Responses of IGF-I to endogenous increases in growth hormone after heavy-resistance exercise

WILLIAM J. KRAEMER, BRIAN A. AGUILERA, MITSUYO TERADA, ROBERT U. NEWTON, JAMES M. LYNCH, GONNY ROSENDAAL, JEFFREY M. McBRIDE, SCOTT E. GORDON, AND KEIJO HÄKKINEN

Center for Sports Medicine, The Pennsylvania State University, University Park, Pennsylvania 16802

Kraemer, William J., Brian A. Aguilera, Mitsuyo Terada, Robert U. Newton, James M. Lynch, Gony Rosendaal, Jeffrey M. McBride, Scott E. Gordon, and Keijo Hakkinen. Responses of IGF-I to endogenous increases in growth hormone after heavy-resistance exercise. J. Appl. Physiol. 79(4): 1310–1315, 1995.—The purpose of this study was to examine the effects of a heavy-resistance exercise protocol known to dramatically elevate immunoreactive growth hormone (GH) on circulating insulin-like growth factor I (IGF-I) after the exercise stimulus. Seven men (23.1 ± 2.4 yr) volunteered to participate in this study. Each subject was asked to perform an eight-station heavy-resistance exercise protocol consisting of 3 sets of 10 repetition maximum resistances with 1-min rest between sets and exercises followed by a recovery day. In addition, a control day followed a nonexercise day to provide baseline data. Pre- and postexercise (0, 15, and 30 min) blood samples were obtained and analyzed for lactate, creatine kinase, GH, and IGF-I. Postexercise values for lactate and GH were significantly (P < 0.05) elevated for lactate, creatine kinase, GH, and IGF-I. Postexercise values for lactate and GH were significantly (P < 0.05) elevated above preexercise and resting baseline values. The highest mean GH concentration after the heavy-resistance exercise protocol was 23.8 ± 11.8 µg/l, observed at the immediate postexercise time point. Significant increases in creatine kinase were observed after the exercise stimulus and during the recovery day. No significant relationships were observed between lactate concentrations and IGF-I concentrations. No significant changes in serum IGF-I concentrations were observed with acute exercise or between the control days. Thus, these data demonstrate that a high-intensity bout of heavy-resistance exercise that increases circulating GH did not appear to affect IGF-I concentrations over a 24-h recovery period in recreationally strength-trained and healthy young men.

creatine kinase; strength; recovery; lactate

THE INSULIN-LIKE GROWTH FACTORS (IGFs) represent a group of growth factors (also called somatomedins) that are produced by many tissues in the body, but few organs are believed to concentrate IGFs. The liver is thought to be the primary source of circulating insulin-like growth factor I (IGF-I), with the serum demonstrating the highest concentrations (10). Yet increases in circulating IGF-I levels are not believed to occur purely with simple stimulation of release of IGF-I stores in the liver and other tissues. IGFs are complexed with high-affinity binding proteins, and six distinct binding proteins have been characterized (12). Four of these binding proteins are found in the serum. More than 90% are bound in the 150-kDa complex that involves IGF I or II, binding protein 3, and an acid-labile subunit (24). Binding proteins are differentially regulated and have different functions in various tissues and cells (12, 22). A primary endocrine stimulus for IGF-I production is growth hormone (GH), which mediates IGF-I synthesis, synthesis of the components of the 150-kDa complex of IGF-I, and binding protein 3 (5, 12, 24). Most of the actions of IGF-I are mediated by the IGF-I receptor (12).

In a study by Cappon et al. (3), it was shown that acute increases in serum concentrations of IGF-I can occur after brief high-intensity aerobic exercise. However, these acute changes are not related to increases in GH and no consistent rise in circulating IGF-I over 24 h were observed. This is consistent with our previous observations of acute increases in IGF-I concentrations after heavy-resistance exercise without any relationship to acute changes in GH over a shorter period of recovery of 1–2 h (18, 19). Nevertheless, the acute responses of IGF-I to heavy-resistance exercise remain unclear. In another study, no changes in serum IGF-I concentrations were observed 24 h after a moderate-intensity and low-volume heavy-resistance exercise protocol. However, the protocol of this study produced only moderate increases in serum immunoreactive GH concentrations (<10 µg/l) (15). We have determined in our studies (16, 18, 19) that not all heavy-resistance exercise protocols produce the same magnitude of serum GH elevations. This difference in the magnitude of GH production consequent to different heavy-resistance exercise protocols might not be important to IGF-I production in the acute recovery period of 1–2 h but may be more important in IGF-I changes over a longer period of recovery after the exercise protocol (e.g., 12–24 h). It is also possible that there are many unrelated acute and chronic effects of exercise on IGF-I not related to GH production (1, 3).

To examine this question of how higher exercise-induced GH concentrations affect serum IGF-I values, we chose to examine the acute 24-h recovery period to allow for an adequate amount of time for DNA-mediated IGF-I synthesis after theoretical GH stimulation from the workout. This time frame was supported by the observed increases in serum IGF-I concentrations in normal control subjects within 24 h after recombinant human GH administration (13, 20, 21). More data are needed to gain a clearer understanding of longer recovery periods after heavy-resistance exercise to determine whether the observations Cappon et al. (3) made in their study with brief intense aerobic exercise are consistent for heavy-resistance exercise as well. Therefore, the primary purpose of this study was to examine the responses of serum con-
centrations of IGF-I over a 24-h recovery period after a heavy-resistance exercise protocol known to dramatically increase endogenous immunoreactive GH concentrations (18, 19).

**METHODS**

*Subjects.* Seven healthy men volunteered and gave informed written consent to participate in this study. The characteristics of the subjects were as follows: age 23.1 ± 2.4 yr, height 170.1 ± 4.0 cm, body mass 74.4 ± 10.3 kg, and body fat 10.3 ± 2.5%. This study was approved by the Institutional Review Board for use of human subjects. Each subject completed a medical history questionnaire and was examined by a physician. All subjects had previous recreational experience with resistance training but were not competitive lifters. The subjects were screened on the basis that each had recreational experience with resistance training (2–3 times a week) over at least the past 1 yr. This was needed to allow them to tolerate the advanced "bodybuilding-type" workout used in this study. None of the subjects had a medical history of endocrine disorders, drug or alcohol abuse (including any anabolic drug use), or any form of exercise-induced health problems (e.g., asthma). The subjects were instructed to abstain from any medications for the duration of the study.

We attempted to control the daily activity and eating habits of the subjects for the 3 days before both the testing and control sessions similar to our previous work to reduce external influences on IGF-I production (19, 24). The subjects were asked to refrain from all strenuous activities, alcohol and tobacco use, caffeine and xanthine derivatives, and sexual activities for the duration of the study. The subjects were educated on nutrition guidelines that were to be followed during these days. They included eating a diet of ~50–60% carbohydrate, 15–20% protein, and 20–30% fat. They were also instructed to eat three meals per day of approximately the same amount while avoiding fatty foods and sweets. Healthy snacks were allowed as desired by the subjects. A registered dietitian and other laboratory staff monitored the dietary and activity patterns, respectively, of the study. Journal entries concerning any and all activity and food intake by the subjects were documented for each of 3 days before all laboratory sessions. Upon supervision and review of the diet and activity journals, it was noted that all requests for subject and activity profiles had been met.

Height and weight were obtained by using a calibrated physician's counterbalance scale. Limb length measurements and excursions for exercises used for the upper and lower limbs were obtained to allow for calculation of total work as previously described (19). Lange skinfold calipers were used for a three-site skinfold analysis (chest, abdomen, and thigh) to assess percent body fat (11).

**Experimental design.** A blocked randomized design was used for this study. Each subject participated in familiarization sessions, a resting control day, and an experimental workout day followed by 1 day of recovery. The exercise protocol used in the experimental trial was similar to ones previously used that demonstrated significant increases in post-exercise serum GH concentrations (18, 19).

The order of exercises was the same for familiarization sessions and the experimental exercise protocol. Resistances used in this study were determined by using a repetition maximum (RM) approach (18, 19). In other words, the resistance used by the subject in a particular exercise was heavy enough to allow only the targeted number of repetitions for a given set. Thus, a 10 RM was a resistance of which the subject could only perform 10 repetitions. Familiarization sessions involved an overview of exercise techniques, repeated 10 RM load verifications, and review of blood drawing procedures. During the familiarization phase of the study, subjects were also tested for their 1 RM for each exercise in the protocol (18). Only 1 min of rest was allowed between each set and each exercise. The experimental heavy-resistance exercise protocol consisted of three sets of eight different resistance exercises performed at a 10 RM (see Table 1). The exercises were completed in the order shown in Table 1. One-minute rest periods between sets and exercises 3–10. Exercises 2, 3, 5, 8, and 10, universal weight machine; exercise 1, TruSquat machine; exercises 7 and 9, free weights. RM, repetition maximum.

### Table 1. Order of exercises performed and number of sets and repetitions

<table>
<thead>
<tr>
<th>Exercise Order</th>
<th>Repetition Maximum and No. of Sets</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tru-squat</td>
<td>1 RM protocol</td>
</tr>
<tr>
<td>2. Shoulder press</td>
<td>1 RM protocol</td>
</tr>
<tr>
<td>3. Bench press</td>
<td>10 RM x 3 sets</td>
</tr>
<tr>
<td>4. Tru-squat</td>
<td>10 RM x 3 sets</td>
</tr>
<tr>
<td>5. Shoulder press</td>
<td>10 RM x 3 sets</td>
</tr>
<tr>
<td>6. Bent-leg sit-ups</td>
<td>10 RM x 3 sets</td>
</tr>
<tr>
<td>7. Bent over rows</td>
<td>10 RM x 3 sets</td>
</tr>
<tr>
<td>8. Calf raises</td>
<td>10 RM x 3 sets</td>
</tr>
<tr>
<td>9. Arm curls</td>
<td>10 RM x 3 sets</td>
</tr>
<tr>
<td>10. Leg press</td>
<td>10 RM x 3 sets</td>
</tr>
</tbody>
</table>

One-minute rest periods between sets and exercises 3–10. Exercises 2, 3, 5, 8, and 10, universal weight machine; exercises 7 and 9, free weights. RM, repetition maximum.

![FIG. 1. Timeline for experimental sessions. Control days had same timeline but with no exercise.](image-url)
trials was randomized and balanced to avoid any statistical order effects. The resting control day consisted of blood samples only in the laboratory, whereas the experimental exercise trial session included a series of blood samples surrounding the resistance exercise protocol followed by a recovery day (with no exercise) in which blood samples were obtained at identical time points as the control day.

Experimental workout day, recovery day, and control day. The experimental trials were conducted between 0800 and 1400. The subjects were not allowed to consume caffeine or alcohol nor were they allowed to participate in strenuous activity during the 72 h before testing. The subjects consumed only water 8 h before the exercise test session.

The experimental timeline can be observed in Fig. 1. After arriving at the laboratory, the subject was allowed to rest for 15 min before the preexercise blood draw. All blood samples were obtained in the same seated position by using a needle, syringe, and vacutainer setup. After the blood sample was obtained, the subject began the workout protocol starting first with the two 1-RM exercises and then moving onto the 10-RM protocol. When the experimental workout was completed, the subject rested in a seated position for postexercise blood samples. The same seated body position was used for all blood samples. Blood samples were also obtained in the laboratory at 0800, 1200, 1600, and 2000 of the next day, the recovery day of the experiment. The control day (no exercise) of the experiment consisted of blood samples at the identical times of day as the experimental and recovery days.

The subjects were asked to duplicate their activity, eating patterns, and sleeping patterns each week for the 5 days encompassing the study (3 days before and 1 day after the scheduled test day) to reduce any variance between treatment and control sessions. Special attention was given not to schedule subjects for testing during periods of high psychological stress (i.e., exams, presentations, and interviews).

Blood collection procedures. Venous blood samples were obtained via needle adapter and 7-ml serum and 4-ml sodium heparin vacuum collecting tubes. Blood was obtained from an antecubital arm vein. Serum blood samples were allowed to clot and then centrifuged at 1,500 g for 15 min at 8°C. The resultant serum for creatine kinase (CK), GH, and total IGF-I radioimmunoassays was immediately stored in plastic Eppendorf tubes and frozen for future analyses at −85°C. Samples that required storage were stored for no longer than 3 mo and thawed only once for analysis. Whole blood samples for lactate, hematocrit, and hemoglobin analyses were obtained from the heparin collection tubes.

Biochemical analyses. Hematocrit was determined in duplicate by using the standard microcapillary technique. Hemoglobin concentrations were analyzed in duplicate by the cyanmethemoglobin method (Sigma Chemical, St. Louis, MO). Whole blood lactate concentrations were determined in duplicate by using a YSI 1500 Sport Lactate Analyzer (Yellow Springs Instruments, Yellow Springs, OH). Serum CK concentrations were determined in duplicate by using a spectrophotometric assay (Sigma Chemical). Serum GH concentrations were determined in duplicate by a 125I liquid phase double-antibody radioimmunoassay (Diagnostic Products, Los Angeles, CA) with an model 1272 LKB Clini-gamma gamma counter with on-line data reduction capabilities (Pharmacia LKB Nuclear, Gaithersburg, MD). The antiseraum used for this procedure is highly specific for immunoactive human GH, exhibiting a cross-reactivity of <0.6% with prolactin. Total IGF-I was analyzed in duplicate with an 125I liquid-phase double antibody radioimmunoassay with an octadecasilyl-silica preliminary column (acid-methanol) extraction to separate IGF-I from its binding proteins. Intra-assay variation for GH and IGF-I was 2.1 and 2.4%, respectively. Due to the within-subject design of this study, all samples for any one subject were analyzed within the same assay to eliminate the effect of inter-assay variance. By using hemoglobin and hematocrit values, plasma volume shifts were calculated by using methods described by Dill and Costill (8).

Statistical analyses. A two-way analysis of variance with repeated measures was used to analyze the data from this study, and, when appropriate, a Tukey post hoc test was used to determine pairwise differences. A one-way analysis of variance was used to analyze the area under the curve (AUC), which was calculated by using a standard trapezoidal technique that we have previously used (19). Bivariate relationships were evaluated with simple regression techniques. A power analysis of 0.71 was determined for this study. Statistical significance in this study was chosen as $P \leq 0.05$.

RESULTS

Lactate concentrations were not significantly different between the preexercise time point (1.2 ± 0.5 mmol/l) and the immediate postexercise time point (1.5 ± 0.5 mmol/l) for the nonexercise control day. There were no significant differences in resting lactate concentrations between conditions. As expected, a significant increase in blood lactate pre- to postexercise (1.3 ± 0.2 to 15.7 ± 1.1 mmol/l) was observed with the performance of the heavy-resistance exercise protocol.

For the experimental trial, significant increases in creatine kinase were observed to be above resting values pre- to postexercise (151 ± 120 to 201 ± 136 IU/l) and were significantly different from preexercise and control day values for the same time point at 0800 (195 ± 131 IU/l), 1200 (191 ± 125 IU/l), and 1600 (183 ± 109 IU/l) of the recovery day. The 2000 value (154 ± 86
IU/l) was only significantly greater than its corresponding control day value. Except for the preexercise value, all other CK values were significantly higher than their corresponding control values. No significant differences were observed over the control conditions at preexercise (103 ± 46 IU/l), postexercise (94 ± 44 IU/l), 0800 (98 ± 52 IU/l), 1200 (97 ± 40 IU/l), 1600 (94 ± 37 IU/l), or 2000 (88 ± 40 IU/l). No significant correlations were observed between CK and IGF-I or GH.

The responses of serum GH are shown in Fig. 2. There were no differences in resting GH concentrations between control day (2.1 ± 3.8 µg/l) and exercise day (0.26 ± 0.6 µg/l). However, GH values for all postexercise time points after the heavy resistance exercise protocol were significantly elevated above rest, and they were significantly higher than their respective control day time points. GH concentrations peaked at the immediate postexercise time point (mean peak GH 23.8 ± 11.8 µg/l) and decreased for each subsequent time point thereafter. Significant differences occurred between the 15 and 30 min postexercise time point (19.3 ± 11.1 and 12.2 ± 9.9 µg/l, respectively).

The total serum IGF-I results are presented in Fig. 3 (AUC in the above insert panel). No significant differences between control day and recovery day values were observed for serum IGF-I at any time point. There were also no significant differences between pre- and postexercise concentrations of serum IGF-I within or between trials. AUC analysis also failed to show any significant differences in total serum IGF-I between the nonexercise control day and the experimental trial (388 ± 83 and 386 ± 93 nmol/l, respectively).

Hematocrit and hemoglobin concentrations measured pre- to immediate postexercise were used to calculate plasma volume changes (8). A plasma volume change of −15.7% was observed after the experimental heavy-resistance exercise protocol. Due to the multitude of influences on serum hormone concentrations and the fact that target tissues are exposed to absolute concentrations, hormonal data were not corrected for plasma volume shifts. Total work of the entire exercise protocol was calculated to be 54,663 ± 10,120 (SD) J by using methods previously described (19).

DISCUSSION

The primary finding of this study was that total serum IGF-I concentrations did not increase the day after a heavy-resistance exercise protocol that produced dramatic increases in immunoreactive GH. Pharmacological investigations demonstrated that exogenous GH administration acutely results in significant increases in serum IGF-I concentrations within 24 h after the initial dose (2, 5, 13, 20, 21), but such comparisons may not be germane to the response of IGF-I to endogenous GH in this study. In pharmacological studies, the peak GH can be >100 µg/l for 6 or more hours, which is different from the acute increases caused by resistance exercise. The feedback axes may also help to partially explain the present results, as the acute rise in GH might have been followed by an absolute or relative refractory period that has the effect of a compensatory decrease in GH concentrations or unchanged integrated levels over a longer period of time, thus influencing the lack of change in circulating IGF-I concentrations. In addition, our data demonstrated a lack of a relationship between circulating serum concentrations of IGF-I and GH over the 24 h of recovery. This finding is consistent with previous studies on resistance exercise (15, 18, 19) and with the data of Cappon et al. (3) for brief intense aerobic exercise recovery over 24 h. All of the data from these studies, including the present one, indicate that IGF-I concentrations in the blood can function independently of any changes in acute GH concentrations.

The magnitude of resting IGF-I concentrations may influence the responsiveness to an exercise-induced GH elevation. In a study by Marcus et al. (20), the responsiveness of IGF-I was blunted by the last day of exogenous GH administration pointing to an upper limit of responsiveness of IGF-I to GH stimulation. One might argue that because our subjects were recreationally weight trained and able to tolerate an advanced bodybuilding workout, they had already reached an upper limit of IGF-I concentrations in the blood. This possibility is also supported by the fact that the IGF-I concentrations demonstrated in our subjects were higher in magnitude than previously observed in untrained control subjects or moderately active individuals (1, 3, 14, 20). The IGF-I concentrations in our present subjects
were even higher than those of our subjects in previous experiments where acute increases in IGF-I were observed (18, 19). This again points to the potential importance of the adaptational changes in resting concentrations of IGF-I being an important factor that determines the responsiveness of circulating IGF-I concentrations. Thus, the lack of change in IGF-I could be due to the training effect that already had taken place in these subjects. The relative fitness of these subjects to tolerate this type of acute exercise stimulus is also demonstrated in the relatively low CK responses to the heavy-resistance exercise protocol.

In the present study and in our previous work, we demonstrated that this type of heavy-resistance exercise results in CK elevations but not of the magnitude observed in muscle damage models studying eccentric damage in untrained subjects (17). Due to the lack of any significant relationships between circulating CK and IGF-I, it is possible that the amount of muscle tissue damage observed in recreationally trained subjects after a heavy-resistance exercise protocol does not require alterations in circulating IGF-I. The relatively low CK response is also indicative that training status may influence the amount of muscle tissue disruption and thus types of operational mechanisms of remodeling (7). Because local tissue disruption is common to resistance exercise, an increase in autocrine and paracrine release of IGF-I may have been adequate to address the anabolic needs due to the low magnitude of muscle fiber damage, but this requires further investigation. In addition, an elevation in IGF-I immunoreactivity in tissue has been observed during regeneration after injury without any GH involvement (22).

There is a growing awareness of the polymorphism of GH molecules contained in and released from the human pituitary. The number of GH variants ranges between 15 and 20 and may be higher due to pre- and posttranslational processing in the pituitary (e.g., phosphorylation and proteolytic cleavage) (4, 9, 23). How heavy-resistance exercise stimulates other GH forms remains unknown but may be important in the understanding of the IGF-I and GH interactions in the circulating blood. The relationship of IGF-I and GH makes it a complex multivariate problem, but our data demonstrate the potential regulatory independence of these two hormones in circulating blood after exercise stress. This is consistent with the findings of other studies (3, 15, 18, 19). Future investigations should include analysis of the type of GH variants stimulated in response to this type of heavy-resistance exercise protocol to determine whether all variants are similarly responsive in the blood to exercise. Differential responses of GH variants could result in different interactive effects with IGF-I concentrations. In summary, the heavy-resistance exercise protocol used in this study dramatically increased serum immunoreactive GH concentrations in the blood, but total serum IGF-I concentrations did not change over 24 h after exercise, indicating that IGF-I concentrations after exercise may be independent of GH stimulatory mechanisms.

The authors thank the following laboratory staff, graduate students, and technicians for their help in data collection, laboratory biochemistry research, test subject supervision, dietetics, data entry, research support, manuscript preparation, and a wide range of logistical support activities for a very busy project: Joann Ruble, Tee McCormick, Matt McCormick, Dr. Kris Clark, R.D., N. Travis Tripelt, Jeff Volek, K.D., Jill Bush, and L. Perry Koziris. Also, we thank Drs. Howard G. Knutgen and Welesy C. Hymer for comments on the manuscript. Finally, we thank a very dedicated group of men who acted as test subjects in this study, without whose hard work and dedication this project would not have been possible. The authors would also like to acknowledge Carol Gardner and Joann Ruble for help in the preparation of this manuscript.

M. Terada is with the Department of Health and Physical Education, Kyoto University of Education, Fushimi-ku, Kyoto 612, Japan. K. Hakkinen is with the Department of Biology of Physical Activity, University of Jyvaskyla, Jyvaskyla, Finland. R. U. Newton is with the Department of Exercise Science and Sport Management, Southern Cross University, Lismore, Australia.

This study was supported in part by a grant from the Robert F. and Sandra M. Leitzinger Research Fund in Sports Medicine at the Pennsylvania State University.

Address for reprint requests: W. J. Kraemer, Center for Sports Medicine, 146 REC Bldg., The Pennsylvania State University, University Park, PA 16802.

Received 2 November 1994; accepted in final form 18 May 1995.

REFERENCES


13. Kassem, M., K. Brixen, W. Blum, L. Mosekilde, and E. F. Eriksen. No evidence for reduced spontaneous or growth-hormone-stimulated serum levels of insulin-like growth factor (IGF-
IGF-I AND RESISTANCE EXERCISE

1315


