Effect of brief exercise on circulating insulin-like growth factor I

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Cappon, James, Jo Anne Brasel, Subburaman Mohan, and Dan M. Cooper. Effect of brief exercise on circulating insulin-like growth factor I. *J. Appl. Physiol.* 76(6): 2490–2496, 1994.—An acute insulin-like growth factor I (IGF-I) response to 10 min of above-lactate threshold cycle ergometer exercise was studied in 10 subjects (age 22–35 yr). Each subject exercised on three separate mornings after ingesting one of two isocaloric isovolemic liquid meals high in either fat or glucose or an isovolemic noncaloric placebo. The high-fat meal attenuated the growth hormone (GH) response (Cappon et al., *J. Clin. Endocrinol. Metab.* 76: 1418–1422, 1993). In contrast, IGF-I increased equally for all protocols [e.g., after the placebo meal IGF-I increased from 21,716 (SE) ng/ml preexercise to 25,316 ng/ml at 10 min of exercise; $P < 0.05$]. IGF-I peaked by the 10th min of exercise, like GH, and remained significantly elevated for only 20 min of recovery. We tested for possible GH-dependent mechanisms in which circulating IGF-I would increase 12–24 h after exercise. Ten subjects (age 23–32 yr) performed 10 min of above-lactacte threshold exercise at 9, 10, and 11 A.M. GH was elevated after the first exercise bout (peak GH 6.05 ± 1.45 ng/ml; $P < 0.001$) but was significantly reduced for the second and third bouts (peak GH 2.52 ± 0.76 and 1.50 ± 0.40 ng/ml, respectively). No increase in IGF-I was observed by 8 A.M. on the following day. Heavy ergometer exercise led to brief and small increases in circulating IGF-I that were independent of circulating GH. The role, if any, of the GH-IGF-I axis in anabolic effects of exercise may be difficult to evaluate from circulating levels of IGF-I measured over short time intervals.

growth hormone; lactate threshold

AT LEAST TWO INDEPENDENT STUDIES of healthy humans have demonstrated significant correlations between physical fitness [determined by the subject's maximal oxygen uptake ($\dot{V}O_{2\,max}$)] and blood levels of insulin-like growth factor I (IGF-I) (30, 41). Presumably, the increased level of IGF-I, which is now known to stimulate growth in almost all tissues (35), reflects the increased anabolism (or, possibly, decreased catabolism) associated with physical fitness. However, the mechanisms linking exercise and IGF-I are unknown. The aims of this research were to determine whether circulating IGF-I increases *1*) immediately after brief high-intensity cycle ergometer exercise in humans and *2*) within a 24-h period after three consecutive brief bouts of high-intensity exercise.

Growth hormone (GH) is likely to play a role in the regulation of circulating IGF-I, since exercise is known to stimulate GH release (19) and GH induces tissue production of IGF-I and elevations in serum IGF-I (36). GH is elevated in the circulation within minutes of the onset of high-intensity exercise (19), but we hypothesized that any acute increase in circulating IGF-I in response to exercise would mechanistically be GH independent. This is because the time required for GH-stimulated tissue production of IGF-I and transport to the blood is on the order of hours rather than minutes in animal studies (36). We tested the hypothesis by measuring the acute GH and IGF-I responses to high-intensity cycle ergometer exercise both under normal conditions and when the GH response to exercise was attenuated by dietary manipulation (6).

We also tested for possible GH-dependent increases in circulating IGF-I after exercise. In human subjects receiving exogenous GH (4, 37, 38), IGF-I usually increases over a 24-h period after the first parenteral dose of GH. Thus, our second hypothesis was that an increase in circulating IGF-I after exercise might be observed between 12 and 24 h after an exercise input of sufficient intensity to stimulate GH release. To investigate this possibility, healthy subjects were observed in the hospital and GH and IGF-I were measured for a 24-h period after three bouts of exercise that were sufficiently intense to increase blood GH.

This research focused on the effect of brief periods of "endurance"-type exercise on circulating GH and IGF-I levels in humans, and, in this context, several points must be emphasized. First, although there are many data supporting a role for GH as a mediator of growth responses resulting from exercise (5, 13), there is also evidence from animal models that GH is not essential for work-induced muscle hypertrophy or improved cardiorespiratory response to training (12, 22, 23). Moreover, IGF-I can be stimulated in skeletal muscle tissues in response to increased muscle load or exercise even in the absence of GH (16, 49, 50). Second, it is not known at this time whether changes in tissue IGF-I are reflected in its plasma concentration. Finally, it is possible that different types of exercise can affect circulating or tissue IGF-I responses in different ways. We used brief periods of cycle ergometer exercise in which whole body oxygen uptake ($\dot{V}O_2$) markedly increases, but resistive exercise can present an even greater stimulus to individual muscle groups without the parallel increase in $\dot{V}O_2$.

METHODS

Hypothesis 1: Any Acute Increase in Circulating IGF-I in Response to Exercise is Mechanistically GH Independent

Subjects. Eleven healthy young adult volunteers (10 men, 1 woman) participated in this study. Mean age was 29 ± 4 yr (range 22–35 yr). All subjects were nonsmokers; none had a history of asthma, endocrine, or other chronic illness; and none was using medications or other drugs including anabolic agents. All subjects engaged in some sort of regular exercise, and the mean $\dot{V}O_{2\,max}$ was 50.5 ± 9.6 $ml \cdot kg^{-1} \cdot min^{-1}$. All body weights were within 1 SD predicted for age and height.

The investigation was approved by the institutional Human Subjects Committee, and each volunteer granted informed consent.

Protocol. All subjects participated in a total of four exercise sessions. Each session was scheduled on a different day separated by at least 5 days. The first session consisted of a progressive cycle ergometer test to determine each subject's $\dot{V}O_{2\,max}$ and anaerobic or lactate threshold (LT) (47). These data were then used to select comparable high-intensity exercise (power corresponding to 50% of the difference between the subject's LT and $\dot{V}O_{2\,max}$) as previously described (19). *Sessions 2, 3,* and *4* consisted of 10 min of constant-power high-intensity exercise performed 45 min after one of three liquid meals. The liquid meals were based in part on the formulas of Penman et al. (40): *1*) placebo meal: one packet of Nutrasweet (4 kcal); *2*) high-fat meal: Double Cream, a highly saturated 48% butterfat product (115 ml); and *3*) high-glucose meal: Polycose, a glucose polymer solution (136.8 g). The high-fat and high-glucose meals each contained 520 kcal. All three beverages were mixed with water to reach a final volume of 260 ml. The order of the three meals was determined randomly for each subject. All studies were performed in the morning hours after an overnight fast to minimize the occurrence of spontaneous GH bursts, and the subjects were instructed to desist from strenuous exercise for 24 h before the exercise session. Breath-by-breath gas sampling for the 20-min period surrounding the exercise bout was accomplished with techniques previously described from our laboratory (3).

Hypothesis 2: Circulating IGF-I Response to Exercise is Observed Between 12 and 24 h After Exercise Input of Sufficient Intensity to Stimulate GH Release

Subjects. Seven men and two women comprised the study sample. Mean age was 28 ± 3 yr (range 23–32 yr). All subjects were nonsmokers, none had a history of asthma or chronic illness, and none was using medications or other drugs. All subjects engaged in some sort of regular exercise, and the mean $\dot{V}O_{2\,max}$ was 42.6 ± 11.5 $ml \cdot kg^{-1} \cdot min^{-1}$. All body weights were within 1 SD predicted for age and height.

Protocol. Each subject performed a progressive cycle ergometer test to determine $\dot{V}O_2$ and LT. On a separate day and within 3 wk of the progressive test, the subject was admitted to the Harbor-University of California at Los Angeles Clinical Study Center after an overnight fast.

The subjects had been instructed to refrain from vigorous physical activity for 2 days before admission. An intravenous catheter was placed for subsequent venous blood sampling. At 9, 10, and 11 A.M. the subject performed 10 min of constant-power cycle ergometer exercise. The power was in the high-intensity range corresponding to 50% of the difference between LT and $\dot{V}O_{2\,max}$ as previously described. Work rates (i.e., power) of this intensity and duration have been shown to elicit GH responses (19). Three exercise bouts were chosen to maximize the morning GH "dose" resulting from exercise. GH was measured every 10 min starting 10 min before exercise and then for 30 min after each exercise bout. Gas exchange was measured breath by breath 5 min before, during, and 10 min after each exercise test. After the exercise bouts, the subjects rested for the remainder of the day and ate a normal diet [~2,200 kcal/day (adjusted to body size); protein 12–15%, carbohydrate 55–60%, and fat 30%]. Venous blood samples were obtained every hour for subsequent measurements of IGF-I until the subjects were discharged the next morning at 9 A.M.

Laboratory Analyses

A radioimmunoassay was used to measure serum GH using World Health Organization standard no. 66/217, polyclonal antisera generated in-house, and human GH from National Institute of Diabetes and Digestive and Kidney Diseases for iodination purposes. The GH intra-assay variability is <10%, interassay variability is 12.6%, and sensitivity is 0.5 g/l. Radioimmunoassays are currently used in our laboratory for human IGF-I with antibodies provided by National Institutes of Health and standards purchased from Bachem. The intra-assay coefficient of variation is 3.3%, and the interassay coefficient is 5.4%. We used the acid ethanol extraction method (14) to extract IGF-I from binding proteins. We made no attempt to adjust the measured plasma concentrations for possible changes in plasma volumes.

Statistical Analysis

For the *hypothesis 1* protocol, a block-design repeated-measures analysis of variance (ANOVA) was used to determine significance of serial changes in IGF-I and to compare the IGF-I responses after the high-fat, high-glucose, and noncaloric placebo meals. For the *hypothesis 2* protocol, a block-design repeated-measures ANOVA was used to compare the peak GH response for the first, second, and third exercise bouts and to test for serial changes in circulating IGF-I over the 24 h observation. In all cases sample distributions met the assumptions for analysis by ANOVA. When ANOVA was significant, modified *t* tests (method of Duncan) was used for specific intergroup comparisons. Statistical significance was taken as $P < 0.05$.

RESULTS

Hypothesis 1

The GH, glucose, lactate, pyruvate, somatostatin, and gas exchange responses of these subjects have been reported elsewhere (6). The mean $\dot{V}O_2$ during exercise represented 72% of the subjects' $\dot{V}O_{2\,max}$. Peak GH was significantly attenuated (54% of placebo) by the high-fat meal. Peak GH was smaller for the placebo than the high-glucose protocol, but the decrease was not statistically significant. IGF-I increased acutely after exercise during each of the three dietary protocols (Fig. 1), and despite the differences in GH there was no difference in the pattern of the IGF-I increase among the groups. Peak IGF-I (mean 14% above preexercise levels) occurred at the end of the 10-min exercise protocol. IGF-I remained significantly elevated above preexercise values for 20 min into recovery. No substantial differences in the time course of the GH and IGF-I responses were observed.

Hypothesis 2

Gas exchange response to the exercise-$\dot{V}O_2$ response was the same for each of the three consecutive exercise protocols (Fig. 2) and represented ~78% of $\dot{V}O_{2\,max}$. $\dot{V}O_2$ increased during the constant work rate exercise for all three bouts in all subjects, and an upward drift of $\dot{V}O_2$ during constant exercise was associated with exercise performed above the subjects' LT (1).

GH response. GH was significantly elevated after the first exercise bout (mean peak GH 6.05 ± 1.45 ng/ml; $P < 0.05$). In contrast to the gas exchange response, there was a systematic reduction in the GH response to exercise with each consecutive 10-min exercise bout (Fig. 2). In fact, the small increases in GH after the second (peak GH 2.52 ± 0.76 ng/ml) and third (peak GH 1.50 ± 0.40 ng/ml) bouts were not significantly greater than their

preexercise levels. The GH response to the three exercise bouts was virtually the same (both qualitatively and quantitatively) in the two women tested as in the men.

IGF-I response. As noted above, acute increases in IGF-I were noted in the first set of experiments but IGF-I levels had returned to baseline in the 1st h of recovery. In this second set of experiments, IGF-I was sampled every ~4 h; thus, the acute increases in IGF-I would not be noticed. Using the longer sampling intervals, we found no significant change in the IGF-I levels over the 24 h of observation (Fig. 3).

DISCUSSION

The data demonstrate the existence of a small but significant acute increase in circulating IGF-I of ~14% after high-intensity exercise. The effect of exercise on IGF-I has been examined by several investigators with differing results (2, 25, 48). For example, Wilson and Horowitz (48) reported no increase in serum IGF-I in children after 15 min of an unspecified cycle ergometer exercise protocol, and Hagberg et al. (25) did not find an increase in IGF-I after 60 min of treadmill exercise comparable to 70% of the subjects' $\dot{V}O_{2\,max}$ in young and old adults. More recently, Bang et al. (2) reported a 26% increase in IGF-I at the 10-min point of a 30-min exercise protocol in six healthy subjects (3 men, 3 women). Finally, heavy-resistance exercise protocols lead to increases in serum GH, but the finding of small but significant increases in serum IGF-I concentrations (32) with certain exercise regimens has not been observed by all investigators (31).

There are a number of possible explanations for these apparent discrepancies. First, the intensity of cycle ergometer or treadmill exercise is frequently determined as a percentage of $\dot{V}O_{2\,max}$, but the subjects' $\dot{V}O_{2\,max}$ is often

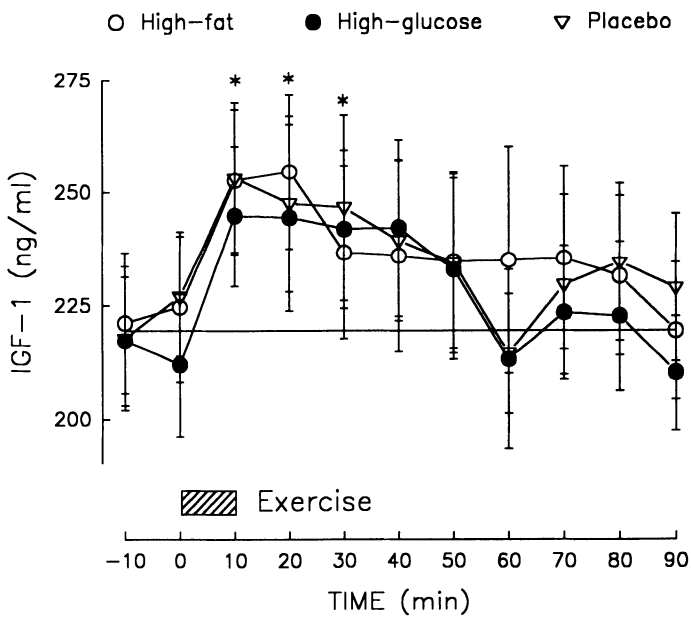

FIG. 1. Effect of brief high-intensity exercise on serum insulin-like growth factor I (IGF-I) (means ± SE) after noncaloric meal (placebo) or meals high in fat or glucose. IGF-I was significantly increased above baseline (* $P < 0.05$) at end exercise (10 min) and at 20- and 30-min sampling intervals. There was no effect of preexercise meal on IGF-I response to exercise.

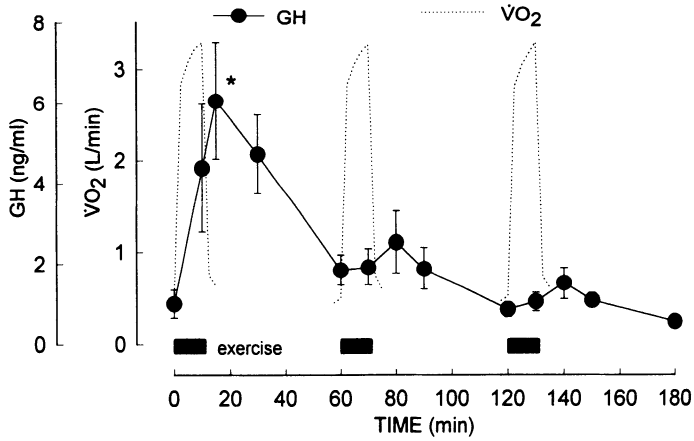

FIG. 2. Growth hormone (GH) (means ± SE) and mean oxygen uptake ($\dot{V}O_2$) of 3 10-min exercise bouts used to test *hypothesis 2*. $\dot{V}O_2$ was same for all 3 exercise tests and demonstrated increasing slope typical of above-lactate threshold work intensities. GH increased significantly after 1st exercise bout (* $P < 0.001$) but was not significantly elevated after 2nd or 3rd bout.

extrapolated from constant-power tests [e.g., the study of Bang et al. (2)] rather than an actually measured value. As noted previously (11), this can lead to a sample population in which some subjects exercise below and others exercise above their LT. This is an important distinction because hormonal and metabolic responses to exercise are not related to work intensity in a simple linear manner. For example, the rate of glucose turnover and serum levels of lactic acid and catecholamines are much higher for above- vs. below-LT exercise (11). In addition, our data and those of Bang et al. suggest that the time course of the IGF-I response is rapid, peaking at ~10 min after the onset of exercise. The IGF-I response simply may not be detectable with longer sampling intervals. It is also important to note that a variety of techniques are currently used to separate IGF-I from its binding proteins (39) and that there is no universally accepted method to completely separate IGF-I from its binding proteins. Indeed, any interpretation of our data or comparison with other works is limited because we did not distinguish free from bound IGF-I.

We believe that some of these confounding variables have been adequately addressed in the present study. Both LT and $\dot{V}O_{2\,max}$ were measured and used to identify a power of the same relative intensity for each subject. IGF-I was measured every 10 min before and after the exercise input. Moreover, the increase in IGF-I after exercise was significant in the subjects under three different conditions. Thus, our data are most consistent with those of Bang et al. (2) and strongly support the existence of a small acute exercise-associated increase in IGF-I after endurance-type protocols.

Our observations support the idea that the acute IGF-I response to high-intensity cycle ergometer exercise is independent of GH for several reasons. The time courses of the GH and IGF-I responses were roughly similar (Fig. 1; Ref. 6). The bulk of current evidence suggests that circulating IGF-I originates in the liver (36). A GH-dependent mechanism for the increase in serum IGF-I with exercise might require GH-stimulated synthesis of IGF-I and its subsequent transport to the circulation. However, the

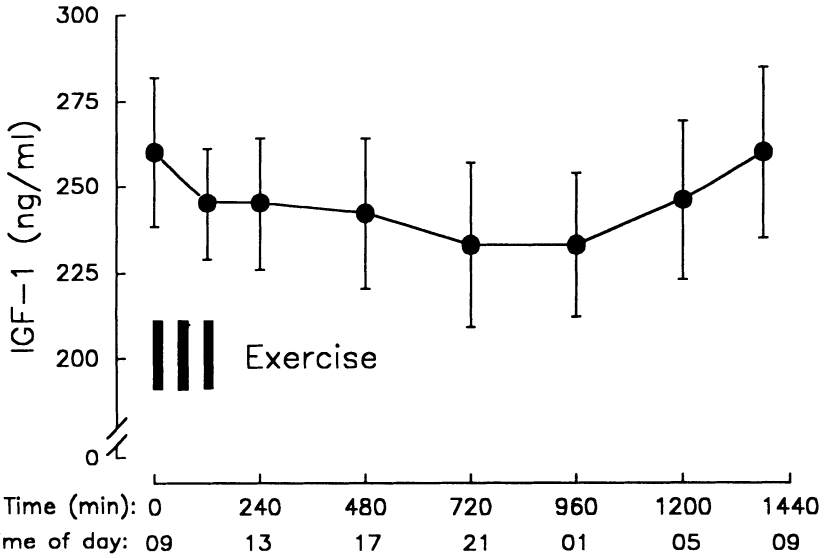

FIG. 3. IGF-I (mean ± SE) during and after 3 high-intensity exercise bouts. There appeared to be no effect of exercise on circulating IGF-I levels over 24 h of observation.

time required for GH-stimulated IGF-I synthesis and transport appears to be much longer than what we observed in the exercise experiments. For example, D'Ercole and Underwood (15) demonstrated that serum IGF-I began to increase only hours after intraperitoneal administration of GH in hypophysectomized rats. As noted above, Marcus et al. (37) demonstrated that an increase in IGF-I was not detectable in the serum for several hours after the administration of exogenous GH in healthy elderly humans. A similar time scale for the IGF-I response after exogenous GH administration was found in GH-deficient prepubertal children (4, 38).

IGF-I increases in serum after stimulation by GH, are, to some extent, dependent on the GH dose (36, 37). But we found that the magnitude of the IGF-I response was not changed even when the GH response to exercise was attenuated by the high-fat meal (Fig. 1). The dissociation between GH and IGF-I under these circumstances further supports the hypothesis that the acute IGF-I response to exercise is GH independent. It is, of course, possible that preformed pools of IGF-I dissociate from their binding proteins under the influence of GH, resulting in a rapid increase in circulating IGF-I. But in the study of Bang et al. (2), an exercise-induced increase in IGF-I was observed even in hypophysectomized patients, rendering any GH control over acute IGF-I increases in the serum highly unlikely.

Diurnal patterns of circulating IGF-I have not been found in humans or other mammals (18, 45), and there appear to be few other physiological stimuli that lead to rapid changes in circulating IGF-I. As noted, GH administration increases circulating IGF-I over hours or days, and caloric restriction decreases IGF-I levels over days (10). The relatively slow changes in circulating IGF-I are consistent with what is currently understood about IGF-I dynamics: ≥90% of IGF-I in the serum is bound to carrier proteins (24), and the half-life of the predominate protein complex is long (~15 h).

Our measurements of total IGF-I (i.e., bound and free) did not allow us to determine the mechanism of the exercise-associated increase in serum IGF-I or whether the elevated IGF-I was bound or free. Bang et al. (2) found no effect of exercise on IGF-I binding protein 1 (known to be insulin dependent), and, to our knowledge, the effect of brief exercise on IGF-I binding protein 3 [the main plasma binding protein (10)] has not been measured. Indeed, the presence of binding proteins and their role in regulating IGF-I biological activity make it difficult to assess the importance of the small increase in circulating IGF-I that we observed. It is known from clinical studies that injections of recombinant IGF-I result in increased blood levels (44) and appear to have substantial anabolic effects in children with Laron type dwarfism (26, 33). The interaction between exercise, circulating IGF-I, and IGF binding proteins is not fully understood.

Clearly, the small increases in circulating IGF-I that we observed could result from some combination of increased influx of IGF-I into the plasma, decreased efflux or metabolism, or changes in the volume of the plasma "compartment" itself. The data that we collected, IGF-I serum concentrations, are insufficient by themselves to determine the possible roles of tissue IGF-I production, subsequent metabolism, or changes in the IGF-I volume of distribution. Dill and Costill (17) presented a calculation to account for exercise-induced changes in plasma volume on the basis of alterations in hemoglobin and hematocrit, and this calculation is widely used to correct plasma concentrations for possible changes in plasma volume. The magnitude of plasma volume reductions during exercise that have been calculated using the formula of Dill and Costill is small (31) and not inconsistent with the increases in circulating IGF-I that we observed.

However, we believe that the hemoglobin-hematocrit approach is inadequate, particularly for brief exercise (such as the 10-min protocol of the present study) during which steady states of metabolic rate or plasma volume redistribution are unlikely to be achieved. Moreover, recent findings that exercise in humans leads to the transfer of hemoconcentrated red blood cells from the spleen to the central circulation (20, 21, 34) calls to question an underlying assumption of the hemoglobin-hematocrit correction. Thus, we have elected to present the IGF-I concentration as we measured it and as "sensed" by other tissues, uncorrected and unmodified. By what-

ever mechanism, it seems that brief high-intensity cycle ergometer exercise is one of the few naturally occurring events identified so far that can rapidly affect circulating IGF-I levels even to the small extent observed in this study.

In testing *hypothesis 2*, we observed that the GH response to exercise was dramatically attenuated by prior exercise (Fig. 2). The mechanism of exercise attenuation of subsequent exercise-induced GH is not readily apparent. Depletion of pituitary GH stores by the first exercise bout is not likely, since the magnitude of the serum GH increase after exercise is substantially smaller than that often occurring even with spontaneous GH pulses (46). GH autoinhibition is known to occur (42), but, as can be seen from Fig. 2, GH was only slightly elevated before the next exercise session had begun. Similarly, IGF-I inhibition of pituitary GH release is also unlikely, since the IGF-I increase after exercise observed in the first set of studies was rapid and returned to preexercise levels by 1 h (Fig. 1) before the next exercise bout (in the *hypothesis 2* protocol) would have begun. Both high- and low-intensity exercise are associated with increases in serum free fatty acids (FFA) [particularly in the recovery phase (27)], and an increase in FFA is known to block GH secretion (9). Perhaps increased FFA after the first exercise bout inhibited GH release in response to subsequent exercise. Alternatively, exercise inhibition of cholinergic tone might attenuate subsequent GH response to exercise (8, 29). How long after an exercise bout the GH response to subsequent exercise returns to normal is not known.

The acute increases in GH associated with the three exercise bouts appeared to have no effect on serum IGF-I over the remaining 24 h (Fig. 3). We did observe acute GH-independent increases in circulating IGF-I in the first set of experiments, but we found no evidence from a single day's observation (as noted, with far longer sampling intervals) that high-intensity exercise stimulates increased circulating IGF-I. Several studies have demonstrated that combinations of diet and physical activity that result in negative energy balance can, after several days, lead to reductions in circulating IGF-I (28, 43), but the relatively brief exercise in our protocol and the unrestricted diet during the course of observation argues against this possibility in our subjects. Perhaps the combination of exercise and increased food intake might have a different effect on IGF-I than the one we observed.

Despite the lack of a clear association between exercise, GH, and IGF-I over 1 day, our data do not rule out a role for exercise-modulated GH and/or IGF-I in the training response for several reasons. First, it is worthwhile to compare the consequences of exogenously administered GH with exercise-induced endogenous secretion of GH on serum levels of GH. For example, Marcus et al. (37) injected 0.03 mg/kg of recombinant human GH in the "low dose" group of their study for which an increase in IGF-I was noted over 24 h. We calculated the area under the curve of serum GH vs. time in their study and found it to be 27 times greater than the area under the curve for serum GH after the three exercise bouts in our experiment. Individual exercise bouts simply may not result in sufficiently elevated serum GH levels to result in an increase in IGF-I in 1 day.

Second, in contrast to the elderly subjects studied by Marcus et al. (37) and GH-deficient children studied by Blethen et al. (4) who, in almost all cases, increased IGF-I after the administration of exogenous GH, our subjects were healthy young adults. Moreover, they were moderately fit (mean $\dot{V}O_{2\,max}$ 43–51 $ml \cdot min^{-1} \cdot kg^{-1}$), suggesting some participation in regular programs of physical activity. Perhaps it is simply more difficult to stimulate GH-dependent IGF-I increases in individuals who are already engaging in physical activity, i.e., those who may have fully or partially stimulated the putative exercise-GH-IGF-I interaction. Interestingly, Marcus et al. found that by the 7th day of their study IGF-I was "chronically" increased and exogenous GH administration no longer stimulated a further increase in circulating IGF-I. Alternatively, like the training response itself in which cardiorespiratory effects of daily exercise become apparent only after several weeks (7), an exercise-associated GH increase might not result in detectable increases in IGF-I for days or weeks.

Finally, it is possible that the correlation between physical fitness and IGF-I cited previously (30, 41) may result from an exercise effect on the overall pattern of GH secretion rather than from the GH effects of single exercise bouts. Recently, for example, Weltman et al. (46) noted a significant increase in the amplitude of spontaneously occurring GH pulses in women after 1 yr of training at above-LT work intensities. The mechanism of this effect is not known.

In summary, we propose two possible mechanisms for the association of increased IGF-I levels with physical fitness: an exercise-GH-IGF-I interaction or a GH-independent direct effect of exercise on IGF-I. A small acute GH-independent increase in IGF-I occurred but was not sustained beyond ~40 min postexercise. Three bouts of exercise increased circulating GH (although GH release in the 2nd and 3rd exercise bouts was attenuated) but did not result in increased IGF-I over 21 h of observation. Possible GH-dependent or GH-independent links between bouts of exercise and the anabolic effects that make up, in part, the training effect may be impossible to detect over 1 day of observation.

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