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High Dose Growth Hormone Exerts an Anabolic Effect at Rest and during Exercise in Endurance-Trained Athletes

M. L. HEALY, J. GIBNEY, D. L. RUSSELL-JONES, C. PENTECOST, P. CROOS, P. H. SÖNKSEN, AND A. M. UMPLEBY

Department of Diabetes and Endocrinology, GKT School of Medicine, St. Thomas Hospital, London, United Kingdom SE1 7EH

The anabolic actions of GH in GH-deficient adults and children are well documented. Replacement with GH in such individuals promotes protein synthesis and reduces irreversible loss of protein through oxidation. Although GH is known to be self-administered by athletes, its protein metabolic effects in this context are unknown. This study was designed to determine whether 4 wk of high dose recombinant human GH (r-hGH) administration altered whole body leucine kinetics in endurance-trained athletes at rest and during and after 30 min of exercise at 60% of maximal oxygen uptake. Eleven endurance-trained male athletes were studied, six randomized to receive r-hGH (0.067 mg/kg·d), and five to receive placebo. Whole body leucine turnover was measured at rest and during and after exercise, using a 5-h primed constant infusion of 1-[^{13}C]leucine, from which rates of leucine appearance (an index of protein breakdown), leucine oxidation, and nonoxidative leucine disposal (an index of protein synthesis) were estimated. Under resting conditions, r-hGH administration increased rate of leucine appearance and nonoxidative leucine disposal, and reduced leucine oxidation ($P < 0.01$). This effect was apparent after 1 wk, and was accentuated after 4 wk, of r-hGH administration ($P < 0.05$). During and after exercise, GH attenuated the exercise-induced increase in leucine oxidation ($P < 0.05$). There were no changes observed in placebo-treated subjects compared with the baseline study. We conclude that GH administration to endurance-trained male athletes has a net anabolic effect on whole body protein metabolism at rest and during and after exercise. (*J Clin Endocrinol Metab* 88: 5221–5226, 2003)

GROWTH HORMONE IS an anabolic hormone that stimulates longitudinal bone growth in children (1) and plays a central role in the control of protein metabolism and body composition in adults (2, 3). Recombinant human GH (r-hGH) is self-administered by athletes and bodybuilders in the belief that it augments performance in both endurance and power sports (4). The expectation that supraphysiological levels of GH will promote an increase in muscle bulk and strength is largely based on evidence from studies in GH-deficient (GHD) adults.

GHD adults have reduced rates of protein synthesis and protein breakdown, but normal rates of irreversible oxidative protein loss (5). These changes are reflected by a reduction in lean body mass (LBM). Replacement of r-hGH in such subjects results in increased protein synthesis, reduced oxidative protein loss, and increased LBM (6). Previous studies investigating the influence of r-hGH on whole body protein turnover in highly trained, GH-replete subjects, however, have reported conflicting findings (7, 8).

Exercise exerts a significant influence on protein metabolism (9). Whole body and muscle protein breakdown increase during exercise, whereas oxidation of certain amino acids, including leucine, increases during exercise. It is therefore apparent that studies of protein metabolism in the resting state may fail to recognize important changes occurring during or after exercise.

The aim of this study was to determine what changes occur in the components of whole body protein kinetics at rest and during and after exercise after the administration of high doses of r-hGH to endurance-trained adult males. The dose of r-hGH administered was chosen based on anecdotal reports of doses self-administered by athletes (10).

Subjects and Methods

Study design

The data presented here are from a 4-wk, double-blind, placebo-controlled trial of the administration of r-hGH to endurance-trained adult males. Subjects attended for four visits. After screening (visit 1), three studies were performed to assess the effects of r-hGH administration on protein turnover at rest and during and after exercise. After the baseline study (visit 2), subjects were randomized to receive either r-hGH or an identical placebo at a dose of 0.067 mg/kg body weight daily. r-hGH was self-administered as a nocturnal sc injection. The placebo vials contained the same vehicle as the r-hGH. Subjects were then studied at 1 (visit 3) and 4 (visit 4) wk after randomization to GH administration or commencement of placebo.

Subjects

Eleven male volunteers were recruited and gave informed written consent to take part in the study, which was approved by the ethics committee of West Lambeth Health Authority.

Selection criteria included male gender; age between 18–40 yr; high level of habitual aerobic activity, defined as at least four 30-min sessions of continuous aerobic-type exercise per week; high aerobic fitness, defined as maximal oxygen uptake (VO_2max) above 45 ml/kg·min; no current participation in competition at a national or international level; and no illness or medications known to impair exercise or alter endocrine function. Subjects were asked not to change their dietary habits or

Abbreviations: BCOADH, Branched chain 2-oxo acid dehydrogenase complex; CV, coefficient of variation; DEXA, dual energy x-ray absorptiometry; fT_3, free T_3; fT_4, free T_4; GHD, GH-deficient; $HOMA_{IR}$, homeostasis model assessment of insulin resistance; α-KIC, α-ketoisocaproate; LBM, lean body mass; NOLD, nonoxidative leucine disposal; Ra, rate of appearance; r-GH, recombinant human GH; VO_2max, maximal oxygen uptake.

training programs during the study. On entry into the study and after 4 wk of treatment with GH or placebo, subjects underwent a full medical history, physical examination, and routine laboratory studies (full blood count, urea and electrolytes, creatinine, total protein, albumin, total bilirubin, glucose, calcium, phosphorus, hepatic enzymes, lipid profile, and urinalysis).

Clinical protocol

All subjects underwent measurements of body composition by dual energy x-ray absorptiometry (DEXA) and whole body protein turnover using 1-[^{13}C]leucine tracer. Total body fat and LBM were measured DEXA, which was performed using a whole body scanner (QDR-2000, Hologic Inc., Bedford, MA). DEXA can be used to estimate fat in specific anatomical regions, and in this study an abdominal region (trunk) was defined to assess abdominal fat mass [coefficient of variation (CV), <2% for all measurements].

On each study day, subjects were fasted overnight. The study was performed between 0900–1600 h. A cannula (Venflon, Helsingborg, Sweden) was inserted into the antecubital fossa of one arm for isotope infusion and the contralateral dorsal hand vein, which was heated, for arterialized blood sampling (11). Subjects were rested in bed in a semi-recumbent position, and blood and breath samples were taken to measure basal enrichment of plasma α-ketoisocaproate (α-KIC) and expired CO_2. A bolus dose of $NaH^{13}CO_3$ (0.2 mg/kg) was given iv to prime the bicarbonate pool, and a primed constant infusion (1 mg/kg; 1 mg/kg·h) of 1-[^{13}C]leucine was then infused for 300 min. The rate of infusion was doubled at the beginning of exercise to minimize the exercise-induced reductions in KIC and CO_2 enrichment (12). After a 160-min equilibration period to reach steady state tracer enrichment, the basal steady state was sampled (−20 to 0 min). Blood samples were taken at the end of 30 min of exercise and 30, 60, and 90 min after completion of exercise.

Exercise testing

Exercise testing was performed using an electromagnetically braked cycle ergometer (Lode Excalibur Sport, Groningen, Holland) and a CPX-D Cardiopulmonary Exercise Testing System (Medical Graphics, Birmingham, UK). Expired gas was sampled continuously at the mouth. The concentration of dried gas was measured with analyzers accurate to ±1% [zirconia oxide O_2 analyzer (response time, <80 msec) and infrared CO_2 analyzer (response time, <130 msec)]. Gas volume was measured with a bidirectional differential pressure prevent pneumotach (accuracy, ±3%).

Screening exercise test

For screening purposes, VO_2max was assessed. Subjects cycled to exhaustion with a starting workload of 1.5 watts/kg body weight using a smooth ramp of 25 watts/min at a cycling cadence of 80 rpm with feet strapped to the pedals. Workload at VO_2max was used to calculate the submaximal protocol for the main studies. The workload at which the oxygen uptake first reached a plateau was regarded as the workload at VO_2max.

Submaximal exercise protocol

All subsequent submaximal exercise tests used an identical protocol, consisting of three consecutive stages: stage 1 was 5 min at 1 watts/kg, stage 2 was 5 min at 2 watts/kg, and stage 3 was 20 min at 65% of VO_2max.

Analytic methods

Plasma IGF-I was measured by RIA after an ethanol-hydrochloric acid extraction (within-assay CV, 7%) (13). Serum free T_4 (fT_4) and free T_3 (fT_3) were measured by RIA (CV, <2%). Insulin was measured by double-antibody RIA (within-assay CV, 6%). Insulin resistance was estimated in each subject using the homeostasis model assessment of insulin resistance ($HOMA_{IR}$) with the following validated formula: fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/liter)/22.5. Plasma cholesterol and triglycerides were measured by an enzymatic method with a colorimetric end point with a Cobas Fara II centrifugal analyzer (Roche, Welwyn Garden City, UK; within-assay CV, <5%). High density lipoprotein cholesterol was measured enzymatically (Roche, Indianapolis, IN) after precipitating the apolipoprotein B-containing particles with dextran sulfate/magnesium chloride (within-assay CV, <5%). Low density lipoprotein cholesterol was calculated using the Friedewald formula.

Plasma α-KIC enrichment was measured as the quinoxalinol (*tert*-butyldimethylsilyl) derivative by selected ion monitoring of fragments at m/z 259 and 260 using gas chromatography-mass spectrometry (5971A MSD, Hewlett-Packard, Bracknell, UK). The analytical precision of the method (CV) has been shown to be less than 8% for isotopic enrichment of α-KIC (6). The plasma α-KIC concentration was calculated using an internal standard of d5 α KIC.

^{13}C enrichment of breath CO_2 was measured on an SIRA series II isotope ratio mass spectrometer (VG Isotech, Cheshire, UK).

Calculation of whole body protein turnover

The assumptions and validity of the whole body leucine turnover technique during exercise have previously been discussed in detail (12). The rate of leucine appearance (Ra) was calculated with the use of the one-compartment model originally proposed by Steele (14), which has been validated for the measurement of leucine metabolism and modified for stable isotopes (15). In this model, α-KIC was used as a measure of intracellular leucine enrichment (16). The calculations have been previously described in detail (17). Leucine oxidation during exercise was calculated as previously described by Wolfe *et al.* (12) and was corrected, assuming 80% of $^{13}CO_2$ at rest and 97% during exercise was expired (18). It has previously been demonstrated that GH administration does not alter the bicarbonate retention factor (19).

Statistical analyses

Results are expressed as the mean ± SE. Statistical analysis was performed using ANOVA, with repeated measures where appropriate. $P < 0.05$ was taken as significant.

Results

We studied 11 males; 6 subjects were randomized to the r-hGH-treated group, and 5 to the placebo-treated group. Mean age, body composition, and VO_2max did not differ between the 2 groups (Table 1). Baseline IGF-I was within the normal laboratory reference range for both groups (Table 2). Compliance, assessed by counting used vials, was 100%. Physical examination and routine laboratory measures remained unchanged in subjects who received r-hGH and those who received placebo. There were few side-effects reported by those who had received r-hGH treatment; 1 individual noted ankle swelling and transient arthralgia, which resolved within 48 h of commencing treatment, and another reported general fatigue and reduced concentration.

There was no change in IGF-I levels in the placebo-treated group throughout the observation period. In contrast, in the r-hGH-treated group, IGF-I levels rose markedly, reaching levels outside the physiological range ($P < 0.001$; Table 2). These changes occurred within 7 d of commencing r-hGH administration and did not change further over the remaining 21-d period of r-hGH administration (Table 2).

TABLE 1. Baseline characteristics of the study subjects

Group	r-hGH-treated (n = 6)	Placebo-treated (n = 5)
Age (yr)	31 (23–40)	33 (27–42)
Height (cm)	175 (174–183)	177 (171–180)
Weight (kg)	76 (68–81)	75 (66–82)
VO_2max (ml/min·kg)	54.2 (50.1–60.0)	53.4 (49.4–60.0)

Values are means (range).

TABLE 2. Endocrine and metabolic profile and body composition at baseline, 1 wk, and 4 wk in athletes who were randomized to treatment with r-hGH or placebo

	r-hGH-treated			Placebo-treated		
	Baseline	1 wk	4 wk	Baseline	1 wk	4 wk
IGF-I (nmol/liter)	24.6 ± 3.0	89.6 ± 12.2[a]	106.3 ± 16.4[a]	25.8 ± 2.7	25.4 ± 2.7	25.2 ± 2.6
fT_3 (pmol/liter)	5.1 ± 0.3	6.0 ± 0.1[b]	6.1 ± 0.2[b]	4.8 ± 0.2	4.9 ± 0.2	4.8 ± 0.1
fT_4 (pmol/liter)	15.5 ± 1.5	11.5 ± 1.0[b]	10.6 ± 0.9[b]	15.8 ± 1.6	15.6 ± 1.7	15.8 ± 1.5
Testosterone (nmol/liter)	18.3 ± 3.2	18.5 ± 3.4	18.5 ± 3.3	16.7 ± 2.6	16.3 ± 2.6	16.4 ± 2.2
Glucose (mmol/liter)	4.7 ± 0.3	5.5 ± 0.5	5.3 ± 0.2	4.5 ± 0.4	4.2 ± 0.2	4.4 ± 0.3
Insulin (mU/liter)	7.9 ± 1.6	22.6 ± 3.9[b]	16.0 ± 9.3[b]	6.0 ± 0.3	5.6 ± 1.9	9.3 ± 2.4
HOMA IR	1.4 ± 0.2	5.1 ± 1.0[b]	3.3 ± 0.6[b]	1.1 ± 0.4	1.0 ± 0.3	1.6 ± 0.5
Total cholesterol (mmol/liter)	4.3 ± 0.3	4.0 ± 0.5	4.1 ± 0.3	3.4 ± 0.3	3.3 ± 0.3	3.5 ± 0.6
Triglyceride	1.1 ± 0.2	2.0 ± 0.5	1.3 ± 0.1	0.6 ± 0.1	0.7 ± 0.1	0.5 ± 0.1
LDL cholesterol (mmol/liter)	2.6 ± 0.3	2.2 ± 0.3	2.3 ± 0.3	1.6 ± 0.4	1.6 ± 0.3	1.6 ± 0.5
HDL cholesterol (mmol/liter)	1.2 ± 0.1	1.0 ± 0.1	1.1 ± 0.1	1.5 ± 0.1	1.5 ± 0.1	1.7 ± 0.2
Body weight (kg)	74.4 ± 1.1	76.5 ± 1.7[b]	77.9 ± 1.6[b]	74.9 ± 3.4	74.9 ± 3.4	74.7 ± 3.3
Lean body mass (kg)	57.6 ± 1.1		61.0 ± 1.2[b]	61.6 ± 2.5		61.8 ± 2.4
Total body fat (kg)	11.4 ± 1.4		11.6 ± 1.7	9.8 ± 1.9		10.1 ± 2.0
Trunk fat (kg)	4.7 ± 0.7		4.5 ± 0.9	2.8 ± 0.9		2.8 ± 0.9

Values are the means ± SEM. LDL, Low density lipoprotein; HDL, high density lipoprotein.
[a] $P < 0.001$ *vs.* baseline.
[b] $P < 0.05$ *vs.* baseline.

TABLE 3. Steady state atom percent excess (APE) of plasma KIC and breath CO_2 at baseline, 1 wk, and 4 wk in athletes who were randomized to treatment with r-hGH or placebo

	Baseline	1 wk	4 wk
r-hGH-treated			
KIC APE (%)	5.523 ± 0.292	4.715 ± 0.184[a]	4.342 ± 0.163[a]
CO_2 APE (%)	0.01106 ± 0.00065	0.00636 ± 0.00033[a]	0.00533 ± 0.00069[a]
Placebo-treated			
KIC APE (%)	4.840 ± 0.502	4.748 ± 0.257	4.558 ± 0.190
CO_2 APE (%)	0.01040 ± 0.00064	0.00942 ± 0.00140	0.01018 ± 0.00044

Values are the mean ± SEM.
[a] $P < 0.01$ *vs.* baseline.

Serum fT_3, fT_4, and TSH all remained unchanged in the placebo-treated subjects throughout the study period. During r-hGH administration, there was an increase in mean fT_3, and a decrease in mean fT_4 ($P < 0.05$; Table 2). fT_3 levels for all subjects reached supraphysiological levels compared with laboratory reference ranges. These changes were detectable by d 7 of treatment with r-hGH and did not change further over the remaining 21-d period of r-hGH administration (Table 2).

There was no change at any time point in fasting plasma glucose or insulin or in $HOMA_{IR}$ in the placebo-treated subjects. Fasting plasma glucose did not change significantly in the r-hGH-treated group, but there were increases in fasting insulin and $HOMA_{IR}$ after 1 and 4 wk of GH administration ($P < 0.05$; Table 2). There was no change in plasma lipid profile in either group.

Body weight, LBM, total body fat, and trunk fat remained stable in the placebo group for the duration of the study. Total body fat and trunk fat did not change significantly in the r-hGH-treated group. In contrast, body weight and LBM increased in the r-hGH-treated group ($P < 0.05$; Table 2).

Leucine turnover at rest

Steady state enrichment values are shown in Table 3. After 1 wk of GH treatment, leucine Ra and nonoxidative leucine disposal (NOLD) increased, whereas leucine oxidation decreased ($P < 0.01$; Fig. 1). After 4 wk of GH treatment, there

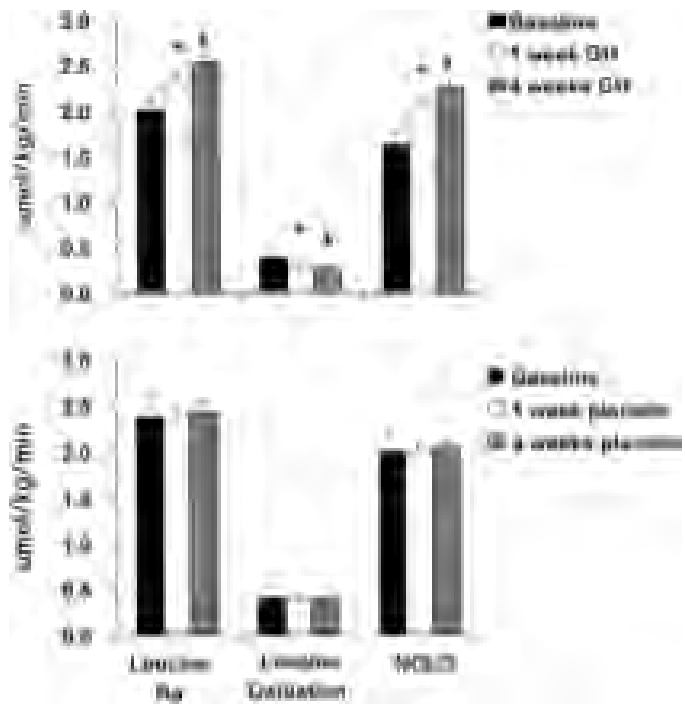

FIG. 1. Steady state indexes, under resting conditions, of leucine Ra, leucine oxidation, and NOLD at baseline and after 1 and 4 wk of r-hGH (*upper panel*) or placebo (*lower panel*). *, $P < 0.01$ *vs.* baseline; §, $P < 0.05$ *vs.* 1 wk.

was a further significant increase in leucine Ra and NOLD and a further significant reduction in leucine oxidation ($P < 0.05$; Fig. 1). None of these variables changed at any time-point in the placebo-treated group.

Leucine turnover during exercise

In the baseline studies, leucine oxidation increased during exercise ($P < 0.01$) and decreased during recovery (Fig. 2). Leucine Ra and NOLD increased during exercise and remained elevated during recovery ($P < 0.01$; Fig. 2).

After 1 and 4 wk of r-hGH administration, leucine oxidation increased during exercise by 50% compared with 160% in the baseline studies ($P < 0.05$; Fig. 2). After 1 and 4 wk of r-hGH administration, leucine Ra and NOLD showed a similar pattern to that in the pretreatment study, increasing with exercise and decreasing during recovery (Fig. 2). Absolute values, however, were higher at all time points compared with the baseline studies ($P < 0.05$; Fig. 2). No changes occurred after 1 or 4 wk of placebo compared with the baseline studies (Fig. 2).

Discussion

This double-blind, placebo-controlled study demonstrates that administration of supraphysiological doses of r-hGH to endurance-trained athletes exerts a protein anabolic effect both at rest and during submaximal exercise. At rest, after 1

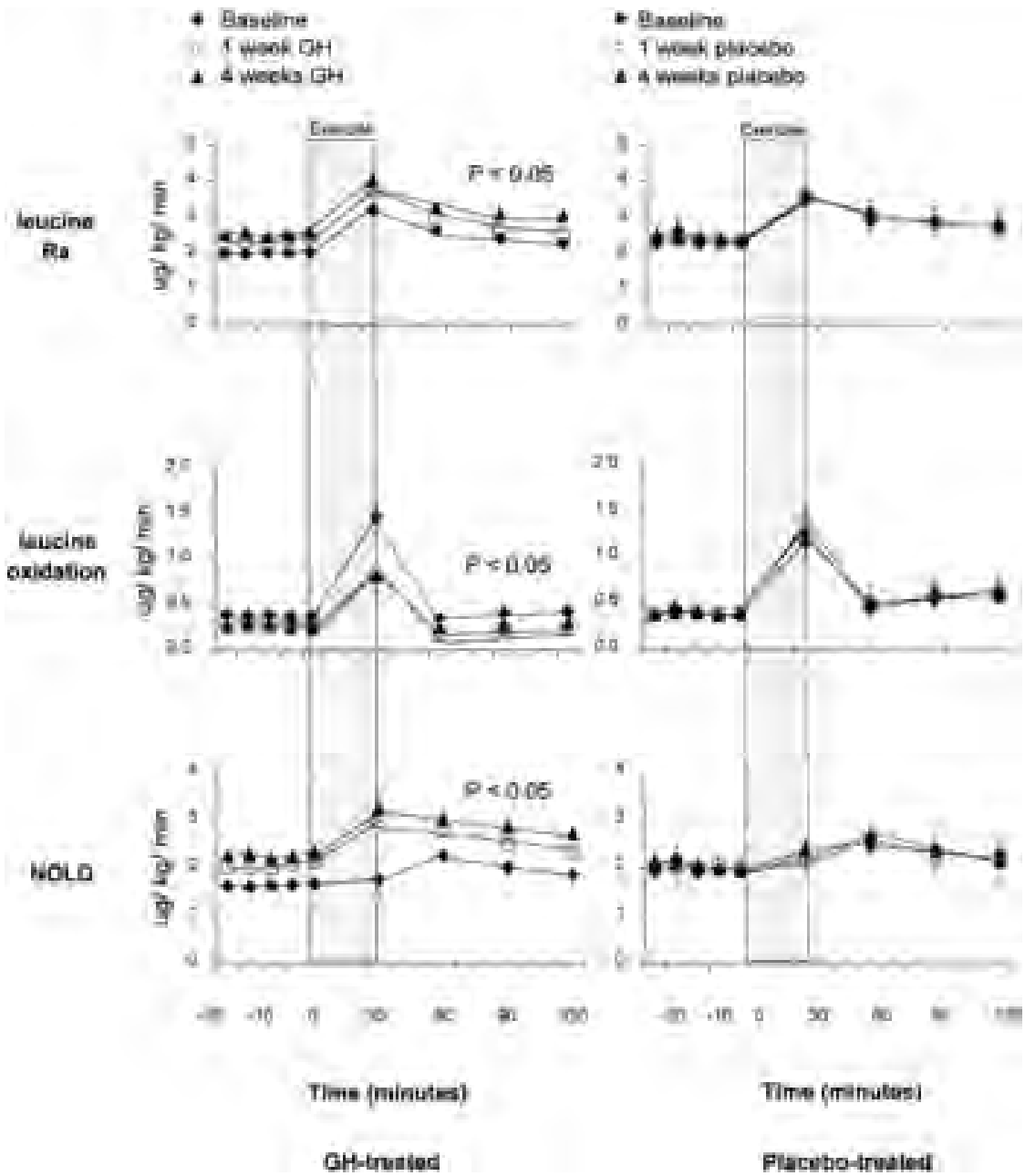

FIG. 2. Leucine Ra, leucine oxidation, and NOLD at steady state and during exercise, at baseline and after 1 and 4 wk of r-hGH or placebo. *P* values refer to differences from the baseline studies.

wk of r-hGH administration, there was a net reduction in leucine oxidation and a net increase in nonoxidative leucine disposal, changes that were accentuated after 4 wk of r-hGH administration. During exercise, after 1 and 4 wk of r-hGH administration, the expected increase in leucine oxidation observed in the baseline studies was greatly attenuated.

Under steady state conditions, the Ra of leucine in the circulation, which provides an index of protein breakdown, is balanced by the sum of the rates of leucine oxidation and NOLD, which provides an index of protein synthesis. In this study we observed an increase in protein breakdown, but also a shift in partitioning between leucine oxidation and protein synthesis in favor of protein synthesis. The overall effect, therefore, was an increase in protein turnover, but an absolute reduction in oxidative leucine loss, highly suggestive of an overall anabolic effect. These metabolic effects were accompanied by a mean increase of 3.4 kg LBM, estimated by DEXA scanning. It is probable that some of this increase reflects changes in total body water secondary to the antinatriuretic effect of GH (20), but in the context of increased protein synthesis and reduced oxidative protein loss, it is likely that it also reflects whole body protein accretion.

There have been conflicting reports of the effects of GH administration on leucine kinetics. Observations vary between studies of athletic and nonathletic subjects, and between those of whole body protein turnover and muscle protein synthesis. Horber and Haymond (19) demonstrated no change in whole body protein breakdown, but an increase in protein synthesis, after the administration of 0.1 mg/kg·d r-hGH to untrained males for 1 wk. Using a lower dose (0.04 mg/kg·d), Yaresheski *et al.* (7) observed an increase in whole body, but not muscle, protein synthesis in untrained men after 12-wk administration of r-hGH. However, the same group observed no change in whole body protein synthesis after 14-d administration of the same dose to experienced weight lifters (8). In contrast, Fryburg *et al.* (21) demonstrated that infusion of GH for 8 h to untrained males resulted in increased muscle, but not whole body, protein synthesis. The observation that whole body protein synthesis did not change in the studies by Fryburg *et al.* (21) may reflect a difference between acute and more long-term effects of GH. Notably, the effects of GH on carbohydrate metabolism are known to differ markedly depending on the duration of exposure to GH (22). The observations by Yarasheski *et al.* (7) that GH increased whole body protein synthesis in normal subjects, but not in weightlifters, might represent a differential response in resistance-trained subjects. Muscle that is already hypertrophied may have less potential to further increase. It is unlikely that the differences between those studies reflect a different period of administration, as measurable effects were clearly demonstrated after 1 wk in both our study and that by Horber and Haymond (19).

As previously observed (9, 23–25), leucine oxidation increased more than 2-fold during exercise. The rate-limiting step for the oxidation of branched chain amino acids, including leucine, is decarboxylation (26), which is catalyzed by the mitochondrial branched chain 2-oxo acid dehydrogenase complex (BCOADH). More than 50% of the body's BCOADH is located within skeletal muscle (27), where its percent activation increases with exercise (24, 28). Thus, it is likely that the observed increase in leucine oxidation during exercise largely reflects changes in skeletal muscle. Administration of r-hGH reduced leucine oxidation by more than 50%, which is suggestive that at least during exercise, the metabolic effects of GH include an anabolic effect in skeletal muscle. This is compatible with *in vitro* studies of GH action and with the observation that replacement with r-hGH increases thigh muscle mass in GHD adults (29).

Although this study provides evidence that GH increases body protein, it is clear from the pathophysiological model of acromegaly that sustained high levels of GH do not lead to any improvement in strength or endurance. In contrast, acromegaly is characterized by abnormal protein remodeling not only in skeletal muscle, but in most organ systems, resulting in tissue disorganization and functional impairment. Despite an increase in muscle mass, physical strength is reduced rather than increased, and histological examination of muscle fibers reveals a myopathic process (30). Whether the increase in protein breakdown, observed in the current study, plays any role in these effects is unknown, but warrants investigation.

Although both GH (31) and IGF-I (32, 33) exert direct anabolic effects, it is possible that some of the observed effects may result from the influence of GH and IGF-I on other endocrine pathways. Fasting insulin and insulin resistance estimated using the HOMA model increased after GH administration. Insulin exerts a powerful antiproteolytic effect (34), and it is possible that resistance to this effect may have contributed to the observed increase in proteolysis. Increased proteolysis may also have resulted from increased fT_3 (35), consistent with the effect of GH to enhance the extrathyroidal conversion of T_4 to T_3 (36). Finally, increases in alternative energy substrates, such as fatty acids, ketone bodies, and pyruvate, inhibit flux through the BCOADH complex and therefore might contribute to reduced leucine oxidation (37, 38).

In summary, these findings demonstrate that short-term administration of supraphysiological GH exerts an anabolic effect at rest and during exercise, supporting the theoretical possibility that acute GH excess may have short-term benefits for physical performance. The effect of GH to conserve protein during exercise has potential therapeutic implications that merit exploration.

Acknowledgments

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Address all correspondence and requests for reprints to: Dr. James Gibney, Department of Endocrinology, St. Vincent's Hospital, Elm Park, Dublin 4, Ireland. E-mail: j.gibney@st-vincents.ie.

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