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Exercise-induced changes in circulating growth factors with cyclic variation in plasma estradiol in women

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Hornum, Mette, Dan M. Cooper, Jo Anne Brasel, Alina Bueno, and Kathy E. Sietsema. Exercise-induced changes in circulating growth factors and cyclic variation in plasma estradiol in women. *J. Appl. Physiol.* 82(6): 1946–1951, 1997.—The effect of 10 min of high-intensity cycling exercise on circulating growth hormone (GH), insulin-like growth factors I and II (IGF-I and -II), and insulin-like growth factor binding protein 3 (IGF BP-3) was studied in nine eumenorrheic women (age 19–48 yr) at two different phases of the menstrual cycle. Tests were performed on separate mornings corresponding to the follicular phase and to the periovulatory phase of the menstrual cycle, during which plasma levels of endogenous estradiol (E_2) were relatively low (272 ± 59 pmol/l) and high ($1,112 \pm 407$ pmol/l), respectively. GH increased significantly in response to exercise under both E_2 conditions. Plasma GH before exercise (2.73 ± 2.48 vs. 1.71 ± 2.09 μ g/l) and total GH over 10 min of exercise and 1-h recovery (324 ± 199 vs. 197 ± 163 ng) were both significantly greater for periovulatory phase than for follicular phase studies. IGF-I, but not IGF-II, increased acutely after exercise. IGF BP-3, assayed by radioimmunoassay, was not significantly different at preexercise, end exercise, or at 30-min recovery time points and was not different between the two study days. When assayed by Western blot, however, there was a significant increase in IGF BP-3 30 min after exercise for the periovulatory study. These findings indicate that the modulation of GH secretion associated with menstrual cycle variations in circulating E_2 affects GH measured after exercise, at least in part, by an increase in baseline levels. The acute increase in IGF-I induced by exercise appears to be independent of the GH response and is not affected by menstrual cycle timing.

human growth hormone; insulin-like growth factor I; insulin-like growth factor II

THE OBSERVATION that exercise stimulates the release of human pituitary growth hormone (GH) suggests the possibility that exercise-induced changes in circulating growth factors might mediate some of the anabolic adaptations induced by exercise, such as muscle hypertrophy, bone mineralization, and local angiogenesis (4, 9, 21). In keeping with this, acute increases in circulating GH are recognized to be associated with heavy resistance-type exercises (24, 37), which induce increases in muscle size and strength. Acute increases in GH are also associated with endurance exercises such as running or cycling, at least when of sufficient intensity to result in an increase in blood lactic acid (13, 26, 34, 36, 38). Although resulting in a lesser increase in muscle volume than high-resistance exercise (11), endurance training also induces structural changes in muscle that may be considered anabolic in nature (31). A potential role for circulating growth factors in mediat-

ing this type of training effect is suggested by the findings that endurance-exercise training increases spontaneous GH secretion in young women (40), that the circulating level of insulin-like growth factor I (IGF-I), which is stimulated by GH secretion, correlates with exercise "fitness" in cross-sectional studies (21, 28), and that circulating IGF-1 levels are increased by endurance exercise training (29). Conditions modifying growth factor responses to either acute or repetitive exercise are, therefore, of interest with respect to both the potential for achieving the training effects of exercise and the mechanisms that mediate these effects.

Plasma estradiol (E_2) concentration is among the multiple factors recognized to regulate or modulate GH secretion, primarily by an increase in pulse amplitude. Serum concentration of endogenous E_2 has been correlated with integrated spontaneous GH secretion (17), peak amplitude of spontaneous GH pulse (12), with GH response to GH-releasing hormone (25), and with "ambulatory" GH levels (14). Because E_2 appears to modulate GH secretion, we hypothesized that the cyclic variation in endogenous E_2 in women throughout the menstrual cycle would also modify the acute exercise stimulation of GH and insulin-like growth factors. To test this, exercise-induced changes in GH were determined in premenopausal eumenorrheic women during paired tests in which endogenous E_2 levels were relatively high and low, associated with the periovulatory and early follicular phases of the menstrual cycle, respectively. In addition, the acute effects of exercise on blood levels of IGF-I, IGF-II, and insulin-like growth factor binding protein 3 (IGF BP-3) were also evaluated because these are regulated, in part, by GH and are known to play a role in tissue growth.

METHODS

Subjects. Healthy nonathletic premenopausal women were recruited from among employees of the Medical Center and from the surrounding community. All participants had a history of regularly spaced menstrual cycles without use of hormonal contraceptives for at least 1 yr before the study. All were nonsmokers who had no chronic medical problems, took no medications, and were not obese (i.e., body mass index <26 kg/m²). The protocol was approved by the institutional Human Subjects Committee, and subjects gave written informed consent before participation.

Protocol. Each subject completed a total of three exercise sessions. The first was a screening incremental exercise study to familiarize the subject with the testing environment and determine work rates corresponding to peak O_2 uptake ($\dot{V}O_{2peak}$) and lactic acidosis threshold (LAT). Subsequently, two studies were performed, which consisted of 3-min unloaded cycling and 10 min of constant work rate exercise at a

work rate corresponding to a standardized work intensity, midway between each subject's LAT and $\dot{V}O_{2\text{peak}}$. This exercise intensity was chosen because it results in an increase in blood lactic acid but can predictably be sustained by motivated volunteers for 10–15 min and has been shown to be effective in eliciting an acute increase in GH in young men (13).

Studies were done under two different conditions of endogenous E_2 : Low E_2 studies refer to those performed during the early follicular phase or *days 1–6* of the menstrual cycle, and High E_2 studies were performed near the expected time of ovulation, usually *days 12–13* of the menstrual cycle. Timing of the High E_2 study was estimated by dates that were based on self-reporting of the dates and lengths of the subjects' previous two menstrual cycles. Subjects were later excluded from analysis if plasma E_2 level on the day of the follicular phase study was greater than the upper limit of the laboratory's normal follicular phase range (514 pmol/l) or if the E_2 level for the periovulatory day did not exceed the value on the follicular phase day by at least 60%. Ordering of the two studies was neither standardized nor randomized but was determined by the constraints of scheduling studies on weekdays corresponding to appropriate dates in the subjects' cycles.

All studies were performed during morning hours after an overnight fast because spontaneous GH pulses are infrequent at this time. Before exercise, a catheter was placed in an antecubital vein and maintained patent with heparinized saline. Subjects then rested quietly for 30 min before data collection was begun. For 5 min before exercise, throughout exercise, and the first 5 min of recovery, subjects breathed through a mouthpiece connected to a turbine volume transducer for measurement of ventilatory volumes. P_{CO_2} , P_{O_2} , and partial pressure of N_2 were determined by mass spectrometry from a sample drawn continuously from a sideport on the mouthpiece. Data from the flowmeter and spectrometer were interfaced with a desktop computer for calculation of minute ventilation, O_2 uptake ($\dot{V}O_2$), and CO_2 output on a breath-by-breath basis as previously described (2). The electrocardiogram was monitored continuously, and heart rate was calculated from the R-R interval.

Blood was sampled from the indwelling catheter at rest in duplicate, at the midpoint and end of the 10 min of exercise, and at 10-min intervals for 1 h of recovery. Blood samples were immediately iced, and serum was separated within 2 h of drawing and frozen at -20°C until assayed. All samples for a given subject were batched for assay at the same time. For each study, samples were obtained for E_2 at rest, for serum GH, IGF-I, IGF-II, and whole blood lactate at all sampling times, and for IGF BP-3 at rest, end exercise, and 30 min recovery. For four subjects, hematocrit was also determined at each sampling time.

Laboratory analysis. GH concentrations were determined for seven subjects by radioimmunoassay (RIA) by utilizing World Health Organization standard no. 66/217, antisera generated in-house, and human growth hormone (hGH) from the National Institute for Diabetes and Digestive and Kidney Diseases for iodination purposes (intra-assay and interassay variability <10 and 12.6%, respectively, sensitivity 0.5 $\mu\text{g/l}$). For the final four subjects, GH assays were performed by two-site time-resolved immunofluorometric assay (33). IGF-I was assayed by RIA with antibodies provided by the National Institutes of Health and standards from Bachem (intra-assay and interassay coefficients of variation 3.3 and 5.4%, respectively) after acid ethanol extraction. IGF-II was assayed by RIA by using monoclonal antibodies to rat IGF-II (Amano; Troy, VA), which is cross-reactive with human IGF-II (intra-

assay and interassay coefficients of variation 7 and 10%, respectively). IGF BP-3 was determined for each sample by RIA (Nichols Institute) and also by Western blot analysis as described by Hossenlopp et al. (19). Serum E_2 was determined by RIA. Whole blood lactate was determined by automated analyzer by utilizing an enzymatic electrode (Yellow Springs Instruments, Yellow Springs, OH), and hematocrit was measured by capillary tube centrifugation.

Data analysis. Baseline values for GH, IGF-I, and IGF-II were taken as the average of two resting samples drawn for each study. The GH values from samples drawn during exercise and the 1-h recovery period were plotted, and the integrated GH response was calculated as the geometric area under the resulting curve (AUC) without additional modeling of the response. Peak GH values, defined as the higher of the end-exercise or the 10-min recovery time sample, were also identified for each study. To determine whether there was an increase in circulating growth factors after exercise, peak values were compared with resting values by using analysis of variance for repeated measures. Levels of IGF BP-3 determined by Western blot techniques were expressed as percentages of the preexercise baseline values, and the paired *t*-test was used to determine whether the 30-min postexercise value differed from baseline. The paired *t*-test was used to test for differences between Low E_2 and High E_2 studies with respect to cardiorespiratory response to exercise ($\dot{V}O_2$, heart rate, and blood lactate) and responses of circulating growth factors [GH (as AUC) peak IGF-I, peak IGF-II] or IGF BP-3 to exercise.

Data are presented as means \pm SD unless otherwise indicated. Hormone levels are presented as actual plasma concentrations, without correction for possible changes in plasma volume. Statistical significance was identified when $P < 0.05$ for analyses of variance. Holm's multiple-test procedure (18) was used to maintain an overall $P \leq 0.05$ when *t*-tests were used in analysis of more than one non-independent variable.

RESULTS

Eleven women meeting inclusion criteria were studied. For 9 of the 11, E_2 levels showed the expected differences on the periovulatory and follicular study days (E_2 levels were $1,112 \pm 408$ and 272 ± 59 pmol/l for periovulatory and follicular phase studies, respectively). For the other two subjects, E_2 values were similar on the two study dates, indicating either anovulatory cycles or ovulatory times that differed from what was assumed. These two subjects were therefore excluded from analysis.

Mean age for the 9 subjects included in the analysis was 34 ± 10 yr (range 19–48 yr), height 165 ± 8 cm (range 150–176 cm), weight 55 ± 8 kg (range 49–72 kg), and body mass index 20.3 ± 2.3 kg/m^2 (range 18.3–25.5 kg/m^2). Their $\dot{V}O_{2\text{peak}}$ values averaged 34.0 ± 5.4 $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}$ body weight $^{-1}$. None of the subjects was engaged in a program of athletic training or in competitive sport.

There were no significant differences for resting or end-exercise $\dot{V}O_2$, heart rate, or blood lactate between the High E_2 and Low E_2 studies. The end-exercise $\dot{V}O_2$ values for the constant work rate exercise averaged 1.65 and 1.62 l/min for Low E_2 and High E_2 study days, respectively, representing a mean of $86 \pm 7\%$ of the subjects' $\dot{V}O_{2\text{peak}}$ values (Fig. 1). End-exercise whole

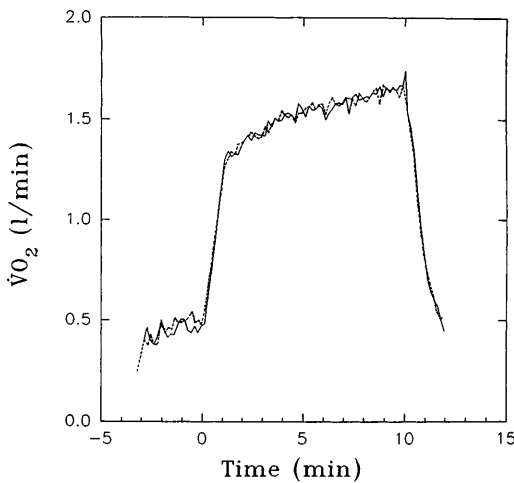


Fig. 1. Mean values for oxygen uptake ($\dot{V}O_2$) in response to 10 min of high-intensity cycling exercise on low endogenous estradiol (E_2 ; broken line) and high E_2 (solid line) study days. There was no significant difference between 2 study conditions for either baseline or end-exercise $\dot{V}O_2$.

blood lactate averaged 5.3 ± 1.2 and 5.3 ± 1.5 mmol/l for the Low E_2 and High E_2 study days, respectively, consistent with exercise performed above the LAT. Hematocrit was not significantly different between the two E_2 conditions (36.6 ± 2.1 and 38.0 ± 0.9 at rest and 41.0 ± 2.2 and 42.3 ± 1.5 at peak exercise for Low E_2 and High E_2 , respectively).

Growth factor responses. Circulating GH increased significantly in response to exercise under both study conditions (Fig. 2). Both the baseline GH and the GH response to exercise, expressed as AUC, were greater for the High E_2 than for the Low E_2 studies (baseline GH, 2.73 ± 2.48 vs. 1.71 ± 2.09 $\mu\text{g/l}$; AUC, 324 ± 199 vs. 197 ± 163 ng for High E_2 and Low E_2 studies, respectively). An acute increase in IGF-I was evident after exercise in both Low E_2 and High E_2 studies (Fig. 3). IGF-II did not change significantly between baseline and end exercise in either condition (Table 1), however, and there was no significant effect of E_2 conditions on baseline or end-exercise levels of either IGF-I or IGF-II.

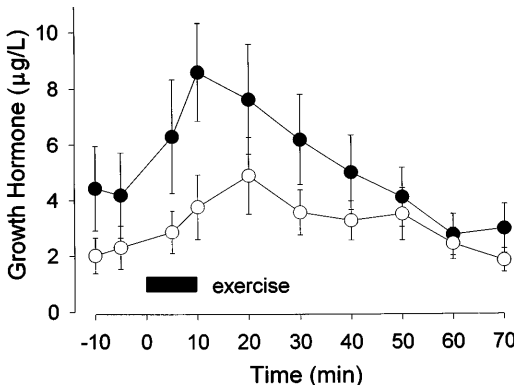


Fig. 2. Mean values \pm SE for growth hormone (GH) for 9 subjects in response to 10 min of high-intensity exercise (0–10 min) and 1-h recovery on Low E_2 (open symbols) and High E_2 (closed symbols) study days. Peak GH values were significantly higher than preexercise baseline for both study conditions.

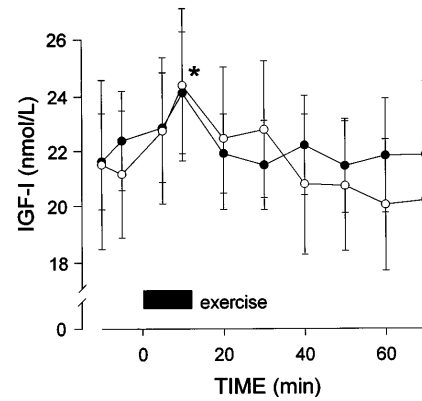


Fig. 3. Mean values \pm SE for insulin-like growth factor-I (IGF-I) for 9 subjects in response to 10 min of high intensity exercise (0–10 min) and 1 h recovery on Low E_2 (open symbols) and High E_2 (closed symbols) study days. Peak IGF-I was significantly higher than baseline values for both study conditions.

Although the level of IGF BP-3 (measured by RIA) tended to be higher at end exercise than at baseline, this difference was not statistically significant (Table 1). Neither was there any significant difference in IGF BP-3 levels between the High and Low E_2 studies. Western blot analysis of IGF BP-3 showed a trend toward increased levels at the 30-min recovery time point. This increase was not statistically significant for samples from the Low E_2 studies but was significant for the High E_2 studies.

DISCUSSION

The effects of acute and chronic exercise on circulating growth factors are the focus of considerable attention because of the potent effects of these hormones on body composition and their potential roles in mediating such processes as maintenance or hypertrophy of muscle mass, bone mineralization, and local angiogenesis (4, 9,

Table 1. Effect of 10 min high-intensity exercise on IGF-I, IGF-II, and IGF BP-3 for testing done at 2 times in menstrual cycle with differing E_2 levels

Test Condition	Preexercise	End Exercise	30-Min Recovery Time Point
Low E_2			
IGF-I, nmol/l	21 ± 8	$24 \pm 8^*$	21 ± 8
IGF-II, nmol/l	105 ± 16	112 ± 16	106 ± 8
IGF BP-3, nmol/l (by RIA)	77 ± 14	84 ± 14	77 ± 11
IGF BP-3, %baseline (by Western blot)	100	103 ± 32	127 ± 24
High E_2			
IGF-I, nmol/l	22 ± 8	$24 \pm 7^*$	22 ± 5
IGF-II, nmol/l	106 ± 15	112 ± 15	104 ± 13
IGF BP-3, nmol/l (by RIA)	81 ± 14	88 ± 18	74 ± 7
IGF BP-3, %baseline (by Western blot)	100	122 ± 17	$198 \pm 68^*$

Values are means \pm SE; $n = 9$ subjects. IGF-I and IGF-II, insulin-like growth factor I and II, respectively; IGF BP-3, IGF binding protein 3; E_2 , estradiol; RIA, radioimmunoassay; Low E_2 , early follicular phase ($E_2 = 272 \pm 59$ pmol/l); High E_2 , periovulatory phase ($E_2 = 1,112 \pm 407$ pmol/l). There was no significant difference between 2 test conditions for any of values shown. $*P < 0.05$ vs. preexercise level.

21), which are also processes characteristic of exercise training (31). That E_2 can modulate GH release is supported by studies in which spontaneous GH secretion in men and women (17), or in women during varying menstrual cycle phases (12), correlated with plasma E_2 concentrations. Similar correlations are reported for hormonally stimulated GH secretion (25). Exogenous E_2 also increases GH secretion in men (14, 41) and postmenopausal women (10, 39) and is effective for "priming" prepubertal children before exercise stimulation for evaluation of GH secretory status (27). Whether these observations reflect effects at the hypothalamus or anterior pituitary remains to be clarified.

Responses of GH to physiological or pharmacological stimuli are characterized by considerable intrasubject variability and appear to be affected by age (8, 17, 25, 30). The cyclic changes of E_2 in premenopausal women, therefore, provide a convenient model for investigating the effects of E_2 on GH responses within the same subjects without the confounding effects of age and group heterogeneity. Reported effects of menstrual cycle variation of E_2 on exercise-induced GH responses in women are inconsistent, however. Although resting levels of GH obtained under well-controlled basal conditions are generally found to be stable throughout the menstrual cycle, plasma GH from ambulatory women has been noted to increase around the midpoint of the cycle near the time of ovulation (14, 15, 42), when there is a peak of E_2 . Hansen and Weeke (16) subsequently reported that the mean GH response to exercise at this time was higher than when measured in the early follicular phase. Bonen et al. (3) found no significant difference in integrated GH responses to exercise in women tested during the follicular and luteal phases; however, this study did not include measures during midcycle. Kanaley et al. (20) found no statistically significant difference between GH responses to exercise at three points of the menstrual cycle, although the mean value reported for integrated GH associated with exercise during the late follicular phase was 65% higher than that during the early follicular phase. The above findings and those of the present study suggest that transient increases in E_2 can amplify the GH response to exercise. Clearly, other factors are also active in regulating the GH response to exercise, and it cannot be excluded that other unmeasured factors covarying with E_2 at the two menstrual cycle phases studied were responsible for the differences in GH response. GH responses to exercise are reported to be as high (20) or higher (7) in amenorrheic female athletes, with chronically depressed plasma E_2 levels, than in age-matched eumenorrheic women, perhaps reflecting the effect of nutritional status and tissue responsiveness to GH on circulating GH levels. Similarly, men may have as high (30) or higher (5) increases of GH in response to exercise than age-matched women.

Although the AUC for GH after exercise in the present study was significantly greater in High E_2 than Low E_2 studies, this could be due, at least in part, to higher baseline values. The finding of elevated values of GH before exercise is consistent with the previously

reported observation of ambulatory levels of GH for young women, which are higher than those measured under true basal conditions (14, 15, 42).

Several studies have reported an acute increase in circulating IGF-I in response to cycling exercise (6, 13, 23). Consistent with these reports, in the present study the increase in IGF-I was coincident with the increase in GH and so cannot be attributed to the GH pulse. This finding contrasts with the failure to elicit an increase in IGF-I in women performing heavy-resistance exercise, despite an acute increase in GH (22).

The observed changes in circulating IGF-I must reflect rapid changes in the balance among 1) release into the circulation from the liver and/or other tissues, 2) distribution within the circulating blood, and 3) removal from the circulation. Exercise has been shown to be accompanied by the rapid "autotransfusion" of hemoconcentrated blood from the spleen into the central circulation (13a), increased blood flow to the exercising muscle, and loss of plasma water from the vascular space (7a). Each of these processes might explain, in part, an increased IGF-I concentration. Measurements of circulating concentrations alone are not sufficient to distinguish between these mechanisms, nor is it clear whether the small transient increase in concentration observed is biologically significant. The transient nature of the increase suggests that hemodynamic or metabolic effects of exercise per se likely play a role. Because the concentration of a humoral agent in perfusing blood is likely to be relevant to the effect of the agent on target tissues, regardless of the mechanism for the change in concentration, actual measured concentrations were used in this analysis, rather than attempting to modify the measured concentrations to account for presumed changes in plasma volume.

Few data are reported regarding the effect of exercise on IGF-II. Our finding of no significant increase in IGF-II contrasts with that of Bang et al. (1), who report a 50% increase in IGF-II in six subjects 10 min into cycling exercise, corresponding to 60% $\dot{V}O_{2\max}$. Resting values of IGF-II in that report were considerably lower than those in the present study. These disparate findings may reflect methodological differences in the IGF-II assay, as well as differences in the intensity and duration of the exercise stimulus.

The protein IGF BP-3 is the most abundant of the binding proteins associated with circulating IGF-I and -II (32). Two methods were used to assay IGF BP-3 because of a recent report in which binding protein levels determined by migration pattern decreased after exercise without a reduction in the levels detected by immunoassay techniques (35), a combination of findings tentatively attributed to proteolysis of the binding protein. Western blot data in the present study, however, suggest an increase rather than a decrease in the amount of intact protein 30 min after exercise and contrast both with the RIA determinations on the same samples and with previous Western blot determinations of IGF BP-3 after exercise reported from this laboratory (35). Although it is of interest that the increase was only significant for the High E_2 studies,

there is little basis for speculating whether the finding is related to higher circulating levels of E_2 , of GH, or neither.

In summary, acute increases in GH and IGF-I, but not IGF-II, are demonstrated after a short bout of high-intensity exercise in healthy young women. Mean baseline, as well as the total AUC for GH after exercise, was significantly greater under conditions of relatively high, compared with low, endogenous E_2 in the same subjects. The increase in IGF-I occurred essentially coincidentally with the GH increase, which is consistent with a GH-independent effect of exercise on IGF-I, and was not affected by menstrual cycle timing.

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