precursors lactate, pyruvate and alanine were unaltered by growth hormone with or without somatostatin infusion. Growth hormone had no effect on serum triglyceride concentrations at any time.

2. Effects of Prolonged (24 h) Growth Hormone Administration

Table 2 shows the fasting concentrations of glucose, ketone bodies, NEFA, glycerol, growth hormone and insulin after prolonged growth hormone administration. Glucose was slightly but significantly increased whilst insulin concentrations had risen twofold. Blood ketone body and glycerol and plasma NEFA concentrations were unchanged after the overnight (12 h) fast.

The effect of prolonged growth hormone excess on the response of blood glucose and serum insulin concentrations to saline and somatostatin infusions is illustrated in Figure 3. During saline infusion after growth hormone blood glucose levels decreased slightly but remained 0.5 mmol/l higher than during the control infusion. Serum insulin concentrations were elevated two to threefold throughout. Somatostatin infusion produced a greater hyperglycaemic effect of growth hormone with blood glucose levels 1–1.5 mmol/l higher than during somatostatin infusion alone. Insulin levels were suppressed as with somatostatin alone.

Ketone body levels did not change during saline infusion but as in the acute experiments an effect of growth hormone to increase ketone body concentra-

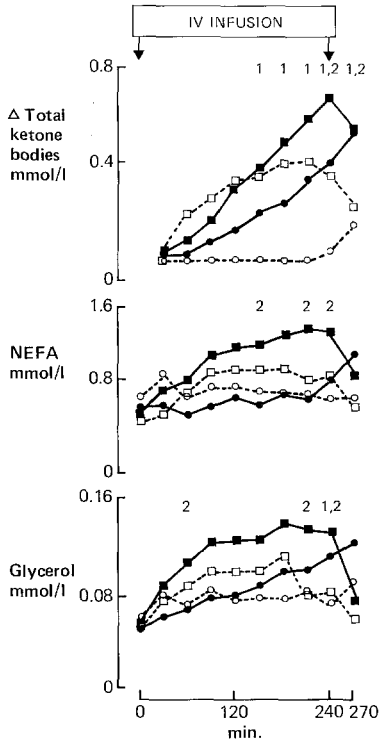

Fig. 2. Plasma non-esterified fatty acids (NEFA), blood glycerol and the change from basal in blood total ketone body concentrations during infusions of saline or growth hormone (500 μg/h) with and without somatostatin (100 μg/h). Conditions and symbols as for Figure 1. Total ketone bodies refers to the sum of blood 3-hydroxybutyrate and acetoacetate concentrations

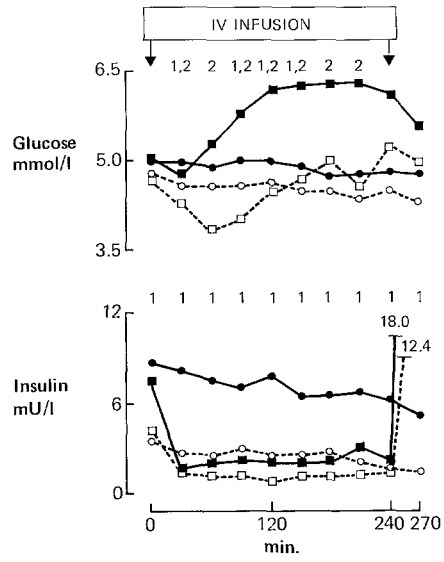

Fig. 3. Blood glucose and serum insulin concentrations during infusion of saline and somatostatin (100 μg/h) with and without administration of human growth hormone, 2 mg intramuscularly 24 h and 12 h earlier. 1 = values during saline infusion after growth hormone administration significantly different from those before ($p < 0.05$). 2 = values during somatostatin infusion after growth hormone administration significantly different from those before ($p < 0.05$). O---O saline infusion, ●——● saline infusion after intramuscular growth hormone, □---□ somatostatin infusion, ■——■ somatostatin infusion after intramuscular growth hormone

Table 2. Effect of 24 h growth hormone administration on overnight (12 h) fasting glucose, ketone body, glycerol, non-esterified fatty acid and insulin concentrations

Hormone or metabolite	Chronic growth hormone	Control	p
Blood glucose mmol/l	5.1 ± 0.2	4.6 ± 0.3	<0.05
Blood total ketone bodies mmol/l	0.28 ± 0.08	0.20 ± 0.05	NS
Blood glycerol mmol/l	0.07 ± 0.02	0.08 ± 0.01	NS
Plasma non-esterified fatty acids mmol/l	0.88 ± 0.13	0.66 ± 0.10	NS
Serum insulin mU/l	8.7 ± 0.9	3.7 ± 0.9	<0.01

Growth hormone, 2 mg IM, was administered 24 h and 12 h before sampling
Significance values obtained by Student's t-test for paired data

tions was unmasked by somatostatin infusion (Fig. 4). During saline infusion plasma NEFA concentrations were elevated by prolonged growth hormone alone. Simultaneous somatostatin infusion revealed a more marked lipolytic effect of growth hormone, producing an exaggerated rise in plasma NEFA and blood glycerol levels.

Concentrations of the gluconeogenic precursors, triglycerides, cortisol and glucagon were unaltered by previous growth hormone administration during both saline and somatostatin infusions (Table 1).

Discussion

The serum growth hormone concentrations obtained during acute intravenous infusions (10–50 μg/l) and after intramuscular injection should be comparable to those found in patients with diabetic ketoacidosis [18, 20], and severely ill traumatised subjects [21]. The growth hormone preparation was obtained from frozen pituitary glands [22] and is relatively free from contamination with other pituitary peptides [23].

A hyperglycaemic effect of growth hormone at pathophysiological concentrations has been known for many years. Hypophysectomy was shown in 1930 [24] to decrease the severity of diabetes in dogs and injection of anterior pituitary extracts produced hyperglycaemia in intact animals [5]. Similarly in non-diabetic hypophysectomised man, administration of pharmacological amounts of growth hormone decreased carbohydrate tolerance [8], while ketoacidosis was induced in hypophysectomised diabetics [7].

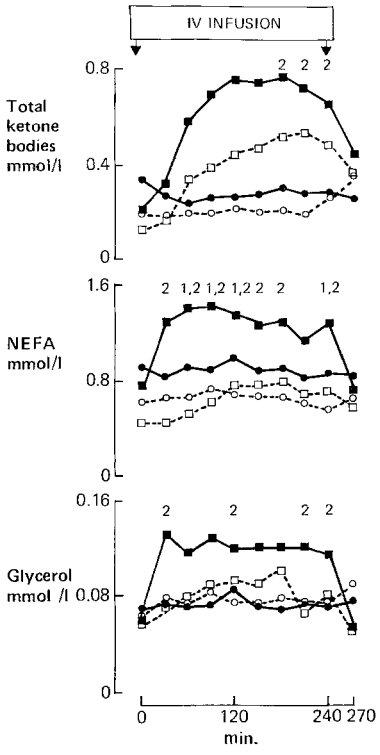

Fig. 4. Blood total ketone body, plasma non-esterified fatty acid (NEFA) and blood glycerol concentrations during infusion of saline and somatostatin (100 μg/h) with and without administration of human growth hormone, 2 mg intramuscularly, 24 h and 12 h earlier. Conditions and symbols as for Figure 3. Total ketone bodies refers to the sum of blood 3-hydroxybutyrate and acetoacetate concentrations

In normal man the evidence for a hyperglycaemic effect of growth hormone is more tenuous. Intravenous administration of pharmacological doses of growth hormone decreases glucose tolerance within 1 to 2 h in normal subjects [25]. In our study growth hormone had no effect on blood glucose levels over the 4 h of acute infusion. The absence of a hyperglycaemic action of growth hormone in normal subjects may be explained by the simultaneous increase in insulin secretion (Fig. 1). This has previously been shown by other workers [26, 27] although a decrease in insulin secretion has also been observed [28].

24 h growth hormone administration was associated with mild fasting hyperglycaemia. This is in keeping with the findings in acromegaly, in which the prevalence of glucose intolerance is ten times greater than in the normal population [29]. Nonetheless the hyperglycaemic action of more prolonged growth hormone elevation may have homeostatic importance as illustrated by the occasional occurrence of hypoglycaemia in children with isolated growth hormone deficiency [30]. In normal man, growth hormone is secreted in a pulsatile fashion with levels frequently approaching those attained in our study. Our data suggests that persistently elevated serum growth hormone concentrations, although having no immediate effect on blood glucose concentrations, may have a longer term hyperglycaemic action in normal subjects.

A more marked hyperglycaemic action of growth hormone was unmasked when insulin secretion was diminished by somatostatin infusion. In the acute studies, this was apparent after 2 h and contrasts with the findings of Gerich et al. [11] who found no hyperglycaemic action of growth hormone in severely insulin-deprived diabetic subjects, although serum levels achieved in their study were considerably lower (6–8 μg/l). Growth hormone stimulates glucagon secretion in the dog [31], but there is no evidence from our or other studies that this is a major action of growth hormone in man.

After 24 h growth hormone administration, its hyperglycaemic action was again exaggerated by somatostatin-induced insulin deficiency. It is apparent that the chronic moderately elevated growth hormone concentrations in poorly controlled, and probably insulin-deficient, diabetics could contribute to the hyperglycaemia observed.

In keeping with other studies [11], a hyperketonaemic action of growth hormone was apparent after both acute and prolonged exposure to high circulating concentrations. This may result from increased lipolysis and increased NEFA supply for ketogenesis or from a primary action of growth hormone on hepatic ketone body production or peripheral utilisation. In vitro and in vivo work has shown a lipolytic action of growth hormone at pharmacological doses [32, 33]; increased lipolysis was not apparent in our acute studies in normal subjects as reflected by plasma NEFA or blood glycerol concentrations, although it was after prolonged exposure. The absence of a lipolytic action in the acute studies may have been secondary to stimulated insulin secretion as lipolysis is exquisitely sensitive to small changes in peripheral insulin concentrations [34]. In addition a lag period of 1–2 h for the lipolytic action of growth hormone has been noted in vitro [35]. When insulin secretion was suppressed by somatostatin the lipolytic effect of growth hormone was seen at 150 min in the acute study and throughout the infusion period after prolonged chronic growth hormone administration demonstrating an important lipolytic action of growth hormone in insulin deficiency.

Increased ketosis in the absence of enhanced lipolysis in normal subjects suggests a direct effect of growth hormone on hepatic ketogenesis. Experiments with isolated perfused liver preparations have failed to demonstrate any such action [36], although there is suggestive evidence from other data in man [37]. The hepatic actions of growth hormone require further study. In insulin-deficiency and after pro-

longed administration in normal subjects, the ketogenic actions of growth hormone are explicable at least in part by the actions on lipolysis, as suggested by others. In diabetic ketoacidosis and in poorly controlled insulin-dependent diabetics the elevated circulating growth hormone concentrations [18, 20] may contribute significantly to the metabolic abnormalities observed.

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