Inhibition of lipolysis during acute GH exposure increases insulin sensitivity in previously untreated GH-deficient adults

Mikael Segerlantz, Margareta Bramnert, Per Manhem, Esa Laurila and Leif C Groop

Department of Endocrinology, University Hospital MAS, S-205 02 Malmö, Sweden

Correspondence should be addressed to M Segerlantz; Email: Mikael.Segerlantz@skane.se

Abstract

Objective: Previous studies evaluating the lipolytic effect of GH have in general been performed in subjects on chronic GH therapy. In this study we assessed the lipolytic effect of GH in previously untreated patients and examined whether the negative effect of enhanced lipolysis on glucose metabolism could be counteracted by acute antilipolysis achieved with acipimox.

Methods: Ten GH-deficient (GHD) adults participated in four experiments each, during which they received in a double-blind manner: placebo (A); GH (0.88±0.13 mg) (B); GH + acipimox 250 mg b.i.d. (C); and acipimox b.i.d. (no GH) (D), where GH was given the night before a 2 h euglycemic, hyperinsulinemic clamp combined with infusion of \([3-^3]H\)glucose and indirect calorimetry.

Results: GH increased basal free fatty acid (FFA) levels by 74% \((P = 0.0051)\) and insulin levels by 93% \((P = 0.0051)\). This resulted in a non-significant decrease in insulin-stimulated glucose uptakes \((16.61±8.03 vs 12.74±5.50 \mu mol/kg per min (S.D.), \(P = 0.07\) for A vs B). The rates of insulin-stimulated glucose uptake correlated negatively with the FFA concentrations \((r = -0.638, P < 0.0001)\). However, acipimox caused a significant improvement in insulin-stimulated glucose uptake in the GH-treated patients \((17.35±5.65 vs 12.74±5.50 \mu mol/kg per min, \(P = 0.012\) for C vs B). The acipimox-induced enhancement of insulin-stimulated glucose uptake was mainly due to an enhanced rate of glucose oxidation \((8.32±3.00 vs 8.88±2.39 \mu mol/kg per min, \(P = 0.07\) for C vs B). The enhanced rates of glucose oxidation induced by acipimox correlated negatively with the rate of lipid oxidation in GH-treated subjects both in basal \((r = -0.867, P = 0.0093)\) and during insulin-stimulated \((r = -0.927, P = 0.0054)\) conditions. GH did not significantly impair non-oxidative glucose metabolism \((6.86±5.22 vs 8.67±6.65 \mu mol/kg per min, P = NS for B vs A). The fasting rate of endogenous glucose production was unaffected by GH and acipimox administration \((10.99±1.98 vs 11.73±2.38 \mu mol/kg per min, P = NS for B vs A and 11.55±2.7 vs 10.99±1.98 \mu mol/kg per min, P = NS for C vs B). On the other hand, acipimox alone improved glucose uptake in the untreated GHD patients \((24.14±8.74 vs 16.61±8.03 \mu mol/kg per min, P = 0.0077 for D vs A) and this was again due to enhanced fasting \((7.90±2.68 vs 5.16±2.28 \mu mol/kg per min, P = 0.01 for D vs A) and insulin-stimulated \((9.78±3.68 vs 7.95±2.64 \mu mol/kg per min, P = 0.07 for D vs A) glucose oxidation.

Conclusion: The study of acute administration of GH to previously untreated GHD patients provides compelling evidence that (i) GH-induced insulin resistance is mainly due to induction of lipolysis by GH; and (ii) inhibition of lipolysis can prevent the deterioration of insulin sensitivity. The question remains whether GH replacement therapy should, at least at the beginning of therapy, be combined with means to prevent an excessive stimulation of lipolysis by GH.
Materials and methods

Subjects

Ten GHD patients, with a mean age of 49.7 ± 12.2 years, body mass index of 29.2 ± 4.0 kg/m², lean body mass of 63.8 ± 11.3 kg and fat mass of 24.8 ± 10.3 kg participated in the study (Table 1). Patients with diabetes mellitus, lipid disorders or medication interfering with glucose/lipid metabolism were excluded. The patients gave their written consent before participating. The study protocol was approved by the Ethics Committee of the Medical Faculty of Lund University, the Isotope Committee at the Malmö University Hospital MAS, and the Swedish Medical Product Agency.

The patients included had severe GH deficiency as defined by a peak plasma GH concentration < 9 mU/l after insulin-induced hypoglycemia or after arginine stimulation (13). The patients had a mean insulin-like growth factor-I (IGF-I) level of 12.6 ± 8.86 nmol/l and a mean IGF-1 standard deviation score of −3.4 ± 3.1. Any additional pituitary replacement therapy was stable, monitored for at least 6 months before inclusion in the study and unchanged during the study period.

Experimental design

The patients were studied on four occasions with at least a 1 week interval. At 2200 h the night before the study, the patients were in a double-blind manner given a GH dose (Genotropin; Pharmacia & Upjohn, Inc., Stockholm, Sweden) of 0.01 mg/kg total body mass (0.88 ± 0.13 mg) or placebo. The four different study conditions consisted of: A. placebo (−GH, −acipimox); B. GH alone (+GH, −acipimox); C. GH plus acipimox (+GH, +acipimox); D. acipimox alone (−GH, +acipimox). All subjects were admitted to a metabolic ward at 0700 h after a 10 h overnight fast. All studies were performed with the patient in a supine position. Prior to the study a catheter was inserted anterogradely into an antecubital vein for infusions, another catheter was positioned retrogradely into a wrist vein for blood sampling. This hand was then enclosed in a heated box (70°C) to achieve arterialization of venous blood, and the wrist catheter was kept open by a saline infusion. At the start of the study and again after 150 min the patients were in a double-blind manner given a capsule of either 250 mg acipimox (Farmitalia Carlo Erba, Milan, Italy) or placebo (Fig. 1). During each study condition a 2 h euglycemic hyperinsulinemic insulin clamp with a variable infusion of 20% glucose labeled with [3-3H]glucose in combination with indirect calorimetry and constant infusion of [3-3H]glucose was performed. Lean body mass was measured with a bioelectrical impedance method.

Methods

Glucose metabolism was assessed by a euglycemic hyperinsulinemic insulin clamp (14) and substrate oxidation by indirect calorimetry (15). Endogenous glucose production (EGP) was measured by infusion of [3-3H]glucose. A primed continuous infusion of human insulin (Actrapid Human; Novo Industri, Copenhagen, Denmark), at a dose of 1110 pmol/m² during a 10 min period was administered to acutely raise the plasma insulin concentration. To maintain plasma insulin concentrations at a desired level throughout the rest of the insulin clamp the patient received a continuous insulin infusion of 70 pmol/m² per minute. A variable infusion of 20% glucose was begun and periodically

Table 1 Medical background of the pituitary disease in patients.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>Etiology</th>
<th>Treatment</th>
<th>Pituitary deficiencies</th>
<th>Hormonal substitution</th>
<th>Medication</th>
<th>Estimated duration of GHD (years)</th>
<th>Stimulation with</th>
<th>Post-stimulation GH peak (mU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>43</td>
<td>NS</td>
<td>op</td>
<td>ATG</td>
<td>cte</td>
<td>CM</td>
<td>25</td>
<td>IH</td>
<td>0.1</td>
</tr>
<tr>
<td>M</td>
<td>25</td>
<td></td>
<td>op</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>F</td>
<td>56</td>
<td>P</td>
<td>op + rtr</td>
<td>ATG</td>
<td>ct</td>
<td>—</td>
<td>16</td>
<td>IH</td>
<td>0.1</td>
</tr>
<tr>
<td>M</td>
<td>48</td>
<td>NS</td>
<td>op</td>
<td>ATGD</td>
<td>ctTd</td>
<td>—</td>
<td>7</td>
<td>IH</td>
<td>2.4</td>
</tr>
<tr>
<td>M</td>
<td>59</td>
<td>NS</td>
<td>op</td>
<td>ATGD</td>
<td>ctTd</td>
<td>F</td>
<td>4</td>
<td>Arginine</td>
<td>0.4</td>
</tr>
<tr>
<td>M</td>
<td>63</td>
<td>CR</td>
<td>op</td>
<td>ATG</td>
<td>ctT</td>
<td>—</td>
<td>4</td>
<td>IH</td>
<td>0.9</td>
</tr>
<tr>
<td>M</td>
<td>43</td>
<td>ES</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>23</td>
<td>IH</td>
<td>0.1</td>
</tr>
<tr>
<td>F</td>
<td>41</td>
<td>CR</td>
<td>op + rtr</td>
<td>TG</td>
<td>te</td>
<td>—</td>
<td>34</td>
<td>IH</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>M</td>
<td>65</td>
<td>CR</td>
<td>op + rtr</td>
<td>G</td>
<td>T</td>
<td>AL + FE</td>
<td>30</td>
<td>IH</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>M</td>
<td>54</td>
<td>ES</td>
<td>op</td>
<td>ATG</td>
<td>ctT</td>
<td>P</td>
<td>13</td>
<td>IH</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Etiology: NS = non-secreting adenoma; ES = empty sella; CR = Craniohypophygioma; I = idiopathic; P = prolactinoma. Treatment: op = surgical operation; rtr = radiation treatment. Pituitary deficiencies: A = Adrenocorticotropin; T = thyrotropin; G = follicle-stimulating hormone/luteinizing hormone; D = anti-diuretic hormone. Hormonal substitution: C = cortisone; t = thyroxine; e = estrogen; T = testosterone; d = desmopressin. Medication: CM = cisaprid monohydrate; F = famotidin; AL = atenolol; FE = felodipin; P = paracetamol. Stimulation test: IH = insulin hypoglycemia.

www.eje.org
adjusted (clamped) to maintain the plasma glucose concentration constant at 5.5 mmol/l. Plasma glucose was measured at 5 min intervals.

EGP was measured by the isotope dilution technique using [3-3H]glucose (Amersham International) administered as a priming dose of 8.3 μCi/m² and a constant infusion of 0.083 μCi/m² per min for 270 min. The basal plasma tracer specific activity is linearly related to the rate of tracer infusion/m² body surface area (16). In order to achieve a similar basal plasma specific activity in all subjects, the tracer amount was adjusted for body surface area (16). To achieve tracer equilibrium in the plasma glucose pool we allowed 150 min before the insulin infusion was started. Plasma glucose was clamped by a variable labeled glucose infusion. The glucose infusion was labeled with [3-3H]glucose to maintain plasma glucose specific activity at baseline levels (17). Labeling of the glucose infusion was based upon previous estimates of the expected glucose infusion and hepatic glucose production rate during the clamp (17). The radiochemical purity of the tracer was 99% as reported by the manufacturer.

Indirect calorimetry was performed in the basal state and during the last 45 min of the insulin clamp to estimate net rates of carbohydrate and lipid oxidation (15). A computerized open-circuit system was used to measure gas exchange through a transparent plastic canopy (Deltatrac; Datex, Helsinki, Finland).

The bioelectrical impedance technique estimates total body water using a two-terminal portable impedance analyzer (BIA 101 RJL; Akern, Copenhagen, Denmark). Electrodes were placed on the dorsal surface of the left hand and foot. Measurements were made in the supine position in the morning after voiding (18).

Samples for measurements of plasma glucose, serum insulin, FFA and [3-3H]glucose specific activity were drawn in accordance with the flowchart (Fig. 1). To prevent in vitro lipolysis, the samples for FFA measurements were collected in prechilled tubes (19). The FFA samples from the entire group were analyzed in one assay run.

The plasma glucose concentration was measured in duplicates on a glucose analyzer (Beckman, Fullerton, CA, USA). Plasma insulin was measured by an ELISA (DAKO Corp., Cambs, UK) with an intra-assay coefficient of variation of 7.5% and interassay coefficient of variation of 7%. FFA were measured using an enzymatic calorimetric ACS-ACOD-MEHA method (Wako Chemicals GmbH, Neuss, Germany), with an intra-assay coefficient of variation of 3.2% and interassay coefficient of variation of 5.7%. [3-3H]glucose specific activity was measured in duplicate from the supernatant of 0.5 M perchloric acid extract of serum samples after evaporation of radiolabeled water. Serum and urinary urea were measured through the oxidation of NADH to NAD by spectrophotometry at 340 nm (Synchron LX Systems).

---

**Figure 1** Experimental design (flowchart).
Chemistry Information, Synchron LX 20; Beckman Coulter, Inc., Palo Alto, CA, USA).

**Calculations**

Fasting EGP was calculated by dividing the [3-3H]glucose infusion rate by the steady-state plateau of [3-3H]glucose specific activity in plasma during the last 30 min of the fasting tracer infusion period. During administration of insulin and glucose a non-steady-state condition in plasma [3-3H]glucose specific activity exists. At high rates of glucose uptake the classical model of Steele is known to produce negative estimates of EGP. When adding [3-3H]glucose to the variable exogenous glucose infusion, the plasma [3-3H]glucose specific activity was maintained constant, and only a few negative numbers of EGP were adapted as zero in calculations. The infusion rate of exogenous glucose was integrated over 20 min intervals and subtracted from the total rate of glucose appearance to obtain the rate of residual EGP during the clamp. Total body glucose metabolism was calculated by adding the mean rate of EGP during the last 60 min of the insulin clamp to the mean glucose infusion rate during the same period.

Non-oxidative glucose metabolism, mainly storage of glucose as glycogen, was calculated as the difference between total body glucose metabolism and glucose oxidation, as determined by indirect calorimetry.

Net rates of glucose and lipid oxidation were calculated from indirect calorimetric measurements in the basal state and during the last 45 min of the insulin clamp.

Protein oxidation was calculated from the overnight urinary urea nitrogen excretion collected by the patient and urinary urea nitrogen excretion obtained during the insulin clamp. Corrections were made for urea clearance (20).

**Statistical analysis**

Values were found to be normally distributed and are presented as means±s.d. Comparisons were made by ANOVA and if significantly different in the four experiments comparisons were tested in pairs by the Wilcoxon signed-rank test. Correlations were calculated using Spearman’s rank correlation coefficients. All statistical analyses were performed with StatView software (Version 4.5 for Windows; Abacus Concepts, Inc., Berkeley, CA, USA). P < 0.05 was considered statistically significant.

**Results**

**Plasma glucose, serum insulin (Fig. 2)**

There were no differences in the plasma glucose concentrations between placebo (A), GH (B), GH + acipimox (C) and acipimox alone (D) either in the basal (5.3±0.5, 5.5±1.0, 5.6±0.8, 5.3±0.6 mmol/l, P = NS) or in the insulin-stimulated (5.4±0.1, 5.5±0.2, 5.5±0.2, 5.6±0.6, mmol/l, P = NS) state.

The basal (before acipimox/placebo administration) serum insulin concentrations were significantly different between the four experiments (P < 0.0001) with the highest values seen during GH treatment. GH increased the basal insulin concentration (110.6±53.9 vs 62.7±45.5 pmol/l, P = 0.0069 for B vs A) which was restored by acipimox (60.9±38.7 vs 51.7±28.9 pmol/l, P = NS for C vs A) during fasting (before clamp) conditions. Acipimox alone did not affect the fasting insulin concentrations (38.3±27.5 vs 51.7±28.9 pmol/l, P = NS for D vs A). There were no differences between serum insulin concentrations during the clamp between the four experiments (213.9±49.4, 202.5±17.8, 217.1±44.2, 242.5±61.7 pmol/l, P = NS).

**FFA concentration and lipid oxidation (Figs 2 and 3)**

The basal FFA concentrations were significantly different between the experiments (P < 0.0001) with the highest values seen after GH treatment. GH increased the basal FFA concentrations (from 449±156 to 859±236 µmol/l, P = 0.0077 for A vs B), which was markedly reduced by acipimox: (130±32 vs 715±149 µmol/l, P = 0.0051 for C vs B) during fasting conditions. Acipimox alone caused a marked decline in
failing FFA concentrations from 537±201 to 129±50 μmol/l. During the insulin clamp, the FFA levels were markedly suppressed in all four experiments but still with significant differences (P < 0.0001). The FFA concentrations during the clamp were higher during GH treatment (213±98 vs 120±52 μmol/l, P = 0.0077 for B vs A), restored by acipimox (108±42 vs 120±52 μmol/l, P = NS for C vs A) but still significantly higher compared with acipimox alone (108±42 vs 81±33 μmol/l, P = 0.0209 for C vs D).

GH also increased the fasting rates of lipid oxidation (from 0.99±0.20 to 1.32±0.28 μmol/kg per min, P = 0.0051 for A vs B), but this was significantly decreased by acipimox (0.97±0.18 vs 1.32±0.28 μmol/kg per kg, P = 0.0125 for C vs B) and restored to placebo levels (0.97±0.18 vs 0.99±0.20 μmol/kg per min, P = NS C vs A). Acipimox alone also resulted in decreased fasting lipid oxidation (0.75±0.20 vs 0.99±0.20 μmol/kg per min, P = 0.0218 for D vs A). The fasting rates of lipid oxidation correlated positively with basal FFA concentrations (r = 0.516, P = 0.0013). Lipid oxidation was less suppressed after GH than placebo (1.12±0.18 vs 0.82±0.19 μmol/kg per min, P = 0.0069 for B vs A) during clamp conditions. However, acipimox was not able to completely improve the impaired suppression of lipid oxidation during GH (0.93±0.25 vs 1.12±0.18 μmol/kg per min, P = 0.093 for C vs B). Moreover, acipimox alone did not significantly affect the lipid oxidation during the insulin clamp (0.67±0.27 vs 0.82±0.19 μmol/kg per min, P = NS for D vs A). The rate of lipid oxidation correlated positively with the FFA concentrations during the insulin clamp (r = 0.513, P = 0.0016).

**Glucose metabolism (Figs 4–6)**

The rates of insulin-stimulated glucose uptakes were significantly different between the four experiments (P < 0.0001). GH resulted in a non-significant decrease in insulin-stimulated glucose uptake (16.61±8.03 vs 12.74±5.50 μmol/kg per min, P = 0.07 for A vs B). However, acipimox caused a significant improvement in insulin-stimulated glucose uptake in the GH-treated patients (17.35±5.65 vs 12.74±5.50 μmol/kg per min, P = 0.012 for C vs B). Also acipimox alone enhanced insulin sensitivity in the untreated GHD patients (24.14±8.74 vs 16.61±8.03 μmol/kg per min, P = 0.0077 for D vs A). The rate of insulin-stimulated glucose uptake correlated negatively with both lipid oxidation (r = −0.475, P = 0.0034) and FFA (r = −0.638, P < 0.0001) concentrations.

The rate of glucose oxidation differed between the four experiments both during fasting (P < 0.0001) and during insulin-stimulated conditions (P = 0.001). GH significantly decreased both the fasting (5.16±2.28 vs 3.09±2.31 μmol/kg per min, P = 0.02 for A vs B) and insulin-stimulated (7.95±2.64 vs 5.88±2.39 μmol/kg per min, P = 0.01 for A vs B) rates of glucose oxidation. Acipimox prevented the decrease in fasting (6.67±3.26 vs 3.09±2.31 μmol/kg per min, P = 0.01 for C vs B) and insulin-stimulated (8.32±3.00 vs 5.88±2.39 μmol/kg per min, P = 0.07 for C vs B) rates of glucose oxidation.
oxidation. Acipimox alone also enhanced fasting (7.90 \pm 2.68 vs 5.16 \pm 2.28 \mu mol/kg per min, \( P = 0.01 \) for D vs A) and insulin-stimulated (9.78 \pm 3.68 vs 7.95 \pm 2.64 \mu mol/kg per min, \( P = 0.07 \) for D vs A) glucose oxidation. The enhanced rates of glucose oxidation induced by acipimox correlated negatively with the rate of lipid oxidation in GH-treated subjects both during fasting (\( r = 0.867, P = 0.0093 \)) and insulin-stimulated (\( r = -0.927, P = 0.0054 \)) conditions.

Energy expenditure

There were significant differences in the fasting rate of energy expenditure between the four experiments (\( P < 0.0001 \)). GH administration to GHD individuals significantly increased the fasting rate of energy expenditure (7761 \pm 1101 vs 7079 \pm 1021 \text{kJ/24 h}, \( P = 0.0051 \) for B vs A); but acipimox did not significantly counteract this increase (7553 \pm 1069 vs 7761 \pm 1101 \text{kJ/24 h}, \( P = 0.008 \)). Neither did acipimox itself significantly change the fasting rate of energy expenditure (7208 \pm 937 vs 7079 \pm 1021 \text{kJ/24 h}, \( P = 0.330 \)). The fasting (\( r = 0.330, P = 0.039 \)) rates of energy expenditure correlated with the rate of lipid oxidation.

Thermogenic response (Fig. 7)

There were significant differences in the thermogenic response to insulin (\( P = 0.01 \)) between the four studies. It was blunted in the GH-untreated subjects and became negative after GH administration (84 \pm 462 \text{kJ/24 h} and \(-197 \pm 335 \text{kJ/24 h} \) for A and B). Pretreatment with acipimox enhanced the thermogenic response to insulin during GH treatment (112 \pm 531 vs \(-197 \pm 335 \text{kJ/24 h}, P = 0.05 \) for C vs B).

Discussion

There is ample evidence that chronic GH replacement therapy in GHD patients induces insulin resistance by...
concomitant activation of lipolysis and that this unto-
ward effect on glucose metabolism can be prevented
by prior inhibition of lipolysis by acipimox (9, 10).
To dissect the effects of GH on lipolysis and glucose
metabolism from other secondary effects we studied
the metabolic effects of GH in previously GH-untreated
patients. This is a clear advantage as chronic GH
therapy is known to cause water retention and to acti-
uate lipolysis and lipid oxidation which, in turn, would
result in a reduction in fat tissue (2, 21). In this study
we could show that the effect of GH on lipid oxidation
(and presumably lipolysis) is an acute effect, as the
first injection of GH already increased the rate of lipid
oxidation by 35%, and consequently decreased glucose
oxidation by 26%. The mechanism by which GH stimu-
lates lipolysis may involve several key steps including
increased expression of β-adrenergic receptors (22),
enhanced activity of the hormone-sensitive lipase (23)
and inhibition of inhibitory G_i proteins (24). A
reduction in fat oxidation could shuttle FFA to re-esta-
erification and fat synthesis unless this pathway is inhib-
ited. As no increase in fat mass is seen with GH (21),
re-esterification of FFA to triglycerides should at least
not be stimulated. In fact, GH have been shown to
inhibit a key enzyme in fat synthesis, acetyl-CoA
carboxylase (25).
Although it has been suggested that GH might also
directly inhibit glucose transport into the cell and
thereby glucose uptake (26) our data show convinc-
ingly that most of the diabetic effect of GH is mediated
by its effect on lipolysis. In fact, when the subjects
were pretreated with the antilipolytic agent acipimox
the decrease in glucose oxidation was completely
prevented. As expected, there was a strong inverse
correlation between the rates of lipid oxidation and
glucose oxidation (\(r = -0.696, P < 0.0001\)), but also
between glucose uptake and lipid oxidation
(\(r = -0.475, P < 0.0034\)) and FFA concentrations
(\(r = -0.638, P < 0.0001\)).

Some (11, 28) but not all (9, 10, 27) studies have
shown that GH might have a direct effect on EGP. It is
well established that elevation of plasma FFA concen-
trations by Intralipid can stimulate EGP (29, 31, 32)
and it has been suggested that the inhibitory effect of
GH on suppression of EGP by insulin is more due to
its effect on glycogenolysis than on gluconeogenesis
(32). However, the effect of FFA on EGP is complex
and requires a finely tuned balance between enhanced
β-oxidation of lipids and inhibition of glycolysis and
the Krebs cycle (33). The putative effect of GH and inhi-
bition of lipolysis by acipimox on EGP was in this study
evaluated during a low-dose insulin infusion. This dose
is particularly well suited to assess effects on EGP as
we know from previous studies (9) that EGP is not com-
pletely suppressed by this low-dose insulin infusion,
particularly not in insulin-resistant individuals such
as patients with GH deficiency (1–6). We also assessed
EGP by the radiolabeled glucose method to avoid
problems from negative values of EGP (17). In keeping
with results during chronic therapy, the acute injection
of GH had no significant effect on EGP in these subjects
and suppression of EGP during the clamp could not be
completely restored by prior administration of acipimox
during GH treatment (9). In contrast and in keeping
with some earlier findings (30), only when FFA levels
were suppressed in due time before the clamp with
acipimox alone suppression of EGP was enhanced.
Furthermore, administration of acipimox alone to
untreated GHD patients resulted in an even greater
enhancement of glucose uptake than seen when acipi-
mox was given to GH-treated subjects. This might be a
direct result of the restraining effect of elevated FFA
levels on glucose metabolism as the FFA levels during
GH with acipimox were significantly higher than with
acipimox alone during the clamp. Acipimox is known
to inhibit lipolysis by decreasing the intracellular
concentrations of cAMP which, in turn, can lead to
decreased activity of a protein kinase B and decreased
activity of the hormone-sensitive lipase (34–36). The
rate-limiting enzyme for glycogen synthesis, glycogen
synthase, is activated by dephosphorylation and deacti-
vated by phosphorylation. It has been proposed that
acipimox may by decreasing the intracellular
CAMP concentrations decrease the activity of the
cAMP-dependent phosphorylating enzyme and thereby
activate glycogen synthase (37). There is also the
possibility that acipimox stimulates glycogen formation
independently of the changes in FFA levels. In support
of this, Fulcher et al. (38) reported a stimulatory
effect of acipimox on non-oxidative glucose metabolism
which was independent of plasma FFA levels. It
should, however, be kept in mind that intracellular

\[
\text{Figure 7 Thermogenic response during placebo (A), GH (B),}
\text{GH + acipimox (C) and acipimox alone (D). Data are shown as}
\text{mean±S.D. B vs C, P = 0.002; B vs D, P = 0.025. n = 10 per}
\text{study group.}
\]
FFA concentrations could differ even in the phase of identical plasma FFA concentrations (39).

In conclusion, the study of acute administration of GH to previously untreated GHD patients provides compelling evidence that (i) GH-induced insulin resistance is mainly due to induction of lipolysis by GH; and (ii) inhibition of lipolysis can prevent the deterioration of insulin sensitivity. The question remains whether prevention of excessive lipolysis at the initiation of GH therapy would have beneficial effects on glucose metabolism.

Acknowledgements

The study was supported by a grant from Pharmacia Upjohn, Stockholm, Sweden, the Skane County Council’s Research and Development Foundation (M S), the Novo Nordisk Foundation and the Swedish Medical Research Council (L C G). We are indebted to Gertrud Ahlqvist, Marianne Lundberg and Dr Ronnie Thomas for their skilful assistance.

References

1 Davidson BM. Effect of growth hormone on carbohydrate and lipid metabolism. Endocrine Reviews 1987 8115–131.


Received 14 April 2003
Accepted 9 September 2003