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

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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 [3-3H]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 μmol/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 (17.39±5.65 vs 12.74±5.50 μmol/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 5.88±2.39 μmol/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 μmol/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 μmol/kg per min, P = NS for B vs A and 11.55±2.7 vs 10.99±1.98 μmol/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 μmol/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 μmol/kg per min, P = 0.01 for D vs A) and insulin-stimulated (9.78±3.68 vs 7.95±2.64 μmol/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.
the concomitant stimulation of lipolysis we inhibited
the rise in FFA by prior administration of acipimox in
ten previously untreated GHD adults. Insulin sensitivity
was assessed by a euglycemic insulin clamp combined
with infusion of [3-3H]glucose and indirect calorimetry.

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 dia-
betes 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 Com-
mittee 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
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 hyperin-
sulinemic 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]glu-
cose 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 pro-
duction (EGP) was measured by infusion of [3-3H]glu-
cose. A primed continuous infusion of human insulin
(Actrapid Human; Novo Industri, Copenhagen, Den-
mark), 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>
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<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>
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Etiology: NS = non-secreting adenoma; ES = empty sella; CR = Craniohypophyseoma; I = idiopathic; P = prolactinoma.
Treatment: op = surgical operation; rfr = radiation treatment.
Pituitary deficiencies: A = Adrenocorticotropicin; 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.

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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 \([3-\text{3H}]\)glucose (Amersham International) administered as a priming dose of 8.3 \(\mu\)Ci/m\(^2\) and a constant infusion of 0.083 \(\mu\)Ci/m\(^2\) per min for 270 min. The basal plasma tracer specific activity is linearly related to the rate of tracer infusion/m\(^2\) 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 \([3-\text{3H}]\)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 \([3-\text{3H}]\)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%. \([3-\text{3H}]\)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).
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
fasting FFA concentrations from $537\pm 201$ to $129\pm 50 \mu mol/l$ ($P = 0.0051$). 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 ($213\pm 98$ vs $120\pm 52 \mu mol/l$, $P = 0.0077$ for B vs A), restored by acipimox ($108\pm 42$ vs $120\pm 52 \mu mol/l$, $P = NS$ for C vs A) but still significantly higher compared with acipimox alone ($108\pm 42$ vs $81\pm 33 \mu mol/l$, $P = 0.0209$ for C vs D).

GH also increased the fasting rates of lipid oxidation (from $0.99\pm 0.20$ to $1.32\pm 0.28 \mu mol/kg per min$, $P = 0.0051$ for A vs B), but this was significantly decreased by acipimox ($0.97\pm 0.18$ vs $1.32\pm 0.28 \mu mol/kg per min$, $P = 0.0125$ for C vs B) and restored to placebo levels ($0.97\pm 0.18$ vs $0.99\pm 0.20 \mu mol/kg per min$, $P = NS$ C vs A). Acipimox alone also resulted in decreased fasting lipid oxidation ($0.75\pm 0.20$ vs $0.99\pm 0.20 \mu mol/kg per min$, $P = 0.0218$ 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 ($1.12\pm 0.18$ vs $0.82\pm 0.19 \mu mol/kg per min$, $P = 0.0069$ for B vs A) during clamp conditions. However, acipimox was not able to completely improve the impaired suppression of lipid oxidation during GH ($0.93\pm 0.25$ vs $1.12\pm 0.18 \mu mol/kg per min$, $P = 0.093$ for C vs B). Moreover, acipimox alone did not significantly affect the lipid oxidation during the insulin clamp ($0.67\pm 0.27$ vs $0.82\pm 0.19 \mu mol/kg per min$, $P = NS$ 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 ($16.61\pm 8.03$ vs $12.74\pm 5.50 \mu mol/kg per min$, $P = 0.07$ for A vs B). However, acipimox caused a significant improvement in insulin-stimulated glucose uptake in the GH-treated patients ($17.35\pm 5.65$ vs $12.74\pm 5.50 \mu mol/kg per min$, $P = 0.012$ for C vs B). Also acipimox alone enhanced insulin sensitivity in the untreated GHD patients ($24.14\pm 8.74$ vs $16.61\pm 8.03 \mu mol/kg per min$, $P = 0.0077$ 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 ($5.16\pm 2.28$ vs $3.09\pm 2.31 \mu mol/kg per min$, $P = 0.02$ for A vs B) and insulin-stimulated ($7.95\pm 2.64$ vs $5.88\pm 2.39 \mu mol/kg per min$, $P = 0.01$ for A vs B) rates of glucose oxidation. Acipimox prevented the decrease in fasting ($6.67\pm 3.26$ vs $3.09\pm 2.31 \mu mol/kg per min$, $P = 0.01$ for C vs B) and insulin-stimulated ($8.32\pm 3.00$ vs $5.88\pm 2.39 \mu mol/kg per min$, $P = 0.07$ for C vs B) rates of glucose oxidation.

**Figure 3** Lipid oxidation during placebo (A), GH (B), GH + acipimox (C) and acipimox alone (D). Unshaded bars in the basal state and shaded bars during the clamp. Data are shown as means±S.D. A basal vs B basal, $P = 0.0051$; A basal vs D basal, $P = 0.02$; B basal vs C basal, $P = 0.0125$; B clamp vs D clamp, $P = 0.0077$. $n = 10$ per study group.

**Figure 4** Glucose oxidation during placebo (A), GH (B), GH + acipimox (C) and acipimox alone (D). Unshaded bars in the basal state and shaded bars during the clamp. Data are shown as means±S.D. A basal vs B basal, $P = 0.02$; A basal vs D basal, $P = 0.01$; B basal vs C basal, $P = 0.01$; A clamp vs B clamp, $P = 0.01$; A clamp vs D clamp, $P = 0.07$; B clamp vs C clamp, $P = 0.07$. $n = 10$ per study group.
There were significant differences in the rates of non-oxidative glucose metabolism between the four studies (P = 0.006). However, GH did not significantly impair non-oxidative glucose metabolism (6.86 ± 5.22 vs 8.67 ± 6.65 μmol/kg per min, P = NS for B vs A) and acipimox did not significantly influence the rate of non-oxidative glucose metabolism in GH-treated subjects (9.03 ± 4.01 vs 6.86 ± 5.22 μmol/kg per min, P = NS for C vs B). Moreover, acipimox alone increased the rates of non-oxidative glucose metabolism in GH-untreated patients (14.36 ± 6.65 vs 8.67 ± 6.65 μmol/kg per min, P = 0.01 for D vs A).

The fasting rate of EGP was unaffected by GH administration (10.99 ± 1.98 vs 11.73 ± 2.38 μmol/kg per min, P = NS for B vs A) and no significant effect was seen after acipimox (11.55 ± 2.70 vs 10.99 ± 1.98 μmol/kg per min, P = NS for C vs B). Acipimox alone did not significantly influence the fasting rate of EGP (11.21 ± 1.59 vs 11.73 ± 2.38 μmol/kg per min, P = NS for D vs A). The fasting rate of EGP was slightly more suppressed by insulin during GH when acipimox was given before the experiment (2.99 ± 2.77 vs 5.36 ± 2.62 μmol/kg per min, P = 0.07 for C vs B).

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 ± 1101 vs 7079 ± 1021 kJ/24 h, P = 0.0051 for B vs A); but acipimox did not significantly counteract this increase (7553 ± 1069 vs 7761 ± 1101 kJ/24 h, P = NS for C vs B). Neither did acipimox itself significantly change the fasting rate of energy expenditure (7208 ± 937 vs 7079 ± 1021 kJ/24 h, P = NS for D vs A). 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 ± 462 kJ/24 h and −197 ± 335 kJ/24 h for A and B). Pretreatment with acipimox enhanced the thermogenic response to insulin during GH treatment (112 ± 531 vs −197 ± 335 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 un-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 activate 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 stimulates 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-esterification and fat synthesis unless this pathway is inhibited. 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 convincingly 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 concentrations by Intralipid can stimulate EGP (29, 31, 32) and it has been suggested that the inhibitory effect of FFA 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 glycogen synthesis and the Krebs cycle (33). The putative effect of GH and inhibition 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 completely 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 acipimox 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 deactivated 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

\[ r_{12} = 0.053, B vs C, P = 0.025, n = 10 \]
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.

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