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Effects of follicular phase exercise on luteinizing hormone pulse characteristics in sedentary eumenorrhoeic women

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Summary

OBJECTIVE Current studies reveal little regarding the inception of exercise-induced LH changes during physical training. This study aimed to assess the susceptibility of the hypothalamic–pituitary axis to the acute physical stress of exercise in untrained, physically inactive women. The acute effects of submaximal endurance exercise upon the pulsatile LH secretion in the follicular phase were compared with those accompanying leisurely strolling for a similar time period.

SUBJECTS All subjects were eumenorrhoeic, as determined by biphasic temperature patterns, detection of the urinary LH surge, and mid-luteal serum progesterone levels. Subjects were not physically active and had little history of strenuous exercise ($Vo_2max = 38{\cdot}0 \pm 1{\cdot}8$) (mean ± SEM) ml/kg/min).

DESIGN All women completed a 13·5-hour pulsatility test which included three consecutive 20-minute runs on a treadmill at 50, 60 and 70% of the subjects' maximum oxygen uptake ($n = 16$). Six of these same subjects completed a separate test on another occasion in which one hour of leisurely strolling was substituted for exercise. Blood was sampled every 10 minutes via an indwelling cannula for 4·5 hours before and 8 hours after one hour of exercise and or strolling.

MEASUREMENTS A pulse algorithm (Pulsar) was used to quantify LH pulse characteristics.

RESULTS Exercise produced no significant effects upon LH pulse frequency or mean serum LH concentration. However, exercise of moderate intensity caused a significant increase in LH pulse amplitude ($P < 0{\cdot}05$). Strolling produced no significant changes in LH secretion.

CONCLUSION Acute exercise of moderate intensity in the follicular phase of untrained women is an insufficient stimulus to inhibit the GnRH pulse generator in the post-exercise period, yet may produce a slight stimulatory effect on the amount of LH released per pulse

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While strenuous endurance training is associated with an increased prevalence of secondary amenorrhoea (Feicht *et al.*, 1978; Sanborn *et al.*, 1982), anovulation (Pirke *et al.*, 1990), and luteal phase defects (Bullen *et al.*, 1985; Beitins *et al.*, 1991), the mechanisms involved are not fully understood. Presumably, reproductive hormonal disturbances involve a central mechanism whereby a single stress or many stressors associated with exercise training impinge(s) upon the functioning of the gonadotrophin-releasing hormone (GnRH) pulse generator leading to an alteration in luteinizing hormone (LH) secretion, and ultimately to reduced gonadotrophic support to the ovary. Most (Baker 1981; Ronkainen, 1985), but not all (Loucks *et al.*, 1989; Boyden *et al.*, 1984) studies of females with exercise-induced amenorrhoea have found low levels of gonadotrophin secretion when compared to sedentary eumenorrhoeic women. Studies of basal LH pulse characteristics have shown a chronic suppression of LH pulse frequency in severely amenorrhoeic and oligomenorrhoeic runners (Veldhuis *et al.*, 1985; Loucks, 1989) and in anovulatory athletes (Pirke *et al.*, 1990). A slowed LH pulse frequency along with decreased (Cumming *et al.*, 1985a) or increased (Loucks, 1989) pulse amplitude have been reported in eumenorrhoeic athletes, and eumenorrhoeic athletes with low luteal phase urinary pregnenadiol glucuronide concentrations, respectively. Regarding the acute effects of exercise, in trained eumenorrhoeic women who exercised in the mid to late follicular phase, an immediate, post-exercise reduction in LH pulse frequency (Cumming *et al.*, 1985b) and in another instance, amplitude (Keizer *et al.*, 1987) have been reported. Based on these data, it is conceivable that the acute effects of exercise on LH secretion gradually become chronic as training progressively increases. However, studies of basal or post-exercise LH secretion in already well trained

Table 1 Characteristics of subjects in exercise and strolling studies ($n = 16$)

	Age (years)	Height (cm)	Weight (kg)	Percentage body fat	VO_2 max (l/min)	VO_2 max ml O_2/kg BW	Age of menarche (years)	Time since menarche (years)
Mean	27	161·4	54·1	26·7	2·15	38·0	11·3	14·1
(SEM)	(1)	(2·7)	(3·7)	(1·0)	(0.12)	(1·8)	(1·1)	(1·5)
Range	(19–35)	(153–173)	(44–67)	(21–32)	(1·22–2·87)	(24·2–47·4)	(11–17)	(7–24)

athletes do not clarify the role of exercise stress *per se*, and reveal little regarding the inception of exercise induced changes in LH secretion, that is, whether changes in LH secretion might occur at the very onset of training, or if other metabolic/neuroendocrine adaptations associated with later stages of training play a role.

The aim of this study was to address the susceptibility of the hypothalamic–pituitary axis to the acute physical stress of exercise in untrained, physically inactive women. Only one study to date has examined the effects of submaximal exercise on LH pulse parameters in untrained women (McArthur *et al.*, 1990). This study, conducted in the mid-luteal phase, disclosed no changes in LH pulse characteristics after one hour of moderately fast treadmill running by normally sedentary, eumenorrhoeic women. The present study, conducted in the mid-follicular phase, was designed to complement the previous investigation and employed essentially the same format. It was performed as a joint investigation in the Department of Endocrinology, St Bartholomew's Hospital, London, and the Department of Health Sciences, Sargent College of Allied Health Professions, Boston University, Boston, Massachusetts, 11 subjects being studied in London and five in Boston.

Methods and materials

Subjects

Sixteen healthy, normally menstruating women between the ages of 19 and 35 (27 ± 1 years) (mean ± SEM) at least 7 years since menarche ($14·1 \pm 1·5$, mean ± SEM), who did not engage in regular physical activity, were recruited (Table 1). The investigation was approved by the ethics committees of the two institutions, and all subjects gave written informed consent.

Screening included a detailed history and physical examination, pelvic examination, routine blood indices and endocrine screening that included determinations of serum luteinizing hormone (LH), follicle stimulating hormone, prolactin, thyroxine (T4), free T4 index and sex hormone binding globulin. All subjects exhibited a mid-cycle LH peak as confirmed with a urinary LH detection kit (First Response, Tambrands, Inc.) and a biphasic body temperature pattern throughout the study. All women in the study had a luteal phase length of at least 9 days as measured from the LH peak and three mid-luteal serum progesterone levels of at least 17 nmol/l. Prior use of oral contraceptives within the last 6 months, narcotics and sedatives were criteria for exclusion. Means for height, weight, percentage body fat as determined by skin-fold measurements (Sloan *et al.*, 1962) and maximal aerobic capacity (Vo_2 max) were typical of sedentary women in their age range. Completion of physical activity questionnaires revealed that subjects were not currently training and that most had little history of regular physical activity.

Maximal aerobic capacity (Vo_2 max (ml/kg/min)) was determined with a graded treadmill test to exhaustion, using the measurement of metabolic gas exchange and minute volume by mass spectrometry alone (Davies & Denison, 1979). The initial treadmill speed was 3 km/h and increased 1 km/h every 3 minutes. The treadmill remained level throughout. Criteria for the attainment of Vo_2 max included a plateau in oxygen uptake and in heart rate despite an increase in exercise intensity, along with a final respiratory quotient in excess of 1.

Study design

All subjects completed a 13·5-hour pulsatility test in the mid-follicular phase on days 4–9 of the cycle ($7 \pm 0·4$ (mean ± SEM)) which included one hour of progressive exercise at approximately 50% (20 min), 60% (20 min) and 70% (20 min) of their predetermined Vo_2 max. To serve as a control for effects of changes in posture and cannulation, six of these same individuals completed an additional 13·5-hour test during the mid-follicular phase (days 4–8; $6·7 \pm 0·5$ (mean ± SEM)) of another menstrual cycle, with leisurely strolling substituted for exercise. For these subjects, the order of trials was randomized. Each subject was familiarized with the testing protocol before undertaking a treadmill

run. Appropriate treadmill speeds representing 50, 60 and 70% of each subject's maximal oxygen uptake were determined from their initial $\dot{V}O_2$ max test. Heart rates were determined each minute during exercise with the use of standard electrocardiographic techniques. Ratings of general perceived exertion (RPE) using the Borg scale (Borg, 1970) were obtained at the end of each successive 20-minute period. Subjects were permitted to drink water and rest briefly after each bout of exercise while the blood sample was being taken. Lactate, haematocrit and haemoglobin levels were determined before and immediately after exercise, and before and after strolling in the control trial. Plasma lactate was analysed using a YSL_{23} Lactate Analyzer (Leavy *et al.*, 1985).

Blood sampling

The subjects reported to the metabolic ward of St Bartholomew's Hospital, London or to the Thorndike Clinical Research Center in the Boston City Hospital at approximately 0800 h for antecubital venous cannulation. Sampling (1·5 ml) for LH commenced at 10-minute intervals at least one hour later and continued until exercise or strolling began between 1330 and 1430 h. During exercise or strolling, one sample was obtained after each of three 20-minute periods. After exercise or strolling, sampling was resumed at 10-minute intervals until approximately 2230 h. Meals were provided according to the routine hospital schedule. Sleep was prevented.

Hormone assays

Blood samples were allowed to clot at room temperature and the serum stored at −20°C. In the subjects tested in London ($n = 11$), the method of Grossman *et al.* (1981) was employed for the radioimmunoassay of LH. The antibody (F 87/2) (Lynch & Shirley, 1975) was kindly provided by Professor Wilfred Butt, and the separation was facilitated by polyethylene glycol. The serum LH values are expressed as IU/l, using the WHO International Pituitary LH Standard (68/40) as the reference preparation. The intra and inter-assay coefficients of variation were 3·7 and 4·9%, respectively. The five subjects tested in Boston (all in the exercise group), had LH measured as described by Midgley *et al.* (1964), with intra and inter-assay coefficients of variation of 9·0 and 17·0%, respectively. The antiserum 391 supplied by the Standard and Reagents Core, Reproductive Sciences Program, University of Michigan, was anti-hCG raised in rabbit and diluted 1:80,000 in PBS. Values for these subjects are expressed as IU/l according to the WHO 2nd International Reference Preparation of pituitary LH (78/549). All samples from a given subject were analysed in the same assay. The two assay standards used in the radioimmunoassays were compared to establish relative potency. A five-point linear regression analysis was performed and both standard curves exhibited linearity ($P < 0{\cdot}0001$) within the normal range of LH values. When slopes (78/549: $-19{\cdot}8 \pm 2{\cdot}9$; 68/40: $-19{\cdot}1 \pm 0{\cdot}4$ (mean ± SD)) of regression lines were compared, a test of non-parallelism was not significant ($P = 0{\cdot}800$). Data were normalized from the 78/549 standard (Boston) to the 68/40 standard (London) by multiplication by 1·19 (ratio of the intercepts). The 78/549 standard (Boston) exhibits parallelism when compared to the standard used in a modification of the in-vitro bioassay method of Dufau *et al.* (1976). The relative potency (ratio of LH bioactivity to LH immunoactivity) is approximately 2·2–2·8 when samples from the early to mid-follicular phase of sedentary women are assessed. No data are available to establish the relative biopotency of the London radioimmunoassay standard. An analysis of variance (ANOVA) revealed no significant differences in LH pulse parameters attributable to the assay method. It should be emphasized that possible differences in results due to assay method are minimal because the statistical comparisons performed on LH data describe intra-subject changes, i.e., pre to post-exercise. Values for LH obtained during exercise were corrected for changes in plasma volume, using the method of Dill and Costill (1974).

Pulse analysis and statistics

The Pulsar program was used to identify LH pulses and to quantify their characteristics. This program was substituted for that of Henery *et al.* (1989), which was employed for the analysis of our previous study (McArthur *et al.*, 1990) and which was suited to the shape of luteal phase pulses, but not to those occurring during the follicular phase. The Pulsar G-values empirically derived from the four original LH calibration sets were used: $G(1) = 3{\cdot}80$, $G(2) = 2{\cdot}60$, $G(3) = 1{\cdot}90$, $G(4) = 1{\cdot}50$ and $G(5) = 1{\cdot}20$. These settings were associated with a 5·1% false-positive detection and a 5·9% false-negative detection rate when LH data sets in the original reference were analysed with Pulsar and compared to peaks chosen visually (Merriam & Wachter, 1982). In a review by Urban *et al.* (1988), Pulsar showed a false-positive rate of less than 0·1% when run on a synthetic data set of signal-free noise designed to simulate the distribution of a range of assay standard deviations. When early and late follicular phase LH pulse patterns were also analysed by Pulsar (using the above-stated G-values) and six other pulse detection algorithms, the number of pulses and pulse

Table 2 Exercise data

Stage	% $\dot{V}O_2$ max	$\dot{V}O_2$ (ml/O_2/kg BW)	Speed (km/h)	Heart rate (bpm)	RPE*	Lactate (mmol/l)
I	50	18·9 (0·9)	6·0 (0·2)	127 (8)	9·3 (0·4)	–
II	60	22·7 (1·0)	7·1 (0·2)	156 (4)	13·2 (0·6)	–
III	70	26·4 (1·2)	8·2 (0·2)	176 (4)	16·0 (0·6)	3·70† (0·5)

Values are mean (SEM).
*RPE, rating of perceived exertion.
†$P < 0·05$ *vs* pre-exercise levels; paired *t*-test; $n = 11$.

amplitudes detected were statistically indistinguishable between programs (Evans *et al.*, 1992).

Pulse variables analysed include pulse frequency (pulses/h), maximal peak amplitude (IU/l), incremental peak amplitude (IU/l) and peak area (IU/l/peak). For a given peak, maximal peak amplitude (IU/l) represents the highest absolute value within the peak. Incremental peak amplitude (IU/l) represents the highest point in a peak relative to a calculated baseline, i.e. maximal peak amplitude – baseline. Area for a given peak was determined by calculating the average rise above baseline and multiplying by the number of minutes over which the peak extended.

To examine the acute effects of exercise on LH secretion, an average of each pulse parameter was computed for each subject, during the pre-exercise (or pre-strolling) time period and during the post-exercise (or post-strolling) time period.

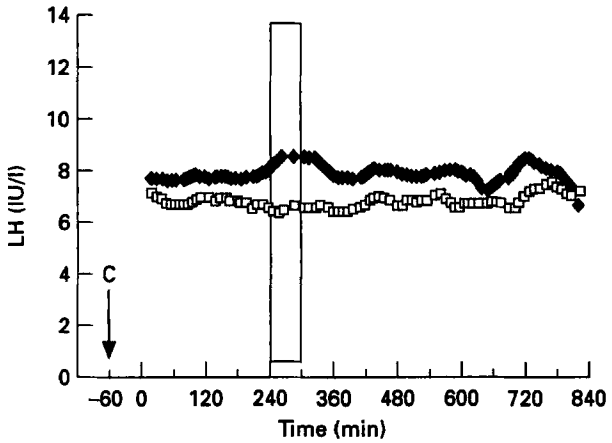

Fig. 1 Composite smoothed mean LH concentrations for ■, the exercise ($n = 16$) and □, non-exercise ($n = 6$) studies. Cannula insertion is indicated by an arrow, with blood sampling commencing 1 h later at time 0. The bar shows the period of exercise.

Group means were then compared using Student's paired *t*-tests. Pulse frequency and amplitude of pulses that occurred during exercise were not included in the analysis because the short duration of exercise precluded the certain capture of a pulse or pulses within that time period. Mean serum LH was analysed before, during and after exercise or strolling using a one-way ANOVA with repeated measures. Significance was defined as $P < 0·05$.

To address whether the stress of cannulation and or the anticipation of exercise (or strolling) produced changes in LH pulse characteristics, data were also quantified during the 2 hours after cannulation and the 2 hours immediately prior to exercise.

Results

Exercise data

The estimated levels of oxygen uptake, corresponding treadmill speeds and actual physiologic data representing each stage of exercise are shown in Table 2. Heart rates were averaged over the last 5 minutes of each stage. Ratings of perceived exertion were obtained at the end of each stage. Scores of 9, 13, and 16 correspond to very light, somewhat hard, and between hard and very hard levels of exertion, respectively. Lactate values rose from a mean resting level of 1·20 to 3·70 mmol/l at the conclusion of exercise.

LH secretion

Figure 1 is a composite graph of mean LH (smoothed as a moving average over seven points) before, during and after exercise and strolling. The two curves exhibit no striking differences apart from a slight rise in LH during exercise in the exercise group. The mean±SEM values for the exercise and strolling studies for each LH parameter as determined using Pulsar are depicted in Table 3. No significant changes

Table 3 LH pulse parameters

	Frequency (pulses/h)		Maximal peak amplitude (IU/l)		Incremental peak amplitude (IU/l)		Mean LH (IU/l)			Peak area (IU/peak)	
	Pre	Post	Pre	Post	Pre	Post	Pre	During	Post	Pre	Post
Exercise ($n = 16$)	0·98 (0·08)	0·95 (0·07)	8·81 (0·66)	9·45* (0·67)	2·66 (0·23)	3·09* (0·33)	7·28 (0·59)	7·85 (0·72)	7·65 (0·57)	76·4 (8·3)	88·2 (9·6)
Strolling ($n = 6$)	0·82 (0·10)	0·84 (0·08)	7·83 (0·63)	7·53 (0·57)	2·47 (0·46)	2·25 (0·21)	6·44 (0·62)	6·62 (0·56)	6·45 (0·71)	84·4 (18·6)	76·1 (11.4)

Values are mean (SEM).
*$P < 0·05$ *vs* pre-exercise levels; paired *t*-test.

in LH pulse characteristics occurred due to strolling. One hour of moderate intensity exercise did not affect LH pulse frequency (0·98 ± 0·08 to 0·95 ± 0·07 (mean ± SEM); pre *vs* post exercise, respectively). Thirteen out of 16 subjects exhibited a pulse during the hour of exercise, and in the three subjects who did not pulse during their run, a secretory episode was present immediately before or just after exercise. However, exercise did produce small but significant increases in maximal peak amplitude (8·81 ± 0·66 to 9·45 ± 0·67 IU/l (mean ± SEM); $P < 0·05$) and in incremental peak amplitude (2·66 ± 0·23 to 3·09 ± 0·33 IU/l ($P < 0·05$)). Data from a representative subject are depicted in Fig. 2. In this subject, maximal peak amplitude increased from 9·86 to 10·60 IU/l and incremental peak amplitude increased from 4·35 to 4·61 IU/l, while pulse frequency was 0·93 peaks/h before exercise and 0·84 peaks/h after exercise. In the exercise group, peak area was 76.4 ± 8.3 IU/peak before exercise, and 88·2 ± 9·6 IU/peak after exercise. Mean serum LH levels did not change significantly with exercise. A further analysis was performed in view of our previous finding of a possible post-cannulation suppression of LH secretion in both groups (strolling and exercise) during the luteal study. No significant differences existed in pulse parameters during the 2 hours after cannulation compared to the 2 hours before exercise or strolling. In addition, a pulsatile episode occurred within 90 minutes of cannulation in all but one subject during one occasion.

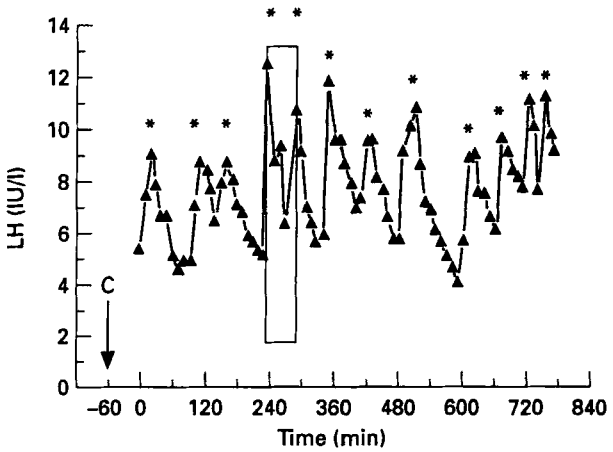

Fig. 2 Representative data from a subject depicts an exercise induced rise in LH pulse amplitude. The bar shows the period of exercise; pulses confirmed by Pulsar are noted by asterisks.

Discussion

Strenuous exercise training that is begun abruptly has been shown to induce luteal phase insufficiency, luteal shortening and anovulation (Bullen *et al.*, 1985; Beitins *et al.*, 1991). Even low intensity recreational running that does not disturb luteal phase length initiates luteal inadequacy (Ellison & Lager, 1986). Little is known regarding the time course of the associated hormonal changes. Previous studies suggest that oligomenorrhoea (Veldhuis & Johnson, 1985) and amenorrhoea (Loucks *et al.*, 1989) are accompanied by an inhibition of the GnRH pulse generator, manifested by a reduction in LH pulse frequency. Few prospective studies attempting to document the evolution of exercise-induced menstrual disturbances (Bullen *et al.*, 1985; Boyden *et al.*, 1984; Keizer *et al.*, 1987) have been performed, and only one (Rogol *et al.*, 1992), has measured LH pulsatile parameters successively with training. In the latter study, women gradually increased their training over a year, and exhibited only a slight decrease in luteal phase length (<2 days) with no concomitant changes in basal LH pulse parameters,

suggesting that substantial changes in reproductive function and associated changes in LH secretion may require a more severe exercise regimen. If acute exercise early in training proves to have little effect on LH secretion, it is likely that other factors associated with training adaptations rather than the immediate effects of exercise itself are responsible for the chronic suppression of LH secretion associated with menstrual disturbances. Alternatively, if isolated bouts of exercise do affect LH secretion patterns, these effects may become chronic with the repetition that occurs with daily training. They might then initiate the evolution of abnormal follicular maturation and ultimately progress to amenorrhoea.

The purpose of this study was to determine whether follicular LH secretion is altered upon pre-training exposure to the stress of a single bout of exercise. Our results agree with those of the complementary study performed during the luteal phase (McArthur *et al.*, 1990) in that no acute exercise-induced suppression of LH frequency was identified when subjects exercised for one hour at a moderate intensity. Suppression of pulse frequency may require more intensive exercise of longer duration, or may not occur until influenced by chronic metabolic and/or neuroendocrine changes resulting from repetitive training. Unlike luteal phase exercise, follicular phase exercise of moderate intensity was found to exert a slight stimulatory effect upon LH secretion in our untrained women. While the rate of LH pulsations was unaffected, the amplitude of the LH peaks was significantly increased after exercise. The physiological significance of a change of the magnitude observed in this study is unknown. Differential effects of GnRH pulse frequency and amplitude have been shown regarding gonadotrophin subunit mRNA concentrations in castrate, testosterone-replaced rats (Marshall *et al.*, 1991). It is difficult to explain with certainty why LH responses to acute exercise would differ with menstrual cycle phase. Variations in circulating steroid levels may have differential effects on the sensitivity of the GnRH pulse generator to excitatory stimuli evoked by exercise, or perhaps play a role at the level of the pituitary by modifying its responsiveness to GnRH. Cyclic changes in other neuromodulatory systems, e.g. opioids, may conceivably cause alterations in GnRH secretion with exercise. Additionally, slight stimulatory effects of exercise may be more difficult to detect in the luteal phase, when the basal frequency of LH pulsations is less and the amplitude of pulses is greater and more variable than in the follicular phase.

The present finding of a slight exercise-induced stimulation of LH agrees with others who have reported an increase in follicular phase LH after exercise (Kuoppasalmi *et al.*, 1980; Schmid *et al.*, 1982; Baker, 1982). However, many of these studies did not examine pulse characteristics and were performed on trained individuals. Few studies have carefully examined the effect of acute exercise on pulsatile LH secretion. Keizer (1983) found an increase in early follicular pulse amplitude and pulse increment (relative difference between pulse peak and nadir) in four untrained but physically active women after four consecutive 15-minute bouts of stationary cycling at 60, 70, 80 and 90% of V_{O_2}max. However, a later report by Keizer and others (Keizer *et al.*, 1987) documents a post-exercise reduction in follicular LH amplitude when exercise is preceded by several days of heavy training. Cumming *et al.* (1985b) observed a decrease in LH pulse frequency in the early follicular phase but no effect of 60 minutes of moderate intensity exercise on pulse amplitude in moderately trained women. In light of these conflicting results, it appears that the effects of acute exercise upon follicular LH pulsatility may be dependent on the training status of the subjects and possibly on the previous days' training regimen.

Studies examining the effects of chronic exercise on the responsiveness of the pituitary to exogenously administered GnRH also show conflicting results. Reduced responsiveness has been noted in male marathon runners (MacConnie *et al.*, 1986), in female runners after weekly mileage had reached 50 miles/week (Boyden *et al.*, 1984), and in the luteal phase of runners averaging 30 miles/week (Ronkainen, 1985). However, the cycling athletes studied by Loucks *et al.* (1989) had greater pulse amplitudes and a greater responsiveness to GnRH than their sedentary counterparts.

Inconsistencies in the reported literature may reflect a continuum of training induced changes in pulse amplitude and/or underscore the complexity of the control of LH secretion. Amplitude modulation can be achieved in several ways; (1) via the level of neuronal activity that influences the firing of the GnRH pulse generator, (2) by modulation of the stimulus–secretion coupling at the neurosecretory terminals (Lincoln *et al.*, 1985) and (3) the responsiveness of the pituitary. As pointed out by Vermeulen and Kaufman (1992), gonadotroph responsiveness is influenced by a variety of factors, that is, the frequency of the GnRH pulses, their duration, the time elapsed since the last pulse, the hormonal environment and intrinsic gonadotroph sensitivity. The LH secretory rate and the distribution and elimination processes, with variable LH half-lives in different subjects, likewise affect the amplitude of the resulting LH pulse. A further complication is introduced by the polymorphism of circulating LH, which results from the secretion of one or more endogenous isoforms with different bioactivity in individual subjects, the LH potency estimates of these isoforms being dependent upon antibody specifications of particular antisera.

Significant variations occur in the steroid environment and in GnRH responsiveness according to the phase of the menstrual cycle as ovarian follicles wax and wane (Yen *et al.*, 1972). Although we did not measure circulating oestrogen levels, follicular phase exercise of an intensity similar to that which we employed is known to be associated with a rise in serum oestrogen levels (Bonen *et al.*, 1979; Jurkowski *et al.*, 1978), presumably due to diminished hepatic clearance. Whether an exercise-induced rise in oestradiol levels might increase the responsiveness of the pituitary to GnRH is doubtful considering the relatively short time of post-exercise exposure to increased levels and the fact that much higher levels of oestradiol are required to elicit a positive feedback response such as that occurring during the LH surge (Karsch *et al.*, 1973).

Another potential factor, more likely but also more difficult to document in humans, is the effect of exercise on the release of central excitatory or inhibitory transmitters which influence the amount of GnRH released from the hypothalamus. This area of future study requires meticulous pharmacological studies in humans and the successful use of an animal model in which exercise is undertaken voluntarily that is, without undue exogenously applied stress (such as foot shock) in order to provide information regarding the effects of the physical stress of exercise alone. Future studies employing such an animal model, combined with advanced methodological techniques for in-vivo and in-vitro assessment, will no doubt reveal much about central mechanisms whereby acute and chronic exercise influence hypothalamic and pituitary function.

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