Acute Growth Hormone Effects on Amino Acid and Lipid Metabolism*

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ABSTRACT

The anabolic actions of GH are well known, although specific tissue responses and the mechanism of nitrogen conservation are less well understood. This study was designed to examine the acute metabolic effects of GH on whole body and regional protein metabolism, using an experimental protocol which controlled for confounding perturbations in other hormones by a simultaneous infusion of somatostatin. Control subjects received replacement doses of insulin, glucagon, and GH for the entire 7-h study period, whereas GH subjects received an identical protocol, except for an increased dose of GH sufficient to increase serum concentrations into the high-physiological range (12-20 ng/mL) for the final 3.5 h of the study (P < 0.001). Thirteen young, healthy male subjects were studied in the postabsorptive period; five served as control subjects and eight as treatment (GH) subjects. Each received continuous iv infusions of somatostatin, L-[3-C]leucine, and L-[13-H]phenylalanine throughout the study. Femoral arterial and venous sampling allowed for simultaneous measurements across the leg and in the whole body.

C-Peptide levels were suppressed throughout the infusion; insulin, glucagon, insulin-like growth factor I, cortisol, epinephrine, norepinephrine, and glucose concentrations were not different between groups. Glycerol concentrations increased 3-fold in GH subjects during the final 3.5-h period (P = 0.04). Concentrations of several amino acids declined through the study, but no differences were observed between treatment groups. Leucine oxidation was reduced in GH compared to control subjects (P = 0.04). No changes in CO2 production or whole body leucine or phenylalanine flux were observed, whereas nonoxidative disposal of leucine was marginally higher in GH compared to control subjects (P = 0.07). By contrast, rates of appearance and disappearance of both leucine and phenylalanine across the leg all were relatively lower in GH compared to control subjects; leucine balance across the leg was reduced by GH (P = 0.05), whereas phenylalanine balance was not influenced by GH. Our data thus demonstrate an acute stimulatory effect of GH on lipolysis, a decrease in leucine oxidation, and no stimulation of muscle protein synthesis in spite of enhanced protein synthesis in nonmuscle tissue. (J Clin Endocrinol Metab 78: 1040–1047, 1994)

G-stimulates nitrogen retention (1) and increases lean body mass in normal (2, 3) and GH-deficient (4, 5) subjects. Few studies have explored which tissues benefit from this protein conservation or the mechanisms involved. Recent reports have demonstrated that patients with GH deficiency have reduced muscle mass, partially reversed by GH treatment (5–8). Although GH excess is associated with increased fat-free mass (9, 10) and visceral enlargement (11), skeletal muscle enlargement is unusual (12), and patients typically have frank muscle weakness (11).

Several human studies have explored whether GH directly stimulates skeletal muscle protein synthesis (13–15). Using a model in which GH was infused directly into the forearm, Fryburg et al. (15) demonstrated an increase in forearm tissue amino acid uptake on exposure to GH for 6 h. More recently, Yarasheski et al. (16) treated normal men with GH for 12 weeks with or without resistance training exercise. Although protein synthesis in the whole body was increased by GH, quadriceps muscle protein synthesis rate and muscle strength were no greater in GH-treated compared to exercise only subjects. The current study was designed to determine acute effects of GH on both whole body and regional amino acid kinetics, using an arteriovenous technique across the leg. This acute study was designed to distinguish the effects of GH from that of its effects induced secondarily by insulin-like growth factor I (IGF-I) or insulin.

Materials and Methods

Subjects

Fifteen male subjects between 20 and 26 years of age were studied, after written informed consent was obtained. All subjects were judged healthy based on a medical history, a normal physical examination, and screening blood tests including a complete blood count, electrolytes, urea nitrogen, albumen, calcium, and phosphorous. Exclusion criteria included diabetes mellitus, hypertension, medications known to influence GH secretion or action, and recent weight loss or gain. The research protocol was approved by the Committee on Human Research of the University of Vermont, and the studies were performed at the University of Vermont Clinical Research Center.

Procedures

Each subject was fed a weight-maintenance diet for 3 days before the study, consisting of protein, fat, and carbohydrate in a ratio of 15:35:50. Fourteen hours after the last meal, peripheral venous catheters were inserted to deliver infusions of stable isotopes and hormones. After an iv priming bolus of [13C]sodium bicarbonate (0.2 mg/kg), L-[13C]leucine (6.1 μmol/kg), and L-[13H]phenylalanine (4.3 μmol/kg), an iv infusion of L-[13C]-leucine (6.1 μmol/kg-h) and L-[13H]phenylalanine (4.3 μmol/kg-h) was begun and continued for 7 h. Simultaneously, an iv infusion of somatostatin (7 μg/kg-h), insulin (7.2 μU/kg-h), and

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GH EFFECTS ON AMINO ACID AND LIPID METABOLISM

Experimental Design

<table>
<thead>
<tr>
<th>Prime</th>
<th>Femoral Catheters Placed</th>
</tr>
</thead>
<tbody>
<tr>
<td>13C-Leu (6.1 μmol/kg/h) &amp; 15N-Phe (4.3 μmol/kg/h)</td>
<td></td>
</tr>
<tr>
<td>SRH (7 μg/kg/h), Insulin (7.2 μU/kg/h), &amp; Glucagon (0.04 μg/kg/h)</td>
<td></td>
</tr>
<tr>
<td>GH 2.0 μg/kg/h (n=8)</td>
<td></td>
</tr>
<tr>
<td>GH 0.5 μg/kg/hr (n=5)</td>
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</tr>
</tbody>
</table>

FIG. 1. The experimental design (see text for details).

Glucagon (0.04 μg/kg·h) was begun and continued for 7 h. Recombinant hGH (rhGH; 0.5 μg/kg·h) also was begun in all subjects and continued for 7 h in five control (C) subjects. In eight subjects (GH subjects), the infusion rate was increased to 2.0 μg/kg·h at 210 min and continued for the remaining 3.5 h of the study. Thus, the two groups were identical in terms of hormonal replacement before 210 min. Femoral arterial (Arrow (Reading, PA) double lumen, 4-French, 12-cm) and venous (Cook (Bloomington, IN) single lumen, 4-French, 13-cm) catheters were placed in retrograde fashion, and patency was maintained by continuous saline infusion as previously described (27). Paired arterial and venous blood sampling was obtained at the intervals indicated (Fig. 1).

Blood was obtained from a heated dorsal hand vein for glucose, insulin, C-peptide, glucagon, cortisol, IGF-I, GH, glycerol, free fatty acids, and amino acids at approximately hourly intervals. Samples also were obtained from the femoral artery and vein at 160, 180, and 210 min (baseline) and 360, 400, and 420 min (end) for whole blood glucose and stable isotopes. Indirect calorimetry was performed (over a 45-min period) on three occasions in each subject, beginning at 150, 240, and 370 min, and expired air for determination of 13CO2 was collected every 30 min throughout the study. Cardio-green dye (17) was infused continuously into the proximal arterial port between 180 and 400 min for determinations of limb blood flow.

Materials

Recombinant hGH was obtained from Genentech, Inc. (South San Francisco, CA). Stable isotopes were obtained from Merck, Sharp, & Dohme/Isotopes (Dorval, Canada), and somatostatin was obtained from Bachem (Torrance, CA). Glucagon and regular human insulin were obtained from Eli Lilly (Indianapolis, IN).

Sample analyses

Glucose was analyzed in whole blood by the glucose oxidase method (Yellow Springs Instrument Co., Yellow Springs, OH; model 23A). GH, IGF-I (after cryoprecipitation and acid-ethanol extraction), insulin, C-peptide, glucagon, and cortisol concentrations were measured by RIA.

FIG. 2. Hormone and substrate concentrations. Samples were obtained from heated dorsal hand veins at the times indicated. The higher dose of GH was infused in GH subjects (solid lines) beginning at 3.5 h. Control subjects (dotted lines) were continued on the same doses of hormones for the entire 7 h (see Fig. 1 and text).
TABLE 1. Plasma amino acids

<table>
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<tr>
<th></th>
<th>Control</th>
<th>GH</th>
<th>Control</th>
<th>GH</th>
<th>Control</th>
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<tbody>
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<td>Asp</td>
<td>245 (25)</td>
<td>244 (23)</td>
<td>247 (10)</td>
<td>240 (20)</td>
<td>258 (17)</td>
<td>260 (22)</td>
<td>254 (19)</td>
<td>253 (13)</td>
<td></td>
<td></td>
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<tr>
<td>Glu</td>
<td>157 (25)</td>
<td>162 (18)</td>
<td>159 (17)</td>
<td>152 (13)</td>
<td>163 (16)</td>
<td>156 (18)</td>
<td>160 (19)</td>
<td>149 (17)</td>
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<tr>
<td>Ser</td>
<td>135 (0)</td>
<td>133 (7)</td>
<td>130 (6)</td>
<td>126 (7)</td>
<td>126 (6)</td>
<td>121 (11)</td>
<td>123 (6)</td>
<td>117 (11)</td>
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<tr>
<td>His</td>
<td>110 (3)</td>
<td>111 (3)</td>
<td>112 (7)</td>
<td>101 (7)</td>
<td>111 (4)</td>
<td>101 (12)</td>
<td>106 (9)</td>
<td>101 (7)</td>
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<tr>
<td>Gly</td>
<td>229 (17)</td>
<td>314 (18)</td>
<td>218 (19)</td>
<td>298 (12)</td>
<td>276 (9)</td>
<td>293 (14)</td>
<td>274 (20)</td>
<td>293 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thr</td>
<td>190 (8)</td>
<td>213 (6)</td>
<td>196 (10)</td>
<td>189 (11)</td>
<td>194 (11)</td>
<td>188 (11)</td>
<td>183 (11)</td>
<td>180 (12)</td>
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<tr>
<td>Ala</td>
<td>236 (28)</td>
<td>343 (31)</td>
<td>311 (40)</td>
<td>305 (23)</td>
<td>292 (28)</td>
<td>285 (36)</td>
<td>286 (38)</td>
<td>274 (31)</td>
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<tr>
<td>Arg</td>
<td>77 (6)</td>
<td>76 (4)</td>
<td>81 (6)</td>
<td>69 (7)</td>
<td>74 (6)</td>
<td>66 (6)</td>
<td>78 (3)</td>
<td>64 (5)</td>
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<tr>
<td>Tyr</td>
<td>61 (2)</td>
<td>61 (4)</td>
<td>55 (3)</td>
<td>52 (4)</td>
<td>50 (3)</td>
<td>59 (5)</td>
<td>47 (4)</td>
<td>47 (5)</td>
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<tr>
<td>Val</td>
<td>231 (15)</td>
<td>228 (14)</td>
<td>219 (5)</td>
<td>209 (9)</td>
<td>207 (15)</td>
<td>194 (15)</td>
<td>199 (10)</td>
<td>187 (12)</td>
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<td>Met</td>
<td>8 (2)</td>
<td>15 (4)</td>
<td>11 (2)</td>
<td>13 (3)</td>
<td>10 (1)</td>
<td>13 (4)</td>
<td>8 (2)</td>
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<td>Phe</td>
<td>52 (1)</td>
<td>55 (2)</td>
<td>51 (2)</td>
<td>51 (3)</td>
<td>53 (2)</td>
<td>51 (3)</td>
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<tr>
<td>Ile</td>
<td>55 (6)</td>
<td>58 (6)</td>
<td>49 (2)</td>
<td>50 (5)</td>
<td>45 (4)</td>
<td>45 (5)</td>
<td>43 (3)</td>
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<tr>
<td>Leu</td>
<td>136 (11)</td>
<td>138 (7)</td>
<td>134 (3)</td>
<td>130 (6)</td>
<td>134 (10)</td>
<td>129 (7)</td>
<td>131 (7)</td>
<td>128 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lys</td>
<td>172 (6)</td>
<td>187 (5)</td>
<td>167 (5)</td>
<td>172 (10)</td>
<td>163 (7)</td>
<td>162 (12)</td>
<td>159 (7)</td>
<td>155 (11)</td>
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</table>

* In micromoles per (SEM).

TABLE 2. Whole-body effects of GH [mean (SEM)]

<table>
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<th>Baseline</th>
<th>Control</th>
<th>GH</th>
<th>End Level of significance P value</th>
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<td>13CO2 production (µmol/min) b</td>
<td>146 (9)</td>
<td>163 (8)</td>
<td>154 (7) 136 (8)</td>
<td>0.02</td>
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<tr>
<td>VCO2 (ml/min)</td>
<td>212 (12)</td>
<td>208 (6)</td>
<td>219 (16)</td>
<td>214 (6)</td>
</tr>
<tr>
<td>Leu flux (µmol/kg.h)</td>
<td>128 (4)</td>
<td>110 (4)</td>
<td>115 (3) 97 (6)</td>
<td>0.96</td>
</tr>
<tr>
<td>Leu oxid (µmol/kg.h)</td>
<td>35 (2)</td>
<td>32 (2)</td>
<td>33 (2)   23 (2)</td>
<td>0.04</td>
</tr>
<tr>
<td>Whole-body protein synthesis (from NODL; mmol/kg.h)</td>
<td>93 (6)</td>
<td>79 (4)</td>
<td>82 (4) 74 (4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Phe flux (µmol/kg.h)</td>
<td>38 (4)</td>
<td>39 (3)</td>
<td>37 (3) 40 (3)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

b Time effects, P < 0.05. No study effects or study/time interactions observed.

**Statistical analyses**

Analysis of variance for repeated measures, analyzing time, study (C vs. GH groups), and combined study/time interactions were performed for each of the hormones and substrates analyzed. All data are expressed as mean ± SEM.

**Calculations**

Flux rates of KIC, leucine, and phenylalanine were calculated using the formula:

\[
\text{FLUX} = \frac{\text{i} \cdot (\text{Ep} - \text{El})}{\text{Ep}}
\]

where \(i\) = infusion rate of tracer in micromoles per kg/h, \(Ei\) = isotopic abundance of tracer, and \(Ep\) = isotopic abundance in plasma (each expressed as atom per cent excess).
Leucine oxidation rates were calculated according to the formula:
LEU_{\text{in}} = F \times (1/E_p - 1/E_v) \times 100,
where $E_p$ = plasma arterial KIC isotopic enrichment (atom per cent excess or APE), $E_v$ = isotopic enrichment (APE) of the leucine infused in atom per cent excess, and $F$ = production rate of $^{13}$CO$_2$. The details of this calculation are given elsewhere (24).

Plasma $^{13}$C\text{KIC} was used for calculations of both leucine flux and leucine oxidation, since $^{13}$C\text{KIC} reflects the intracellular $^{12}$C\text{leucine enrichment better than the plasma leucine enrichment (21, 25). The nonoxidative portion of leucine flux was calculated by deducting leucine oxidation from leucine flux and was used as an index of whole body protein synthesis as previously described (26).}

For across-the-leg studies, the following calculations (27) were made:

1) Phe rate of disappearance = balance (bal) + Phe rate of appearance,
2) Phe balance = [(Phe$_{\text{in}}$ - Phe$_{\text{out}}$) × F],
where Phe$_{\text{in}}$ is the arterial, and Phe$_{\text{out}}$ is the venous concentration, and F is blood flow, calculated from dye dilution curves obtained from the infusion of cardio-green.

3) Phe rate of appearance = Phe$_{\text{in}}$ + Phe$_{\text{out}}$ - 1) × F,

where Phe$_{\text{in}}$ and Phe$_{\text{out}}$ represent the $^{12}$C\text{Phe enrichments in arterial and venous blood, respectively.}

4) In addition, tissue disposal of phenylalanine (Rd) was calculated directly from the measured fractional extraction of its tracer (28) according to the formula:
Rd = [Phe$_{\text{in}}$ - Phe$_{\text{out}}$/Phe$_{\text{in}}$] [Phe$_{\text{in}}$] × F.

### Results

**Hormone delivery and effects on endogenous substrates and hormones**

Basal serum GH concentrations were similar in the two groups (2–4 ng/mL) and remained unchanged until 210 min, at which time levels in GH subjects increased into the high-physiological range (12–20 ng/mL), whereas levels in C subjects remained at basal levels (Fig. 2) for the final 3.5 h of the study (study/time effects, $P < 0.0001$). In response to the insulin infusion, serum insulin levels (Fig. 2) increased in both groups approximately 2-fold above basal levels, whereas C-peptide levels (Fig. 2) remained suppressed throughout the infusions (time effects only; $P < 0.0001$). Serum glucagon and plasma IGF-I concentrations were not different between groups, and levels remained constant throughout the infusions (Fig. 2). Femoral arterial glucose concentrations declined from 180 min onward in both groups and were not increased by the higher dose of GH infused (time effects only; $P = 0.0007$). Femoral arteriovenous whole blood glucose differences between groups were not observed at any time point (data not shown). Serum cortisol levels declined slightly throughout the study in both groups (Fig. 2) and were not different between groups (time effects only; $P = 0.0012$), whereas plasma epinephrine and norepinephrine levels were not different between groups and unchanged throughout the study (data not shown).

**Effects on amino acid and lipid concentrations**

The period of high-physiological GH infusion was not associated with alterations in heated dorsal hand vein concentrations of any amino acid, although levels of several amino acids declined progressively in both groups throughout the study (Table 1). Arterial glycerol concentrations (Fig. 2) increased approximately 3-fold above basal levels in GH compared to C subjects (study/time effect; $P = 0.038$), whereas levels remained unchanged in C subjects. Although arterial free fatty acid levels (Fig. 2) increased in both groups and were slightly higher throughout the study in GH compared to C subjects (time effect, $P = 0.003$; study effect, $P = 0.05$), study/time interactions were not significantly different between groups.

**Effects on whole body amino acid kinetics**

The most impressive amino acid kinetic effect of GH was on leucine oxidation (Fig. 3 and Table 2). Leucine oxidation was reduced approximately 25% below baseline in GH subjects, compared to a 5% reduction in C subjects ($P = 0.04$). This reflected a reduced ($P = 0.02$) rate of $^{13}$CO$_2$ production.
Across-the-Leg

![Graph](image)

**FIG. 4.** Across-the-leg kinetic data, obtained using $^{[13]C}\text{leucine}$ as isotopic tracer. **A,** Rates of appearance and disappearance (sum of Ra + balance) expressed as percent of change from baseline; **B,** leucine balance expressed in micromoles per min in control (solid bars) and GH (cross-hatched bars) subjects.

with no differences in VCO$_2$ observed. Leucine flux declined in both groups; however, since leucine flux was not different between groups, this translated to a relatively higher rate of nonoxidative disposal of leucine in GH compared to C subjects ($P = 0.07$). Phenylalanine flux was marginally higher in GH compared to C subjects ($P = 0.07$).

**Effects on amino acid kinetics across the leg**

No differences in leg blood flow were detected during the high-physiological GH infusion period. Mean ± sem leg blood flow for C subjects was 418 ± 69 mL/min, with a range between 263–547 mL/min. Mean ± sem blood flow for GH subjects was 394 ± 52, with a range between 232–602 mL/min. GH treatment was not associated with changes in either leucine or phenylalanine concentrations in either the artery or vein compared to controls, and no effect on arteriovenous differences was seen (Table 3). Treatment with GH inhibited the negative leucine balance ($P = 0.03$) observed across the leg in the control group (Table 3 and Fig. 4B), although neither leucine Ra nor Rd achieved statistical significance ($P = 0.09$ and $P = 0.27$, respectively; Fig 4A). Phenylalanine rates of appearance and disappearance (Fig. 5A) both were marginally reduced by GH (compared to C subjects; $P = 0.05$ and $P = 0.10$, respectively), whereas balance (Fig. 5B) was unchanged. The phenylalanine disappearance rate (Table 3 and Fig. 5C) calculated directly (28) also was marginally
TABLE 4. Relationship between whole-body and skeletal muscle effects

<table>
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<tr>
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<th>Baseline</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>GH</td>
</tr>
<tr>
<td>Estimated Phe hydroxylation (% of Phe flux)</td>
<td>72.7</td>
<td>70.9</td>
</tr>
<tr>
<td>Estimated rate of Phe incorporation into whole-body protein</td>
<td>1932</td>
<td>1939</td>
</tr>
<tr>
<td>(mg/h)</td>
<td>010</td>
<td>320</td>
</tr>
<tr>
<td>Estimated rate of Phe incorporation into skeletal muscle</td>
<td>882</td>
<td>1080</td>
</tr>
<tr>
<td>(mg/h)</td>
<td>145</td>
<td>178</td>
</tr>
</tbody>
</table>

* Assuming that the rate of Phe hydroxylation equals the same percentage of Phe flux as the nonoxidized percentage of leucine flux (from Table 2, Ref. 33).

* Assuming a 70-kg body wt.

* From Table 3, assuming a 70-kg body wt, and that one leg represents approximately one-third of the skeletal muscle protein mass in the body.

Our data also suggest that the acute GH-induced increase in whole body protein synthesis occurs primarily in nonskeletal muscle tissues, as indicated by the directional changes in leucine and phenylalanine disappearance rates across the leg. The magnitude of this discordance between whole body and skeletal muscle may be physiologically important (Table 4). Given the assumptions noted in Table 4 (33) and the conditions of the protocol design, GH treatment resulted in an hourly net accretion of 32 mg whole body protein but an hourly loss of 77 mg skeletal muscle protein (relative to baseline values). Assuming continued unperturbed biological action of GH (including confounding effects by IGF-I or insulin), this would translate to an average loss of 1.8 g skeletal muscle protein each day. It is well known, however, that GH treatment invariably is followed some 6–8 h later by a significant increase in blood IGF-I (34), which may stimulate skeletal muscle protein anabolism.

This observed relative increase in whole body protein synthesis without concomitant increase in muscle protein synthesis is consistent with the report of Yarasheski et al. (16), who observed no stimulation of muscle protein synthesis during chronic administration of GH when combined with exercise. By contrast, Fryburg et al. (15, 35) demonstrated that GH infused directly into the brachial artery stimulates protein synthesis. This increase in muscle protein synthesis occurred only after a longer exposure to GH than the current study. In addition, in that study an increase in blood flow was observed, whereas in our study the systemic administration of GH was not associated with an increase in blood flow in the leg. Recently, these same investigators reported data on regional effects after a systemic infusion of GH, using a design similar to ours but without a concomitant infusion of somatostatin (36). They observed acute increases in forearm blood flow and amino acid uptake across the arm after GH, without evidence of increased protein synthesis in the whole body. However, increasing both insulin and IGF-I concentrations were induced by the GH infusion, which may account for some of the differences observed between their studies and ours (36).

We believe it is possible that in our study, GH stimulated fast turning-over proteins in organs such as gut and liver, which may have rendered muscle less accessible to amino acids for protein synthesis. An alternative explanation is that the period of GH administration was too short to stimulate local productions of IGF-I in muscle, which may have caused an increased rate of muscle protein synthesis. Recent studies, however, have not shown any stimulation of muscle protein synthesis by IGF-I in humans (37, 38). We suspect that the increase in muscle mass observed in GH-treated adults (5–8) represents a chronic effect on inhibited proteolysis, mediated by IGF-I.

The current study also confirms the lipolytic actions of GH (39). This finding was surprising, considering the relatively high circulating concentrations of insulin in our study, and suggests that under proper experimental conditions, the potent antilipolytic effects of insulin (at the replacement doses chosen) can be overcome by rather modest doses of GH.
These data are consistent with numerous reports demonstrating a reduction in body fat both in GH-deficient (4, 5) or normal (2) subjects treated with GH and in subjects with acromegaly (9, 10).

In conclusion, this report confirms the leucine-sparing action of GH in the whole body but provides no evidence for an acute stimulation of muscle protein synthesis. It does not exclude an effect of GH in stimulating protein synthesis if infused directly into a limb, or a chronic anabolic effect on skeletal muscle via inhibited proteolysis, either directly or mediated through IGF-I or insulin. These data also suggest that the acute protein anabolic actions of GH may be nonhomogeneous in muscle and nonmuscle tissue.

Acknowledgments

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