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Increased physical activity and the growth hormone-IGF-I axis in adolescent males

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Eliakim, Alon, Jo Anne Brasel, Subburaman Mohan, Wai Lee T. Wong, and Dan M. Cooper. Increased physical activity and the growth hormone-IGF-I axis in adolescent males. *Am. J. Physiol.* 275 (*Regulatory Integrative Comp. Physiol.* 44): R308–R314, 1998.—Insulin-like growth factor-I (IGF-I) is associated with muscle hypertrophy, and circulating IGF-I levels are correlated with fitness. To test the hypothesis that IGF-I increases with increased physical activity in adolescent males, 38 subjects (16 ± 0.7 yr old) were randomized to control (n = 18) or increased physical activity groups for 5 wk. Before and after the intervention, we measured thigh muscle volume using magnetic resonance imaging and serum levels of mean growth hormone (GH) by overnight multiple sampling, GH binding protein (GHBP), IGF-I, and IGFBPs 1–5 by standard assays. Energy expenditure was assessed with the doubly labeled water technique toward the end of the study. In the training subjects there was *1*) a significant increase in thigh muscle volume (+3.6 ± 1%), *2*) 15.5 ± 3.3% greater energy expenditure than in controls, and *3*) no evidence of weight loss (+1.44 ± 0.4%). In contrast to our hypothesis, but similar to our recent observations in adolescent females, training decreased IGF-I (−12 ± 4%, $P <$ 0.005). Moreover, training substantially reduced GHBP (−21 ± 4%, $P <$ 0.00002) and increased IGFBP-2 (+40 ± 16%, $P <$ 0.008). Brief training increased muscle volume in weight-stable adolescent males and, surprisingly, influenced not only IGF-I but GHBP and IGFBP-2 as well in a manner typically found in energy-deficient states.

binding proteins; muscle volume; energy expenditure; magnetic resonance imaging; insulin-like growth factor-I

EXERCISE TRAINING can lead to tissue growth, and many of the health benefits accrued to fitter individuals are related to these anabolic effects (7, 36). Growth hormone (GH) and insulin-like growth factor-I (IGF-I) likely play a role because fitter people tend to have higher circulating levels of GH and IGF-I (16, 26, 38, 53), and IGF-I plays a role in muscle hypertrophy (1). It would seem reasonable to predict that fitness training would lead to increases in circulating IGF-I. But in experiments designed to test this hypothesis in both humans and animals, an increase in IGF-I following exercise training is not consistently observed (8, 24). In fact, we recently observed that 5 wk of increased physical activity led to a 14% drop in circulating IGF-I in healthy adolescent females despite training-induced increases in muscle volume (16).

We hypothesized that in a well-controlled, prospective study of increased physical activity, GH and IGF-I would, in fact, be found to increase in adolescent males, a group characterized by rapid growth and marked changes in GH secretory pattern and circulating IGF-I. Understanding the mechanisms that link exercise and growth in adolescence is of particular importance because levels of physical activity not only determine the subject's fitness but likely also influence maturation and the ability of the organism to adapt later in life. The results presented in this paper are part of a larger data set, portions of which have been presented elsewhere (17).

It is becoming increasingly clear that analyses of the GH-IGF-I axis require measurements not only of circulating GH and IGF-I but also measurements of GH pulsatility. In addition, GH activity depends, in part, on its circulating binding protein (GHBP). IGF-I is also bound in the circulation and tissues to a variety of binding proteins (IGFBPs), which may alter IGF-I biological activity (15). Thus, in the present study, we measured GH pulsatility and circulating levels of GHBP and IGFBPs 1–5.

METHODS

Sample population. Forty-four boys volunteered to participate in the study. The subjects were all students at Torrance High School (Torrance, CA) enrolled in an anatomy and physiology class during the summer of 1996 (July–August), with class hours from 8:00 AM to 12:30 PM. The ethnic configuration of the group was 71% Asian, 20% Caucasian, and 9% Hispanic. No attempt was made to recruit subjects who participated in competitive extramural athletic programs. The study was designed to examine late pubertal subjects with an age range of 15–17 yr (mean 16 ± 0.7 yr). Measurements of height and weight were made using standard techniques. Assessment of pubertal status was performed by physical examination in all of the subjects. Thirty-one (70%) of the subjects were found to be at Tanner level V, 11 (25%) at Tanner level IV, and 2 (5%) at Tanner level III.

The participants were randomized to a control (n = 22) or training group (n = 22). All subjects participated in the 2-h daily teaching program. During the remaining time, the training group members underwent endurance-type training consisting of running, aerobic dance, competitive sports (e.g., basketball), and occasional weight lifting. The intervention was designed to mimic the type and intensity of exercise that high school boys normally perform. These activities were varied in duration and intensity throughout the week primarily to encourage enthusiasm and participation of the subjects. On average, "aerobic" or endurance-type activities accounted for ~90% of the time spent in training. Of these ~50% involved running, 40% team sports, and 10% aerobic dance.

Training was directed by a member of the Torrance High School faculty.

The control group subjects participated in a computer workshop designed to improve their computer skills. No attempt was made to influence extracurricular levels of physical activity in either the control or trained groups, but participants were asked not to change their activity patterns from those before the study. The study was approved by the Institutional Human Subject Review Board, and informed consent was obtained from the subjects and their parents or guardians.

In setting up this protocol we balanced the need for a easily reproducible protocol (e.g., one that would involve a specified number of minutes on a cycle ergometer at a particular work rate) with a set of exercises that would be adhered to by "real life" children and adolescents. Our subjects were not drawn from a population of athletes, and many of the subjects were not used to any form of training per se. In discussions with the physical education instructors at our participating schools, we reached the conclusion that the compliance would likely be greater if we used the more flexible approach.

One subject did not participate in the blood sampling protocols. In addition, during the course of the summer, five subjects (3 from the control group and 2 from the training group) withdrew due to academic and/or disciplinary reasons. The two subjects who withdrew from the training group did so 2 days before the final examination and reported that the difficulty of the training protocol was not the reason for their decision. Thus, at the end of the study, 38 subjects (18 from the control group and 20 from the trained group) completed all pre- and postinterventional aspects of the protocol. As noted, related results from this study have been published elsewhere (15, 17).

Measurement of total energy expenditure. The doubly labeled water (DLW) technique was used to measure total energy expenditure (TEE) for a 10-day period beginning on *week 3* of the protocol. This approach is now the state-of-the-art methodology for estimating energy expenditure in human subjects under natural conditions and relies on the discrepancy between the washout kinetics of deuterium-labeled vs. ^{18}O-labeled water following a bolus ingestion of the DLW (44). Ideally, pre- and postintervention measurements of TEE using DLW would have been performed; however, this was prohibited by the extremely high cost of $H_2{}^{18}O$. Based on a power analysis, subjects from the control and training groups ($n = 10$ each) were randomly selected for TEE measurements.

After a baseline urine sample was obtained, each subject was given a standard oral dose of DLW. To minimize calculation error, a standard dose of 25 ml of a 1:1 mixture of ^2H_2O and $H_2{}^{18}O$ (99% enriched from Isotec, Williamsburg, OH) was given. The dose is calculated to provide an average of 0.22 g/kg of ^2H_2O or $H_2{}^{18}O$ with a range of 0.15–0.29 g/kg. A urine sample was obtained 2 h later and daily for the next 10 days. Oxygen and hydrogen isotopic ratios were measured by standard techniques with a Finnegan Delta-S gas isotope-ratio mass spectrometer. The isotope ratio data were analyzed using linear regression analysis after log transformation (44). Converting CO_2 production rate to TEE was done according to methods recommended by the International Dietary Energy Consultancy Group in 1990 (13).

It is important to note that an underlying assumption in our comparison of TEE between the two groups was that there was no group difference in TEE before the study. Ideally, measurements before and during the study should have been made, but the cost of the DLW prohibited pre- and poststudies. A more thorough discussion of the potential weaknesses of the current approach can be found in a related publication (2).

Magnetic resonance imaging of thigh musculature. Studies were done before and immediately after the 5-wk protocol in all subjects. We chose to examine the musculature of the right thigh because these muscles would be largely involved in the endurance-type training program described above. Magnetic resonance imaging (MRI) has been used previously to assess muscle volume in response to training (14, 37, 42). MRI was performed on a General Electric 1.5-tesla whole body MRI system. A body coil was used for both signal detection and for radio frequency transmission for imaging. The subject was positioned with the lower extremities at the isocenter of the magnet bore. Pilot image coronal slices of the right thigh were obtained to select an image that included the distal femur. Twelve axial slices from above the knee to below the femoral neck were obtained. These axial slices were 20 mm thick with no gap and obtained with a T1 weighted sequence with a time-to-echo of 12 ms and repetition time of 400 ms. The matrix was 192 × 256, with two acquisitions at each phase encode step.

The thigh muscle cross-sectional areas (CSA) of consecutive 2-cm slices were easily recognizable and measured using computerized planimetry. The volume (cm^3) of each slice was estimated as CSA (cm^2) × 2 cm. These were then summed to calculate the muscle volume.

Blood sampling protocols. Subjects were admitted to the Clinical Research Center (CRC) at Harbor-University of California Los Angeles Medical Center, and an indwelling heparin lock catheter was inserted in a forearm vein at 6:00 PM. Baseline blood samples were collected for circulating GHBP, IGF-I, IGF-II, IGFBPs 1–5, and testosterone. Serial blood sampling for GH was initiated at 8:00 PM and continued for 12 h. Samples were collected at 20-min intervals, which has been demonstrated previously to permit an accurate determination of GH pulsatility (9). The subjects' physical activity was limited (i.e., walking in the confines of the CRC). The overnight protocol occurred the week before and during the week after the completion of the training intervention. No subjects trained during the day preceding the overnight blood sampling. All blood samples were immediately centrifuged, and the serum was frozen for subsequent analysis.

GH. GH serum concentrations were determined using the fluoroimmunoassay technique (47). The monoclonal antibody pair was obtained from Medix Biotex (San Carlos, CA). Europium-labeled streptavidin was obtained from Delfia (Wallac, Gaithersburg, MD). Interassay coefficient of variation (CV) was 5.7–10.1%, and intra-assay CV was 4.9–8.3%. Assay sensitivity was 0.1 ng/ml.

GHBP. GHBP was measured using the ligand-mediated immunofunctional assay (6). Interassay CV was 9.7–12.9%, and intra-assay CV was 6.3–8.9%. Assay sensitivity was 7.8 pmol/l.

IGF-I and IGF-II. IGFs were extracted from IGFBPs using the acid-ethanol extraction method (11). Double-antibody RIA was performed to measure IGF-I and IGF-II serum concentrations. Polyclonal recombinant IGF-I antiserum was obtained from the National Institutes of Health (Bethesda, MD). Radioactively labeled ^{125}I-IGF-I tracer was purchased from Amersham (Arlington Heights, IL). IGF-I was obtained from Bachem Chemicals (Torrance, CA). IGF-I interassay CV was 5.4–7.5%, and intra-assay CV was 4.5–6.2%. Assay sensitivity was 0.1 ng/ml. IGF-II monoclonal antibody was purchased from Amano International (Troy, VA). IGF-II was obtained from Bachem Chemicals (Torrance, CA). ^{125}I-IGF-II tracer was iodinated using the modified chloramine-T method. IGF-II interassay CV was 5.1–7.6%, and the intra-assay CV was 4.4–6.8%. Assay sensitivity was 0.1 ng/ml.

IGFBPs 1–5. IGFBP-1 and -3 were measured by coated-tube immunoradiometric assays. IGFBP-2, -4, and -5 were measured by RIA. IGFBPs 1–3 were measured using commercially available kits (Diagnostic System Laboratories kits, Webster, TX). IGFBP-4 and -5 were measured in S. Mohan's laboratory, as recently described (32, 33). For IGFBP-1, interassay CV was 1.7–6.7% and intra-assay CV was 2–4%. Assay sensitivity is 0.11 ng/ml. For IGFBP-2, interassay CV was 6.4% and intra-assay CV was 6.5%. Assay sensitivity is <0.6 ng/ml. For IGFBP-3, interassay CV was 0.6–1.9% and intra-assay CV was 1.8–3.9%. Assay sensitivity is 0.5 ng/ml. For IGFBP-4, interassay CV was <8.1% and intra-assay CV was <5%. Assay sensitivity is <0.5 ng/ml. For IGFBP-5, interassay CV was <8% and intra-assay CV was <4%. Assay sensitivity is <5 ng/ml.

Testosterone. Testosterone was measured by RIA using the Diagnostic System Laboratories kit (DSL-4000). Interassay CV was 8.4–9.1%, and intra-assay CV was 7.8–9.6%. Assay sensitivity is 0.08 ng/ml.

Statistical analysis. GH peaks (number, width, amplitude) were determined using the statistical algorithms developed previously (50). Unpaired *t*-tests were used to determine differences in circulating components of the GH-IGF-I axis between control and training group subjects before the training intervention. Unpaired *t*-tests were also used to compare the measurements of TEE (made during the intervention) between the two groups. Paired *t*-tests (within group) were used to compare the effects of training on the hormonal data and thigh musculature. The data were also analyzed using repeated-measures ANOVA. In addition, we calculated before-and-after changes in the body weight, muscle volume, and hormonal variables for each subject and used unpaired *t*-tests to test between-group significance. Statistical significance was taken at the $P < 0.05$ level and, when appropriate, only if both within- and between-group differences, as well as repeated-measures ANOVA analyses, were found to be significant. Data are presented as means ± SE.

RESULTS

Body height and weight. At the beginning of the study, there were no significant differences between the control and training groups with respect to height or weight. There was a significant increase in body weight in the training group, but not control group, by paired *t*-test. However, between-group differences were not statistically significant. There was no change in height in either group (Table 1, Fig. 1).

Effect of training on thigh muscle volume. Thigh muscle volume increased significantly in the training group but not in the control group by both within-group and between-group analysis (Table 1, Fig. 1).

TEE. There was no significant difference in body weight between the subset of control group and training group subjects who participated in the DLW measurements. TEE was 15.5% higher in the training (2,425 ± 22 kcal/day, $P < 0.00001$) compared with the control group (2,099 ± 47 kcal/day).

Effect of training on the GH-IGF-I axis. There was no change in mean GH level, the number of GH peaks, GH peak width, and GH amplitude in either group over the 5-wk period of observation. There was a significant reduction in circulating GHBP and IGF-I in the training group by both within-group and between-group testing (Table 1, Fig. 2).

Table 1. *Effects of 5-wk endurance training intervention on anthropometric, muscle volume, and hormonal variables*

	Control Group ($n = 18$)		Trained Group ($n = 20$)	
	Pre	Post	Pre	Post
Height, cm	170.3 ± 1.6	170.5 ± 1.8	169.2 ± 1.6	169.3 ± 1.8
Weight, kg	66.2 ± 3.5	66.8 ± 3.3	61.0 ± 1.8	61.8 ± 2.0
Thigh muscle volume, cm^3	1,442 ± 60	1,441 ± 62	1,357 ± 35	1,404 ± 32*
Mean 12-h GH level, ng/ml	2.52 ± 0.58	2.34 ± 0.6	2.83 ± 0.33	2.61 ± 0.32
GH peak frequency, per 12 h	1.9 ± 0.6	1.8 ± 0.3	2.5 ± 0.3	2.2 ± 0.3
GH peak width, min	121 ± 14	131 ± 11	118 ± 9	136 ± 11
GH peak height, ng/ml	9.42 ± 1.48	8.33 ± 1.53	10.30 ± 0.92	10.19 ± 1.38
GHBP, pmol/l	220 ± 28	219 ± 28	201 ± 19	158 ± 17*
IGF-I, ng/ml	226 ± 14	215 ± 14	224 ± 12	195 ± 12*
IGF-II, ng/ml	671 ± 52	613 ± 49	704 ± 47	653 ± 57
IGFBP-1, ng/ml	7.0 ± 3.0	8.6 ± 3.0	10.7 ± 2.8	11.5 ± 3.2
IGFBP-2, ng/ml	234 ± 25	224 ± 28	189 ± 20	258 ± 32*
IGFBP-3, ng/ml	3,430 ± 90	3,345 ± 106	3,567 ± 128	3,301 ± 107
IGFBP-4, ng/ml	173 ± 11	198 ± 9†	167 ± 12	189 ± 10†
IGFBP-5, ng/ml	271 ± 11	281 ± 15	261 ± 11	264 ± 10
Testosterone, ng/ml	3.0 ± 0.2	3.3 ± 0.3	3.6 ± 0.2	3.6 ± 0.3

Results are represented as mean values for the whole group (trained vs. control) ± SE. GH, growth hormone; BP, binding protein; IGF, insulin-like growth factor. *Significant difference between control and training groups for both between- and within-group comparison ($P < 0.05$). †Significantly increased in both control and training groups ($P < 0.05$).

IGFBP-3 was reduced in the training group subjects ($P < 0.003$) but not in the control subjects by within-group tests; however, neither the between-group comparison nor ANOVA with repeated measures was significant. There was a significant increase in IGFBP-2 in the training group but not control subjects using both within-group and between-group testing. IGFBP-4 was significantly elevated following the interventional period in both the control and trained groups. Finally, there were no changes observed in circulating IGF-II, IGFBP-1 and -5, and testosterone.

DISCUSSION

The 5-wk intervention of increased physical activity successfully led to a 15.5% difference in TEE between the control and training groups. Training increased thigh muscle volume and, as noted previously, cardiorespiratory fitness (17). Despite these local anabolic changes, and in contrast to our hypothesis, IGF-I did

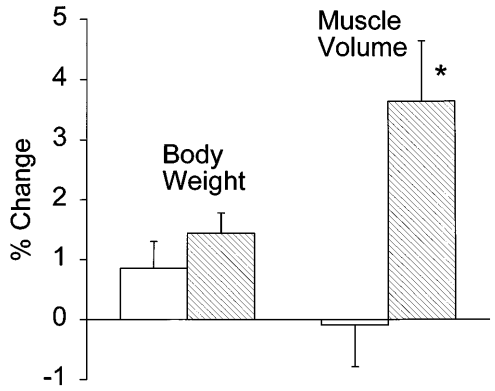

Fig. 1. Changes in body weight and thigh muscle volume following the 5-wk protocol in control (open bars) and trained (hatched bars) subjects. Body weight increased by within-group analysis only in the trained group ($P < 0.003$), but the change was not statistically different from the control group by between-group analysis. Muscle volume increased significantly in the trained compared with the control group by both within- and between-group analyses (*$P <$ 0.0008 and <0.003, respectively).

not increase as a result of training. In fact, we found a small but significant decrease in circulating IGF-I, similar to our recent results in a training study in adolescent females (16). Moreover, IGFBP-2 was significantly elevated. Although these specific changes in IGF-I and IGFBP-2 are commonly observed in energy-deficient states like food deprivation or disease-associated malnutrition (34, 46, 49, 51), the increased energy expenditure in the training group was not accompanied by weight loss, indicating that overall energy metabolism was balanced as the subjects became fitter.

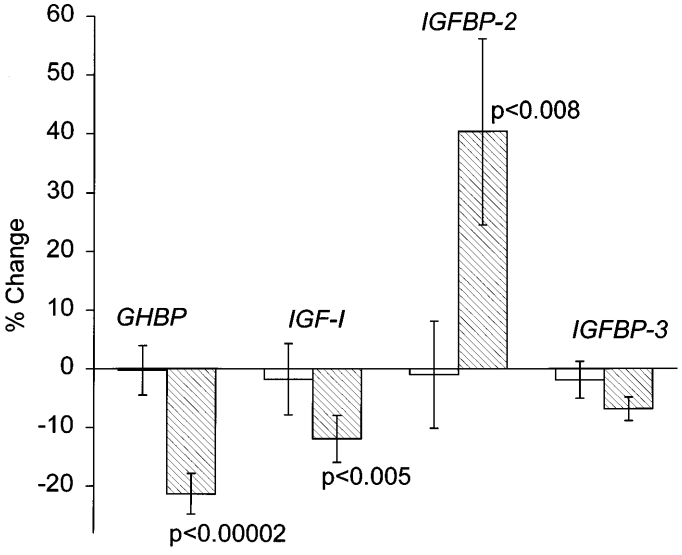

Fig. 2. Changes in growth hormone binding protein (GHBP), insulin-like growth factor-I (IGF-I), IGFBP-2, and IGFBP-3 following the 5-wk protocol in control (open bars) and trained (hatched bars) subjects. GHBP, IGF-I, and IGFBP-2 significantly changed in the training but not control group (P values shown are for within-group comparisons). IGFBP-3 was significantly lower following training by within-group testing, but this change was not statistically different from the control subjects using between-group testing. In contrast to our hypothesis, the response of the GH-IGF-I axis was indicative of a catabolic rather than anabolic state, with reductions in GHBP and IGF-I and an increase in IGFBP-2.

A potential mechanism for this seemingly paradoxical adaptation may be the substantial reduction in circulating GHBP in the trained subjects. GHBP in humans is known to be the extracellular portion of the GH cellular receptor; hence, lower circulating levels may reflect fewer tissue receptors and reduced tissue responsiveness to GH in many tissues, including the liver (43). If true, the lower circulating levels of IGF-I found in the training group might occur as a result of reduced GH-induced hepatic production (30).

The dissociation of the relationship between GH and GHBP during increased physical activity observed here appears to be unique. In malnutrition, GHBP is also low but is accompanied by elevated GH (39). Conversely, in obesity, low levels of GH are observed but they are associated with increased GHBP (25). Both of these instances suggest the well-described phenomenon of ligand-induced receptor regulation. In this study, training did lead to a reduction in GHBP (Table 1, Fig. 2), but without any measurable change in mean GH or GH pulsatility. The mechanism for such a direct training effect on GH receptors or GHBPs is not known.

As noted, reductions in GHBP, IGF-I, and IGFBP-3 are characteristic of a variety of energy-deficient states, such as fasting and disease-associated malnutrition. In these cases, the alterations appear to be closely tied to GH. In contrast, the regulation of IGFBP-2 in the circulation may be influenced by insulin-dependent factors of glucose homeostasis (41) rather than by direct GH-dependent factors. Furthermore, elevated circulating IGFBP-2 has been noted in pathological states associated with malnutrition (34, 46, 49). Our observation of significant increases in IGFBP-2 in the trained subjects further supports the hypothesis that the training intervention, despite increase in muscle volume and no weight loss, led to an adaptation of the GH-IGF-I-IGFBP axis previously described primarily in energy deficiency.

It is important to note that IGF-I and IGFBP responses to acute exercise may differ from those observed in response to training or to chronic changes in levels of physical activity. IGF-I and IGFBP-3, for example, increase to a small but significant degree with short bouts of exercise (3, 5, 45), but values return to pre-exercise levels fairly quickly. Similarly, Suikkari et al. (48) observed an increase in IGFBP-1 after 3 h of moderately intense cycle ergometer exercise and after 7.5 h of cross-country skiing.

It is also possible that our results were influenced by training-induced proteolysis of IGFBP-3. This phenomenon was first observed during pregnancy (19, 27). The proteolysis has been postulated to be a mechanism by which free IGF-I might be redistributed from the circulation to tissues, but increased IGFBP-3 proteolysis is found in conditions both of increased circulating IGF-I, e.g., pregnancy (22), and decreased circulating IGF-I, e.g., in gastric cancer patients and in patients with human immunodeficiency virus infection (18, 29). IGFBP-3 proteolysis does follow acute exercise (45).

The effect of exercise training on IGFBP-3 proteolysis is not yet known.

There still is substantial variability in the literature regarding mean values of circulating IGF-I. Our mean value (~225 ng/ml for all subjects, pre-exercise) tends to be lower than those reported by Le Roith (28); however, our mean values were quite consistent with those of Blum et al. (4). The reason for the variability in reported measurements of circulating IGF-I is not known, but recent preliminary work by Quarmby et al. (40) suggests that many IGF-I materials used as standards are variable in purity. Importantly, all pre- and postsamples in our study were analyzed simultaneously using the same standards.

These data suggest that local anabolic responses can occur despite whole body or systemic neuroendocrine adjustments that are commonly observed in true catabolic states (i.e., where weight loss is documented to occur). This is not unique to exercise training; for example, in hypoxia, overall growth is impaired and circulating IGF-I reduced while the growth of local tissues (e.g., lung or heart) is enhanced (35). Moreover, attenuating GH and circulating IGF-I by either hypophysectomy or immunotherapy (20, 54) does not inhibit the training response in rats. In fact, local muscle gene expression and production of IGF-I were increased following training in rats whose circulating IGF-I was undetectable. The interaction of the two systems, local target organ and systemic neuroendocrine, is not yet understood. However, we speculate that the neuroendocrine mechanisms may influence factors such as overall growth, body composition, and fat deposition rather than local muscle or other tissue responses to a specific exercise input.

It is noteworthy that IGFBP-4 was increased in both the control and the training groups. Little is known about the physiological role or regulation of IGFBP-4. It is elevated in elderly human subjects in whom IGF-I levels tend to be low (23), but in the present study, IGF-I levels were reduced only in the training group. The mechanism for the global increase in IGFBP-4 is not readily apparent. Our program started at the end of the school academic year, just after final examinations, in the early summer, and it is possible that these changes in and of themselves might influence some components of the GH-IGF-I axis in as-yet-undiscovered ways. The role of factors such as stress or season on GH secretory patterns have been examined, but there are very few studies in humans (31, 52) and no consistent relationships have emerged. Moreover, to our knowledge, there are no reports regarding seasonal effects, if any, on circulating levels of IGFBPs. Finally, we found no effect of training on IGF-II or on testosterone levels. Although these factors can be influenced by brief exercise (3, 10), their role in the overall response to training remains unknown.

These data also support the growing awareness that training effects vary considerably in magnitude from system to system. That the training intervention "succeeded" was corroborated by the 15.5% difference in energy expenditure between the two groups. The increase in muscle volume [note bene, endurance-type training increases in muscle volume are observed in both human and animal studies (16, 21)] was very consistent (observed in 17 of 20 subjects), but was relatively small (although a 3.6% change in muscle size over a short period of time is remarkable). Similarly, the increases in maximal oxygen uptake ($\dot{V}O_{2max}$) and peak oxygen pulse ($\dot{V}O_{2max}$/maximum heart rate) [reported elsewhere (17)] were also small (mean, 3.5% for $\dot{V}O_{2max}$ and 7.6% for peak O_2 pulse). This was not entirely unexpected because the adolescent males in the present study were relatively fit, and increases in $\dot{V}O_{2max}$ in response to training tend to be lower in individuals whose pretraining fitness levels are high (14).

In contrast, the reduction in GHBP and the increase in IGFBP-2 were in the range of 20–40%. In addition, circulating markers of bone formation [reported elsewhere (17)] increased substantially in the training subjects (osteocalcin by 15%, bone-specific alkaline phosphatase by 21%, and COOH-terminal procollagen peptide by 30%), with virtually no change in the control subjects. How these circulating signals relate to increase in local thigh muscle, or what effects these substantial changes in the GH-IGF-I axis have on other target organs, remains unknown.

Perspectives

Although reductions in circulating IGF-I have been observed in human subjects in whom exercise training was combined with volitional dietary restriction [e.g., female gymnasts (24)], we believe this is one of the first studies to demonstrate neuroendocrine catabolic-type responses in training subjects who were weight stable, not food restricted, and in whom an increase in muscle volume was demonstrated clearly. But a seeming paradox remains: how can the observation of catabolic-type responses to 5 wk of exercise training be reconciled with studies from this and other laboratories demonstrating that fitter individuals tend to have higher circulating levels of GH and/or IGF-I?

We speculate that there are at least two phases in the GH-IGF-I response to a training program: the first is an acute catabolic-type response initiated by lower GHBP. At some later point (presumably after 5 wk) and dependent on the nutritional and energy balance of the individual, a chronic anabolic adjustment of the GH-IGF-I axis occurs. During this initial phase, local muscle IGF-I might actually increase (12, 54) as circulating IGF-I falls, reflecting an important mechanistic role for autocrine/paracrine effects of IGF-I in the response to training.

Finally, our data also are relevant to current attempts to define a possible therapeutic role for growth hormones and other growth factors in a variety of clinical situations. Indeed, if some "downregulation" of these circulating factors is a necessary component of the complete adaptation to increased physical activity, then the timing of exogenous administration is critical. Moreover, the optimization of using exercise with (or without) exogenous growth factors must ultimately

rest on greater understanding of the interaction between local tissue growth responses to exercise and the seemingly paradoxical catabolic-type, neuroendocrine responses to brief exercise training observed in the present study in adolescent males and in our previous work in adolescent females (16).

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