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β -Endorphin/ β -lipotropin release and gonadotropin secretion after acute exercise in normal males

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ELIAS, ALAN N., KRISH IYER, M. R. PANDIAN, PAUL WEATHERSBEE, SERGIO STONE, AND JONATHAN TOBIS. *β -Endorphin/ β -lipotropin release and gonadotropin secretion after acute exercise in normal males.* J. Appl Physiol. 61(6): 2045–2049, 1986.—The plasma β -endorphin (β -EP) and β -lipotropin (β -LPH) response to acute exercise and the relationship of these opioid peptides to basal and luteinizing hormone-releasing hormone (LRH)-stimulated luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion was studied in eight normal male volunteers. Acute exercise resulted in a rise in plasma β -LPH levels that returned to base line when measured 60 min after exercise. Plasma β -EP levels did not demonstrate any rise when measured immediately after 20 min of exercise or at 60 min after exercise. Serum LH concentrations in individual volunteers declined to nadir values 60–180 min after exercise after which they showed a rebound to levels higher than the preexercise values in three of five volunteers in whom nadir LH levels were attained before the final (180 min) measurement. Serum FSH concentrations were unaltered by exercise. Acute exercise similarly did not alter the LH/FSH response to exogenous LRH stimulation. Pretreatment of the volunteers with the narcotic antagonist, naloxone, failed to alter the postexercise or LRH-stimulated LH and FSH release. The data suggest that β -EP does not exert a suppressive effect on LH secretion after acute exercise in normal human males. Whether the suppression of LH secretion after acute exercise in unconditioned males is due to factor(s) cosecreted with β -LPH, an increase in brain β -EP or to alternate mechanisms such as alteration in central dopaminergic or GABAergic tone remains to be established.

luteinizing hormone; follicle-stimulating hormone; opioid peptides; naloxone

PHYSICAL ACTIVITY is known to stimulate the release of a number of anterior pituitary hormones such as growth hormone, prolactin, and adrenocorticotropin and to depress the secretion of the gonadotropic hormones (8, 12, 20). The endogenous opioid peptide β -endorphin (β -EP) is elevated after acute (13) and endurance exercises (4) and may be implicated in the genesis of the so-called runner's high (1).

A role for the endogenous opioids in the regulation of gonadotropin secretion is well established (15, 23). Endogenous opioids and their analogues decrease the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (2, 15, 23), whereas opioid antagonists elevate the secretion of the gonadotropic hormones (19).

To date, most studies of the effects of exercise on gonadotropic function have focused primarily on the effects in female endurance athletes (6, 9, 10). The effects of acute exercise on gonadotropic function in males has not been as intensively investigated. The present study was conducted to investigate the relationship between β -endorphin (β -EP) and β -lipotropin (β -LPH) release with acute exercise and the effects, if any, on the basal and luteinizing hormone-releasing hormone (LRH)-stimulated gonadotropin release in unconditioned male volunteers.

MATERIALS AND METHODS

Population

Eight normal male volunteers aged between 20 and 41 yr (means $\pm$ SD: 26.8 ± 8.6 yr) participated in the study. The volunteers were physically unconditioned premedical and medical students and house officers known to be in excellent health. The heights of the volunteers ranged from 165 to 183 cm (means $\pm$ SD: 175.6 ± 6.1 cm). The weights ranged from 61.4 to 80 kg (means $\pm$ SD: 71.3 ± 5.7 kg). None of the volunteers were taking any medication for at least 6 mo preceding the study, which was conducted in four phases performed in random sequence. Each phase of the study was performed ~ 1 wk apart at 1,300 h after the subjects had been on a 4- to 6-h fast. All subjects remained in the same state of physical conditioning during the entire study. Approximately 20 ml of blood were withdrawn during each phase of the study.

Phase 1. Control Study

After a 30-min period of recumbency, blood was removed from the antecubital vein via an indwelling heparinized catheter for measurement of base-line concentrations of LH, FSH, β -EP, and β -LPH. The volunteers then received an intravenous injection of 100 μ g LRH (Ayerst Laboratories, New York, NY), and blood was removed at 20, 30, and 60 min later for measurement of LH and FSH concentrations. The 100- μ g dose was chosen because it is the standard stimulatory dose used to assess gonadotropin reserve in humans (16, 22, 24).

Phase 2. Exercise on Treadmill

Base-line measurements of serum LH, FSH, β -EP, and β -LPH were made as in *phase 1* of the study. The

subjects were then exercised on a treadmill for 20 min at 80% of their predicted maximum heart rates. The predicted maximum was obtained as previously described by subtracting the age of the volunteer from 220 (11). The speed and inclination of the treadmill was adjusted so that the heart rate was maintained as close as possible to the 80% predicted maximum. Each subject was gradually brought up to the 80% predicted maximum heart rate over a 5-min period. At the end of the exercise period, with the subjects in recumbency, blood was withdrawn through the intravenous catheter for measurement of LH, FSH, β -EP, and β -LPH. The volunteers then received an injection of 100 μ g LRH, and blood was sampled at 20, 30, and 60 min after the LRH injection for measurement of LH and FSH as in *phase 1*. β -EP and β -LPH measurements were also made 60 min after LRH to determine whether they had returned to baseline levels.

Phase 3. Naloxone and Exercise

Base-line measurements of serum LH, FSH, β -EP, and β -LPH were made as in *phase 2*. The volunteers were then given an intravenous bolus injection of 1 mg of naloxone. The protocol was then carried out as in *phase 2*.

Phase 4

This phase was conducted as in *phase 2*. However, at the end of the exercise period, blood was withdrawn at 15, 30, 60, 90, 120, and 180 min for the measurement of FSH and LH. An LRH stimulation test was not performed in this part of the study.

Radioimmunoassays

LH and FSH. Radioimmunoassays for LH and FSH were performed as previously described using radioimmunoassay kits (Diagnostic Products, Los Angeles, CA) (7). Blood for gonadotropin assay was collected in siliconized glass tubes containing no preservatives or anticoagulants. Sensitivities of the assays for FSH and LH were 1 and 1.5 mIU/ml, respectively. Intra-assay coefficients of variation for low and stimulated values of FSH were 5 and 2%; coefficients of variation for low and stimulated values of LH were 6 and 4%. Corresponding interassay coefficients of variation were 6 and 3% for FSH and 7 and 6% for LH.

β -EP and β -LPH. The β -EP and β -LPH measurements were made on blood that was collected in polypropylene tubes containing ethylenediaminetetraacetic acid (EDTA) and assayed by Nichols Institute (San Juan Capistrano, CA) using a modification of the radioimmunoassay procedure described by Carr et al. (3). To eliminate nonspecific interfering factors in the radioimmunoassay, the plasma samples were routinely extracted using silica (Prepak 500, Waters Associates, Milford, MA) before radioimmunoassay. In a typical assay, 1 ml of plasma was mixed with 75 mg of silica and vortexed for 10 min at room temperature. After centrifugation the supernatant was discarded. The peptide adsorbed to sil-

ica was washed twice with distilled water and eluted with 1 ml of acidified aqueous acetone (50% acetone vol/vol, 49% water vol/vol, and 1% of 1 N hydrochloric acid). The elution was repeated with an additional 1 ml of acidified acetone. The pooled eluate was dried under N_2 , and the dried eluate was reconstituted with 0.5 ml of assay buffer (0.1 M sodium phosphate, pH 7.4, 0.05 M sodium chloride, 0.01 M EDTA, 2% aprotinin (Trasylol) (vol/vol), and 0.05% crystalline bovine serum albumin). After reconstitution and centrifugation, 0.2 ml of clear supernatant was mixed with 0.2 ml of anti-endorphin (rabbit) and incubated at 4°C. After 20 h of incubation, 0.1 ml of ^{125}I - β -EP was added and the incubation continued for 20 h at 4°C. At the end of the incubation 0.1 ml of 4% normal rabbit serum was added as carrier protein. The bound-to-free separation was achieved using a second antibody (goat anti-rabbit γ -globulin) accelerated by polypropylene glycol. The radioimmunoassay is sensitive to 1.6 pg/tube. Interassay variation is 16% and intraassay variation is 9.2%.

The anti-endorphin used in this assay has equimolar cross reactivity with β -EP and β -LPH and has <1% cross reactivity with leu-enkephalin, met-enkephalin, α -endorphin, γ -endorphin, and adrenocorticotropin. Since the antibody has cross reactivity with lipotropin, the silica extracted samples were also assayed after fractionation on a calibrated Sephadex G-25 column (0.5 $\times$ 40 cm). The column was eluted with the assay buffer. The fractions corresponding to β -LPH and β -EP were pooled separately and assayed by the above procedure. For the column chromatography studies, 3–5 ml of samples were extracted and reconstituted in 0.5 ml volume and loaded onto the column for separation. After separation each fraction was pooled and concentrated in a Speed Vac Concentrator (Savant) and assayed by radioimmunoassay. Extraction efficiency for β -EP was 71% and for β -LPH was 68%. The values for the samples that went through the column were corrected for loss in the column (10%). The rest of the samples were corrected only for extraction efficiency (~70%).

Statistical Analysis

Statistical analysis was performed using analysis of variance, linear regression analysis, and Student's *t* tests for paired and grouped data. Level of significance was *P* < 0.05.

RESULTS

Effect of Exercise on Heart Rate

All results are expressed as means $\pm$ SD. The 80% predicted maximum heart rate in the volunteers was 154.9 ± 8.5 beats/min. The actual rate achieved during exercise was 154.1 ± 8.6 beats/min. All the volunteers tolerated the exercise without experiencing any untoward effects.

Effect of Exercise on Base-Line LH/FSH Concentrations

Serum LH and FSH concentrations immediately after exercise (20 min) were not significantly different from

the preexercise levels during any phase of the study. Preexercise LH levels in phases 2–4 were 5.5 ± 2.3 , 4.5 ± 3.4 , and 4.3 ± 2.0 mIU/ml, respectively. Corresponding values obtained 20 min after exercise were 5.2 ± 2.0 , 5.7 ± 3.3 , and 4.0 ± 1.6 mIU/ml. Pretreatment of the volunteers with 1 mg of naloxone before exercise in phase 3 also failed to influence the postexercise LH and FSH concentrations (Table 1).

In phase 4 of the study where gonadotropin measurements were made up to 180 min after exercise, serum LH concentrations declined from preexercise values of 4.3 ± 2.0 to nadir values of 2.8 ± 1.14 mIU/ml ($P < 0.05$). Nadir LH values were obtained 60–180 min after exercise. In three volunteers the lowest LH values were recorded 180 min after exercise. In the remaining five volunteers serum LH concentrations rebounded to higher values (7.1 ± 1.8 mIU/ml) exceeding base line in three of five volunteers within 30–60 min after reaching the nadir value. Because of the variation in the time that the nadir LH concentration occurred in different volunteers, the mean LH concentration at different times of the group as a whole showed no significant change after exercise (Table 2). Serum FSH concentrations were not significantly altered by exercise. Nadir postexercise serum FSH concentrations (2.0 ± 0.9 mIU/ml) were similar to the preexercise concentrations (2.6 ± 1.0 mIU/ml, $P = \text{NS}$).

Effect of Exercise on LRH-Stimulated LH and FSH

Peak serum LH concentrations after LRH injection were not significantly different before and after exercise. Peak preexercise LRH-stimulated LH concentrations were 52.9 ± 29.8 mIU/ml vs. peak postexercise LH concentrations of 53.1 ± 24.1 mIU/ml ($P = \text{NS}$). Corresponding peak LRH-stimulated FSH concentrations were 5.4 ± 3.0 vs. 5.0 ± 2.5 mIU/ml ($P = \text{NS}$).

Effect of Exercise and Naloxone Premedication on Plasma β -EP and β -LPH Concentrations

Plasma β -LPH concentrations showed a significant rise when measured immediately after exercise in phases

TABLE 1. Base-line and LRH-stimulated LH serum concentrations

Phase	Preexercise	0 min Post-exercise	Peak LH Response
1	NP	NP	52.9 ± 29.8
2	5.5 ± 2.3	5.2 ± 2.0	53.1 ± 24.1
3	4.5 ± 3.4	5.7 ± 3.3	45.4 ± 17.6
4	4.3 ± 2.0	4.0 ± 1.6	NP

Values are means $\pm$ SD and are given in mIU/ml. LRH, luteinizing hormone-releasing hormone; LH, luteinizing hormone; NP, not performed.

TABLE 2. Serum LH concentrations in phase 4

Pre-exercise	Postexercise, min						
	0	20	30	60	90	120	180
	4.3 ± 2.0	4.4 ± 1.3	3.6 ± 1.2	3.4 ± 1.5	4.2 ± 2.3	4.9 ± 2.2	4.4 ± 2.3
							4.6 ± 2.7

Values are means $\pm$ SD and are given in mIU/ml. LH, luteinizing hormone.

2–4 of the study (Fig. 1) Naloxone premedication (phase 2) failed to blunt the β -LPH elevation. In phases 2–4 plasma β -LPH concentrations were 23.0 ± 5.1 , 21.0 ± 3.6 , and 19.1 ± 3.4 pg/ml before exercise; corresponding plasma β -LPH concentrations after 20 min of exercise were 30.3 ± 5.5 , 30.0 ± 7.6 , and 25.6 ± 6.5 pg/ml ($P < 0.01$). The elevated β -LPH concentrations in the plasma returned to base-line levels when measured at 60 min after exercise (e.g., 25.1 ± 3.6 mIU/ml in phase 1). Plasma β -EP concentrations did not show a demonstrable elevation when measured either immediately or at 60 min after exercise (Fig. 1).

DISCUSSION

The present study demonstrates that plasma β -LPH is released after acute exercise. This elevation of plasma β -LPH is not associated with a parallel increase in plasma β -EP concentrations. Our data are in contrast to the observations of Gambert et al. (13) who reported a rise in β -EP after acute exercise on a treadmill in 9 unconditioned volunteers (5 men and 4 women). Since Gambert et al. (13) did not measure β -LPH separately from β -EP, one explanation for the discrepancy in their findings and our own may be that β -EP antisera that they used, which had 60% cross reactivity with β -LPH, would show increased β -EP immunoreactivity after exercise that was actually due to β -LPH. The increase in plasma β -LPH after exercise in our study returned to base-line values 60 min after exercise, suggesting that acute exercise does not produce a prolonged increase in endogenous opioid secretion once the stimulus is discontinued.

Our inability to demonstrate a rise in β -EP with acute exercise may also be related to the intensity and duration

FIG. 1. Plasma β -lipotropin (β -LPH) and β -endorphin (β -EP) concentrations before (open bars) and after (shaded bars) 20 min of exercise in phases 2–4. Values are means $\pm$ SD. * $P < 0.01$.

of the exercise in our volunteers and their level of physical conditioning. There is some evidence to suggest that there may be a difference in endogenous opioid release in the untrained volunteer and the trained athlete (3, 4). Carr et al. (3) have shown that physical conditioning facilitates the exercise-induced secretion of β -EP/ β -LPH, at least in women runners. The effect of physical conditioning is also apparent on the release of other opioidergic peptides such as met-enkephalin. Grossman et al. (14) showed no effect of acute exercise on met-enkephalin release in normal male volunteers who exercised on a bicycle ergometer. This contrasts with the observations of Howlett et al. (17) who demonstrated a significant increase in met-enkephalin release in ~50% of women who were physically unconditioned. After physical conditioning this pattern of met-enkephalin release was completely abolished. Studies such as these serve to emphasize the possible contributions of gender and physical conditioning on endogenous opioid release in humans.

Immediately after exercise, the secretion of LH was not significantly different from the preexercise base-line values. However after exercise, serum LH concentrations continued to decline and reached nadir values 30 to 180 min postexercise, suggesting a possible inhibitory effect of exercise on LH secretion. Since the rise in β -LPH preceded the fall in plasma LH concentrations, it is possible that β -LPH or cosecreted factor(s) may be responsible for the decrease in endogenous LH secretion. Since the rise in β -LPH preceded the fall in serum LH concentrations, and since β -LPH per se has not been shown to inhibit LH secretion, the rise in β -LPH with exercise may be an associated rather than a causative event in the decrease of serum LH after acute exercise. In view of the fact that β -EP levels were unchanged after treadmill exercise, the decrease in serum LH after acute exercise could involve other factors that regulate LRH release, such as alteration in dopaminergic or GABAergic tone (18, 21). Our data do not exclude the participation of elevated brain β -EP or other endogenous opioids as a factor responsible for the depression of LH secretion after acute exercise. However the failure of naloxone to modify the postexercise LH concentrations favors a nonopioidergic mechanism for the decrease in LH secretion after exercise. Since we did not sustain opioid blockade with a continuous infusion of naloxone after the bolus injection of this drug, it is possible that complete blockade of opioid receptors may not have been achieved. Other investigators however, have shown that the administration of naloxone to women with exercise associated amenorrhea does not produce an increase in LH levels that would be expected if increased opioid secretion was inhibiting LRH secretion (5). Furthermore, the rebound in serum levels after reaching nadir values after exercise indicates activation of compensatory mechanisms to maintain LH at near normal levels.

Whether the suppression of LH secretion after acute exercise in unconditioned males is due to factor(s) cosecreted with β -LPH secretion or to alternate mechanisms, such as an increase in brain β -EP or other opioidergic

peptides, or to a change in central dopaminergic or GABAergic tone remains to be established.

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