Growth Hormone Receptor Antagonist Treatment Reduces Exercise Performance in Young Males

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Context: The effects of GH on exercise performance remain unclear.

Objective: The aim of the study was to examine the effects of GH receptor (GHR) antagonist treatment on exercise performance.

Design: Subjects were treated with the GHR antagonist pegvisomant or placebo for 16 d. After the treatment period, they exercised to determine exercise performance and hormonal and metabolic responses.

Participants: Twenty healthy males participated in the study.

Intervention: Subjects were treated with the GHR antagonist (n = 10; 10 mg/d) or placebo (n = 10). After the treatment period, they performed a maximal oxygen uptake ($\dot{V}O_{2max}$) test and a prolonged exercise test, consisting of 60 min of submaximal cycling followed by exercise to fatigue at 90% of $\dot{V}O_{2max}$.

Main Outcome Measures: $\dot{V}O_{2max}$ was measured before and after the treatment period. Hormonal and metabolic responses and time to exhaustion during prolonged exercise were determined.

Results: Resting serum IGF-I concentration decreased by 20% in the GHR antagonist-treated group ($P < 0.05$), whereas no change was observed in the placebo group. Conversely, resting serum GH concentration was significantly higher in the treatment group compared with the placebo group ($P < 0.01$). $\dot{V}O_{2max}$ did not change significantly in either group after the treatment period. Time to exhaustion at 90% of $\dot{V}O_{2max}$ was significantly shorter in the treatment group ($P < 0.05$). No significant differences were observed between the groups in terms of changes in serum free fatty acids, glycerol, $\dot{V}O_2$, or relative fat oxidation.

Conclusion: GH might be an important determinant of exercise capacity during prolonged exercise, but GHR antagonist did not alter fat metabolism during exercise. **(*J Clin Endocrinol Metab* 94: 3265–3272, 2009)**

GH treatment has become a popular doping technique (1). GH abuse in sports is believed to be widespread (2, 3) and is not confined to power sports or bodybuilders; endurance athletes (*e.g.* cycling, swimming) may also use GH to enhance performance in competition (4). At rest, GH infusion increases lipolysis (5) and fat oxidation (6). The administration of GH also increases the blood concentrations of glycerol and free fatty acids (FFAs) during exercise both in GH-deficient (GHD) patients (7, 8) and in healthy people (9, 10), including well-trained endurance athletes (9, 11).

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Abbreviations: CV, Coefficient of variation; FFA, free fatty acid; GHD, GH-deficient; GHR, GH receptor; HR, heart rate; HR_{max}, maximal HR; IGFBP-3, IGF binding protein-3; RER, respiratory exchange ratio; RPE, ratings of perceived exertion; TTE, time to exhaustion; $\dot{V}O_{2max}$, maximal oxygen uptake.

Exercise capacity is reduced in adults with GH deficiency, and GH replacement increases maximal oxygen uptake ($\dot{V}O_{2max}$) (12–15). Furthermore, prolonged GH treatment increases exercise duration, peak power output, and anaerobic threshold in patients with chronic heart failure (16). In contrast with these findings, the effect of GH on exercise performance in healthy people is less clear (17, 18). Berggren *et al.* (4) demonstrated that administration of supraphysiological doses of GH over a 4-wk period (a low or a high GH dose) does not improve maximal power output and oxygen uptake in active young people. Irving *et al.* (19) reported that acute administration of GH does not affect total work and ratings of perceived exertion (RPE) during 30-min submaximal exercise; however, GH reduces oxygen uptake during exercise. Theoretically, when administered before exercise, GH may increase relative fat oxidation during submaximal exercise by increasing FFA release. These effects may in turn increase time to exhaustion (TTE) in submaximal exercise by sparing glycogen in the muscle and liver.

Somewhat in contrast, data from our lab indicated that acute administration of GH 4 h before exercise reduced performance in well-trained young people (10). Surprisingly, in this study, two subjects were unable to complete the 90-min moderate- to high-intensity exercise in the GH treatment trial. The authors noted that a possible cause of this fatigue was a greater increase in plasma lactate during exercise in response to GH administration, although the mechanism for this effect is unknown.

Pegvisomant is a novel GH receptor (GHR) antagonist that competes with native GH for the GHR, thereby preventing the functional dimerization of GH and signal transduction (20). GHR antagonist reduces blood IGF-I concentration within approximately 2 wk in people with acromegaly (21), along with reductions in glucose and insulin concentrations (21–25). The suppression of GH action appears to alter substrate metabolism and subsequent exercise performance; however, the effect of GHR antagonist on exercise performance in healthy young people is currently unknown.

The effect of GH administration on lipolysis is well established (5, 6, 9, 10, 26–28). To investigate the influence of GH during exercise in more detail, this study examined the impact of blocking GH action on exercise performance in healthy men, focusing on changes in lactate concentrations and TTE after treatment with the GHR antagonist pegvisomant. We also determined hormonal responses and substrate metabolism to address whether GH is a determinant stimulus for enhancement of fat metabolism during exercise.

Subjects and Methods

Subjects

Twenty healthy sedentary men [(mean ± SE) age, 24 ± 1 yr; height, 183 ± 1 cm; body mass, 81 ± 1 kg; body mass index, 24.2 ± 1.0] participated in this study. Before inclusion, each subject underwent a medical evaluation, including medical history, physical examination, and routine blood tests. Exclusion criteria were metabolic, cardiac, and malignant diseases; anemia; hormonal replacement therapy; and medication with α- or β-blockers. All subjects gave their informed consent after receiving oral and written information. The study protocol was approved by the Ethical Committee of Copenhagen and Frederiksberg Communities, Denmark (KF01-258765), and conformed to the guidelines of the Declaration of Helsinki.

Study design and experimental protocol

The study was a randomized, placebo-controlled, double-blinded design. Subjects visited the laboratory five times (visits 1–5) through the experimental period (Fig. 1A). On the first visit (visit 1), $\dot{V}O_{2max}$ was measured using a cycle ergometer (818, Monark Exercise, Vansbro, Sweden), as described below. All subjects were subsequently randomized to either a GHR antagonist treatment group (n = 10) or placebo treatment group (n = 10). Subjects went through medical evaluation three times (visits 2, 3, and 5) after treatment had started.

The subjects received either the GHR antagonist pegvisomant (Somavert; Pfizer Inc., New York, NY; 10 mg/d as a single sc injection) or placebo for 16 d. The treatment was given by sc injections in the abdominal skin every second evening. The first injection was conducted with a doctor in attendance to ensure correct procedure; thereafter, the subjects were able to inject themselves every second evening for the remainder of the study. After the treatment period (visit 4), the $\dot{V}O_{2max}$ test was repeated. On visit 5, the subjects performed a prolonged exercise trial consisting of 30 min of cycling at a load eliciting 55% of

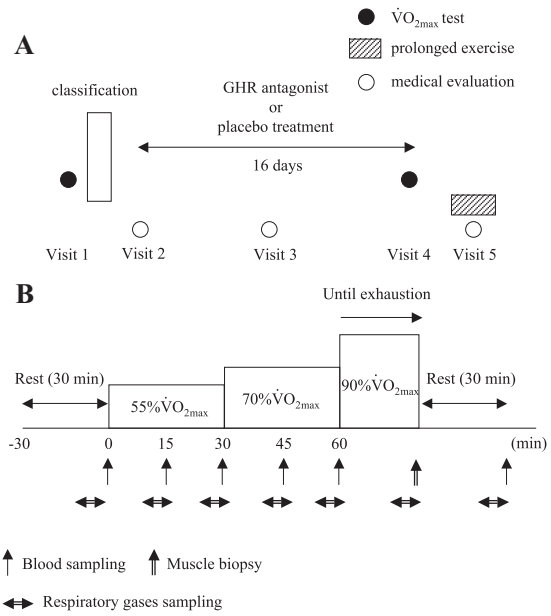

FIG. 1. Overall experimental design (A) and protocols for blood sampling, respiratory measurements, and muscle biopsy in a prolonged exercise trial (B).

$\dot{V}O_{2max}$, followed by 30 min of cycling at a load eliciting 70% of $\dot{V}O_{2max}$. After 60 min of submaximal exercise, they subsequently cycled at a load eliciting 90% of $\dot{V}O_{2max}$ until exhaustion. The TTE at 90% of $\dot{V}O_{2max}$ was measured as an indication of exercise performance. As soon as possible after exercise to exhaustion, muscle biopsies were taken from vastus lateralis. After exercise, they rested again in a supine position for 30 min to evaluate substrate metabolism during the recovery period (Fig. 1B).

$\dot{V}O_{2max}$ test and prolonged exercise trial

Before (visit 1) and after the treatment period (visit 4), the subjects performed an incremental exercise test on a cycle ergometer to assess $\dot{V}O_{2max}$. The test began at 70 W; the load was then increased progressively at 35 W every 2 min until exhaustion. The test was terminated when the subject failed to maintain the prescribed pedaling frequency of 70 rpm or reached a plateau in $\dot{V}O_2$. Respiratory gases (averaged for each 15-sec period) were collected continuously using an automatic gas analyzer (AMIS 2001, Innovision, Odense, Denmark). The mean of the three highest 15-sec values was recorded as $\dot{V}O_{2max}$. Appropriate calibrations of the O_2 and CO_2 sensors and the volume transducer were conducted before the start of exercise. Heart rate (HR) was monitored continuously by using a wireless HR monitor (Acculex Plus; Polar Electro Oy, Kempele, Finland).

After 16 d of treatment (visit 5), the subjects arrived at the laboratory after overnight fasting or postabsorptive condition and then performed 60-min submaximal exercise. Subsequently, the workload was set at 90% of $\dot{V}O_{2max}$, and subjects conducted exercise until exhaustion. Workload at each stage was determined using a linear regression of data obtained during the $\dot{V}O_{2max}$ test on visit 4. The pedaling frequency was set at 70 rpm. The subjects were instructed to exercise at a prescribed constant cadence with the aid of a metronome. To ensure that subjects did exercise to exhaustion, exercise was terminated when the pedaling frequency was less than 60 rpm for a consecutive period of 5 sec. The TTE was measured to evaluate performance during prolonged exercise. RPE were determined every 15 min using a Borg 15-point scale (29). Respiratory gases were measured repeatedly (using the same method as the $\dot{V}O_{2max}$ test) over the exercise session.

Blood sampling and analysis

Venous blood samples were obtained from an antecubital vein at rest, during 60 min of exercise, and 30 min after exercise (Fig. 1B). Serum samples for measurements were obtained by 10 min of centrifugation and were stored at −80 C until analysis. Serum GH concentration was measured using RIA with kits (SRL Inc., Tokyo, Japan). The interassay and intraassay coefficients of variation (CVs) were 3.7 and 4.7%, respectively. Serum IGF-I concentration was measured in acid-ethanol serum extracts using an in-house monoclonal antibody-based time-resolved immunofluorometric assay. Serum FFA and glycerol concentrations were analyzed using an enzymatic method. Concentrations of plasma epinephrine and norepinephrine were measured using HPLC with kits (Tosoh Corp., Tokyo, Japan). The intraassay CV was 5.9% for epinephrine and 6.7% for norepinephrine. Serum insulin concentration was determined using a chemiluminescent enzyme immunoassay (Fujirebio Inc., Tokyo, Japan). The inter- and intraassay CVs were 2.4 and 3.1%, respectively. Concentrations of blood lactate (YSI1500 Sport; Yellow Springs Instrument Co., Inc., Yellow Springs, OH) and glucose (ACCU-Check Inform; Roche, Basel, Switzerland) were determined using an automatic analyzer.

Muscle biopsies and analysis

Muscle biopsies were obtained from the vastus lateralis muscle, at the midthigh level, immediately after completion of the prolonged exercise. The overlying skin was anesthetized with 5 ml of 1% lidocain, and sampling was performed through an incision using a 5-mm Bergstrom needle with suction (30). Muscle samples were immediately frozen in isopentane cooled with liquid N_2 and stored at −80 C until analysis.

The frozen sample was weighed before and after freeze-drying to determine water content. After freeze-drying, the muscle samples were dissected free of blood, fat, and connective tissue. Dry weight tissue (~2.5 mg) was extracted with a solution of perchloric acid and $KHCO_3$. Muscle lactate content was subsequently analyzed by fluorometric assay (31, 32).

Statistical analysis

All data are expressed as means ± SE. The effects of time and treatment (GHR antagonist or placebo) on concentrations of serum hormones, and blood metabolites and physiological variables at rest and during exercise were analyzed using a two-way ANOVA. When ANOVA revealed significant interaction or main effect, a Tukey-Kramer test was performed for *post hoc* analyses to assess differences. For comparison of TTE and muscle lactate, a Mann-Whitney unpaired test was applied to compare differences between groups. Missing values (three subjects were not able to complete the exercise protocol) were estimated by extrapolation, as used in a previous study (10). Pearson's correlation coefficients were computed to evaluate relationships between physiological variables (*e.g.* RPE, lactate concentrations) and TTE. For all tests, $P < 0.05$ was inferred to be significant.

Results

The physical characteristics (*e.g.* height, body mass, body mass index) were similar between the two groups. Three subjects in the treatment group did not complete the experimental protocol. Two subjects experienced side effects after the initial injections of GHR antagonist, including headache and nausea, and one subject could not complete the experimental protocol because of personal reasons. In the placebo group, one subject was asked to withdraw from the study because of low hemoglobin concentrations. Data from these four subjects were excluded from all analyses. None of the remaining participants reported discomfort or any side effects after treatment, and no objective side effects where observed during medical examination. Based on inspection of injection marks and empty vial as well as serum GH/IGF-I measurements, treatment compliance was 100%.

TABLE 1. Baseline levels of serum GH, IGF-I, and IGFBP-3 before and after treatment period

	Treatment	Placebo	Interaction
GH (μg/liter)			
Before	0.8 ± 0.29	1.0 ± 0.53	$P < 0.01$
After	18.5 ± 1.43[a,c]	0.1 ± 0.04	
IGF-I (μg/liter)			
Before	270 ± 26	267 ± 17	$P < 0.05$
After	213 ± 37[b]	268 ± 30	
IGFBP-3 (μg/liter)			
Before	4164 ± 207	4370 ± 147	$P < 0.05$
After	3585 ± 256[a]	4212 ± 198	

Values are means ± SE (n = 9 for each group).

[a] $P < 0.01$.

[b] $P < 0.05$ *vs.* Before.

[c] $P < 0.01$ *vs.* Placebo.

Resting concentrations of serum GH, IGF-I, and IGF binding protein-3 (IGFBP-3)

Before the treatment period, resting serum concentrations of GH, IGF-I, and IGFBP-3 were similar between the groups (Table 1). After treatment, serum GH concentration increased markedly in the treatment group ($P < 0.001$), whereas it did not change significantly in the placebo group (time × treatment interaction, $P < 0.001$). Serum IGF-I concentration decreased significantly in the treatment group after the treatment period ($P < 0.05$), whereas it did not change significantly in the placebo group (time × treatment interaction, $P < 0.05$). Serum IGFBP-3 decreased significantly in the treatment group only ($P < 0.01$). A significant time × treatment interaction was observed ($P < 0.05$).

$\dot{V}O_{2max}$ test

Before the treatment period, respiratory data, maximal HR (HR_{max}), and maximal workload were similar between the groups (Table 2). $\dot{V}O_{2max}$ did not change significantly in either group after the treatment period. In addition, no significant changes were observed in other respiratory parameters in either group after the treatment period.

Blood lactate and glucose

No significant differences were observed in pre-exercise concentrations of blood lactate and glucose between the groups. Blood lactate concentrations increased significantly ($P < 0.01$) during exercise in both groups. However, no interaction between treatment and time for lactate was observed ($P = 0.18$). In addition, no interaction was observed for blood glucose ($P = 0.80$).

Circulating IGF-I, IGFBP-3, and hormones

In both groups, exercise increased IGF-I and IGFBP-3 significantly ($P < 0.01$), without significant interaction between time and treatment. However, concentrations of IGF-I and IGFBP-3 were consistently higher in the placebo group than in the treatment group over the exercise session (group, $P = 0.08$ for IGF-I; $P < 0.05$ for IGFBP-3).

Before exercise, with the exception of serum GH concentration, no significant differences were observed in serum insulin concentration or the plasma concentrations of epinephrine and norepinephrine (Fig. 2). Serum GH concentration increased significantly during exercise ($P < 0.01$), but the values were significantly higher in the treatment group over the exercise session (time × treatment interaction, $P < 0.01$). Plasma epinephrine concentrations also increased significantly during exercise in both groups ($P < 0.01$), but values were significantly higher in the treatment group during the first 30 min of exercise ($P < 0.05$). No significant differences in norepinephrine response were observed between the groups (treatment by

TABLE 2. Respiratory data, HR, and workload during $\dot{V}O_{2max}$ test before and after treatment periods

	Treatment	*P* value	Placebo	*P* value
$\dot{V}O_{2max}$ (ml/min)				
Before	3419 ± 179	NS	3462 ± 151	NS
After	3447 ± 172		3334 ± 117	
$\dot{V}E_{max}$ (liters/min)				
Before	132 ± 8	NS	134 ± 8	NS
After	138 ± 8		128 ± 6	
$\dot{V}CO_{2max}$ (ml/min)				
Before	3974 ± 169	NS	3972 ± 81	NS
After	4013 ± 174		3746 ± 130	
HR_{max} (beats/min)				
Before	192 ± 3	NS	189 ± 3	NS
After	191 ± 3		192 ± 3	
Maximal workload (W)				
Before	280 ± 13	NS	296 ± 10	NS
After	291 ± 14		292 ± 10	

Values are means ± SE. *P* values indicate comparison between periods before and after treatment. NS, No significant difference; $\dot{V}E_{max}$, maximal minute ventilation; $\dot{V}CO_{2max}$, maximal carbon dioxide production.

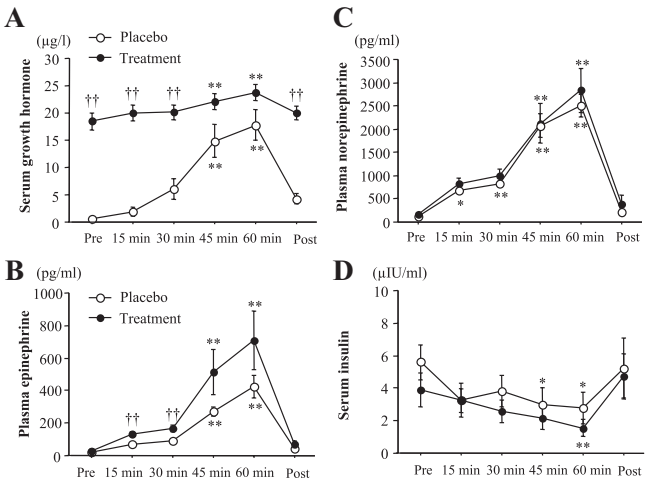

FIG. 2. Serum GH (A), plasma epinephrine (B), norepinephrine (C), and serum insulin (D) concentrations. **, $P < 0.01$ *vs.* pretreatment (Pre); *, $P < 0.05$ *vs.* Pre; ††, $P < 0.01$ between groups.

time interaction, $P > 0.05$; treatment, $P > 0.05$). Serum insulin concentrations decreased significantly during exercise in both groups ($P < 0.05$), with no difference between the groups (time × treatment interaction, $P > 0.05$; treatment, $P > 0.05$).

FFA and glycerol

Serum FFA and glycerol concentrations increased significantly during exercise ($P < 0.01$), but no significant treatment × time interaction was observed (Fig. 3).

RPE

The RPE values were significantly higher in the treatment group compared with the placebo group over the exercise ($P < 0.01$). Average values of RPE during the exercise were significantly higher in the treatment group

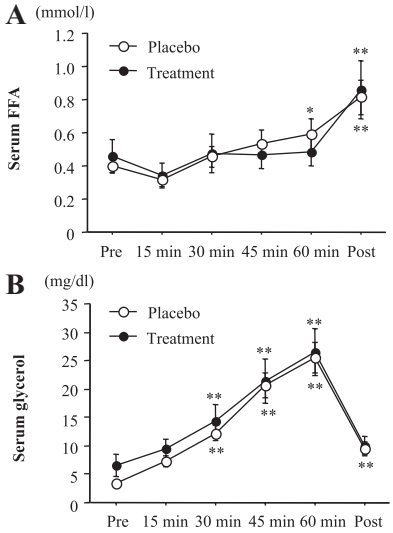

FIG. 3. Serum FFA (A) and glycerol (B) concentrations. Values are means ± SE. **, $P < 0.01$ *vs.* pretreatment (Pre); *, $P < 0.05$ *vs.* Pre.

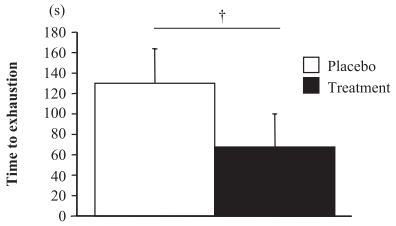

FIG. 4. TTE at 90% of $\dot{V}O_{2max}$ in a prolonged exercise trial. Values are means ± SE.†, $P < 0.05$ between groups.

(16.2 ± 0.3) compared with the placebo group (14.5 ± 0.4; $P < 0.01$).

Respiratory measurements

Before exercise, $\dot{V}O_2$ and calculated respiratory exchange ratio (RER; $\dot{V}CO_2/\dot{V}O_2$) did not differ between the groups. During and after exercise, no significant differences in $\dot{V}O_2$ and RER were observed between the groups (time × treatment interaction, $P > 0.05$).

TTE at 90% of $\dot{V}O_{2max}$

Figure 4 shows TTE after prolonged exercise. All subjects in the placebo group completed 60 min of submaximal exercise. In contrast, three subjects in the treatment group were exhausted before the end of 60 min of exercise. In addition, one subject in the treatment group reported maximal exhaustion at the end of the 60-min exercise. The average value of TTE was significantly shorter in the treatment group than in the placebo group ($P < 0.05$).

Muscle lactate

No significant differences were observed in muscle lactate content between the treatment (30 ± 5 mmol/kg dry weight) and placebo groups (23 ± 4 mmol/kg dry weight; $P = 0.29$).

Discussion

The present data demonstrated that 16 d of GHR antagonist treatment did not affect $\dot{V}O_{2max}$ and maximal power output, whereas it reduced TTE during prolonged exercise. The treatment did not influence responses of blood lactate, lipolysis, and fat oxidation during exercise, but subjects in the treatment group reported greater subjective fatigue associated with exercise. These findings indicate that GHR antagonist attenuated prolonged exercise performance, suggesting a potential role of GH in exercise capacity. From a clinical viewpoint, it is an important finding that three subjects in the treatment group were unable to complete 60 min of submaximal exercise.

Serum GH concentrations were markedly elevated at rest and during exercise in the treatment group compared

with the placebo group ($P < 0.01$; Table 1 and Fig. 2). These results are consistent with previous studies using GHR antagonist in patients with acromegaly (21, 23–25). In addition, the serum concentrations of IGF-I and IGFBP-3 were significantly lower at rest in the treatment group after the treatment period, whereas they did not change in the placebo group. Previous studies have shown that lower serum IGF-I concentration after pegvisomant treatment is accompanied by a dose-dependent increase in serum GH concentration (21, 33). In the present study, the magnitude of the decrease in serum IGF-I concentration (approximately 21%) was smaller than that reported previously using daily administrations (10–40 mg) in patients with acromegaly. This difference is due to the lower dose (10 mg) and frequency of injection (every second day) used in the present study in healthy individuals. Nevertheless, the present data show that the GHR antagonist altered the serum concentrations of IGF-I and GH, as expected, and that this effect had a significant influence on exercise performance despite a substantial amount of IGF-I still being present.

$\dot{V}O_{2max}$ did not change significantly in either group after the treatment period (Table 2). Furthermore, no significant changes were observed in maximal minute ventilation ($\dot{V}E_{max}$), maximal carbon dioxide production ($\dot{V}CO_{2max}$), HR_{max}, or maximal workload during the $\dot{V}O_{2max}$ test, which lasted around 14 min. GH administration increases aerobic capacity in patients with GH deficiency (12–15, 34, 35). Only one study in healthy adults has reported that acute GH administration reduces oxygen uptake during submaximal exercise, indicating an improvement in exercise economy (19). On the other hand, most studies do not demonstrate any beneficial effect of exogenous GH on maximal power output and oxygen uptake in healthy people (4). Based on these findings, GH does not appear to influence aerobic capacity during relatively short-duration exercise (*e.g.* $\dot{V}O_{2max}$ test) in healthy adults.

The main purpose of the present study was to determine the effects of GHR antagonist on exercise capacity during prolonged exercise. To evaluate prolonged exercise performance, TTE was measured at 90% of $\dot{V}O_{2max}$ after 60 min of low- to moderate-intensity exercises. This exercise test was chosen to imitate conditions encountered in sports training, as well as competitive cycling. TTE was significantly shorter in the treatment group compared with the placebo group (Fig. 4), indicating that suppression of GH action reduced exercise capacity. Furthermore, three subjects in the treatment group could not complete 60 min of submaximal exercise, and another subject was exhausted at the end of 60 min of exercise. These results are consistent with our previous study using GH administration in young men (three subjects were unable to finish the prescribed exercise after GH administration), although the two studies manipulated the physiological GH actions in an opposite manner. Lange *et al.* (10) noted that enhanced lactate production might explain reduced exercise capacity. In contrast, the present study revealed no significant difference between the treatment and placebo groups with regard to blood lactate concentration during exercise and the muscle lactate content after the exhaustion. The present data indicate that GHR antagonist reduced exercise capacity via mechanisms independent of lactate production.

RPE during exercise was significantly higher in the treatment group compared with the placebo group. Furthermore, RPE at the end of exercise was inversely correlated with subsequent TTE. Factors related to central and peripheral fatigue influence RPE during exercise. $\dot{V}O_2$ and blood glucose responses during exercise did not differ significantly between the two groups. Therefore, these metabolic factors cannot account for the higher RPE values reported by subjects in the treatment group. The higher RPE in the treatment group might suggest exaggerated central activation during exercise, leading to reduced performance. Hansen *et al.* (9) suggested that elevated GH concentration might stimulate the sympathetic nervous system. The present results partly support this idea because plasma epinephrine concentration during the exercise was significantly higher in the treatment group (Fig. 2). Kanaley *et al.* (7) demonstrated that epinephrine was higher during exercise in GHD patients without GH administration compared with the trial in which the same subjects were treated with GH. It appears that GH deficiency (in GHD patients or by administration of GHR antagonist) augments epinephrine response during exercise, possibly as a compensatory effect, which then leads to higher subjective fatigue.

The second focus of the present study was to address the influences of treatment with GHR antagonist on exercise-induced lipolysis and fat oxidation. GH has lipolytic effects at rest (5, 6, 8, 11). Data from our lab demonstrated that administration of GH before an exercise bout markedly increased the plasma concentrations of FFA and glycerol during subsequent exercise (9, 10). Furthermore, recent studies suggest that the exercise-induced increase in GH may stimulate lipolysis in the postexercise recovery period (36, 37). However, the present results do not support these earlier findings because the serum concentrations of FFA and glycerol during and after exercise were similar between the two groups. In addition to lipolysis, fat oxidation (expressed by RER) was similar between the groups during and after exercise. The present findings suggest that suppression of GH activity did not significantly

impact fat oxidation pattern during exercise, at least in healthy young men.

In summary, short-term treatment of GHR antagonist reduced TTE during prolonged exercise. These results suggest that GH might be an important determinant of exercise capacity during prolonged exercise. Greater subjective fatigue during the exercise could explain the decline in exercise performance after treatment with GHR antagonist. GHR antagonist treatment augmented exercise-induced epinephrine responses but did not influence lipolysis and substrate oxidation pattern. The present study was carried out in healthy individuals, but the findings of a reduced exercise capacity associated with administration of a GH antagonist may be important for patients who chronically receive such drugs as part of their therapy.

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