

Pulsatile Secretion of Gonadotropins and Prolactin in Male Marathon Runners

Relation to the Endogenous Opiate System

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We tested the hypothesis that sustained, strenuous physical training alters the neuroendocrine regulation of pulsatile gonadotropin and/or prolactin secretion in men. Blood was sampled at 20-minute intervals over 8 hours in five endurance-trained men after a 10–15 mile run in the middle of the active training season, and in 11 nonendurance trained normal controls. In these two groups, basal patterns of physiologically pulsatile secretion of LH, FSH, and prolactin (PRL) were not significantly different in relation to the following parameters: mean serum concentration of each of the three hormones (N = 25 samples); areas under the hormone concentration vs. time curves; fractional, incremental, and absolute pulse amplitudes; and pulse frequency, or periodicity. To test for enhanced suppressive effects of endogenous opiates in trained male marathon runners, subjects were administered the potent opiate-receptor antagonist, naltrexone (1 mg/kg). This antagonist significantly stimulated pulsatile LH secretion by increasing mean serum LH values from 10.94 to 13.58 mIU/ml ($P = 0.007$); area under the LH concentration vs. time curve increased from 5370 to 6510 mIU/ml \times 8 hours ($P = 0.05$) and, pulse frequency rose from 2.8 to 4.9 pulses/8 hours ($P = 0.006$). Naltrexone also enhanced pulse frequency of FSH secretion from 3.4 to 5.4 pulses/8 hours ($P = 0.009$), but did not alter serum prolactin concentrations. None of these responses differed significantly from those in normal sedentary controls. We concluded that 1) detailed parameters of physiologically pulsatile LH and FSH secretion, even in men of endurance training, are not distinguishable from

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those of normal sedentary controls; 2) secretion of PRL basally and in response to opiate-receptor blockade is not significantly perturbed; and 3) LH release in male athletes appears to be under tonic inhibitory control by endogenous opiate systems, but the inhibitory influence of these opiates is not markedly exerted.

Key words: gonadotropin, prolactin, endurance-training, marathon runners, pulsatile secretion, opiates, Naltrexone.

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Concentrations of gonadotropins in the blood exhibit episodic fluctuations, which are believed to be controlled by neuroendocrine mechanisms that regulate the discontinuous release of hypothalamic LHRH into the pituitary portal circulation (Knobil, 1980; Wildt et al, 1981; Nankin and Troen, 1971; Santen and Bardin, 1973; Carmel et al, 1976). Based upon this physiological precept, quantitative studies of the frequency of pulsatile gonadotropin secretion in peripheral blood have been used to explore brain mechanisms that control periodic hypothalamic LHRH release. With the aid of com-

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puter algorithms, discrete and reproducible patterns of pulsatile gonadotropin secretion have been characterized in normal men and in certain disease states. For example, significant alterations in the amplitude and frequency of pulsatile LH secretion can be demonstrated in relation to the stages of the normal menstrual cycle (Brody et al, 1982), or in relation to various pathologic states of the gonadal axis (Santen and Bardin, 1973; Yen et al, 1975; Santen, 1981). In the present study, we have utilized this strategy to characterize the physiologic patterns of episodic gonadotropin release in endurance-trained male athletes of marathon-level performance.

Strenuous exercise is associated with delayed pubertal progression, hypogonadism, and/or oligomenorrhea and amenorrhea (Warren, 1980; McArthur et al, 1980; Wakat et al, 1982). These hypogonadal states may be reversible since Warren (1980) reports the return of menstrual function without change in body weight in some ballet dancers who must cease training for several months. There are a number of anecdotal reports of the return of menses in long-distance runners when endurance training is interrupted. Although the proximate mechanism(s) subserving such alterations in reproductive function are not known, sustained aerobic exercise effectively stimulates the endogenous opiate system (Colt et al, 1981; Carr et al, 1981). Moreover, studies in both experimental animals and in man indicate that endogenous opioids and exogenous morphinomimetic compounds inhibit—whereas opiate-receptor antagonists acutely stimulate—LH (and FSH) secretion (Blank et al, 1979; Meites et al, 1979; Cicero et al, 1980; Sylvester et al, 1982; Wehrneberg et al, 1982; Stubbs et al, 1978; Morley et al, 1980; Moulton et al, 1981; Delitala et al, 1981; Ellingboe et al, 1982). In addition, stimulatory responses to opiate-receptor antagonists have suggested increased activity of endogenous opiates in certain hypogonadotropic states in man (Quigley et al, 1980).

Acute strenuous exertion also elicits a demonstrable increase in serum PRL concentrations in man (Wakat et al, 1982; Shangold et al 1981). Although hyperprolactinemia of diverse pathophysiologic causes can be associated with clinical or biochemical hypogonadism, the role (if any) of exercise-facilitated PRL secretion in reproductive disturbances attributed to strenuous exercise is not defined.

In the absence of any published data regarding

pulsatile gonadotropin secretion in strenuously exercising men, we have chosen to test the following three hypotheses: 1) basal patterns of physiologically pulsatile gonadotropin secretion are altered in endurance-trained male athletes, reflecting altered hypothalamic or pituitary function; 2) alterations in gonadotropin secretion are associated with exercise-stimulated hyperprolactinemia; and 3) endurance-trained male athletes demonstrate an accentuation of normal opiate-related suppression of gonadotropin secretion. To test these hypotheses, we have characterized the episodic patterns of LH, FSH, and prolactin secretion by quantitative computerized analyses of pulse frequency and amplitude in five endurance-trained male athletes, and compared their patterns with those of a group of 11 nonendurance-trained young men. Athletes and controls were each studied twice, once after placebo administration, and once after ingestion of naltrexone, a potent opiate-receptor antagonist. This narcotic antagonist has been effectively employed in man and experimental animals to unmask neuroendocrine activity normally under endogenous opioid control (Mendelson et al, 1979; Ellingboe et al, 1982).

Materials and Methods

Subjects

Five endurance-trained male athletes (26–42 years) who were running at least 50 miles per week and who had completed two or more races of marathon distance of 26.2 miles up to 100 miles volunteered for this study. Their weight was 90% to 95% of ideal, and all had less than 10% body fat content as calculated from skin fold measurements at four sites. The control group consisted of 11 (in some cases five, see below) young men who were within 15% of ideal body weight. They did not run more than 1 mile per week, nor were they receiving any medications. The controls, as well as the five athletes, all had normal physical examinations (including testicular size) and normal sexual developmental histories. All subjects had basal serum T_4 , TSH, PRL, LH, FSH, testosterone and estradiol concentrations within normal limits for adult males. Tests of hepatic and renal function were also normal. All procedures were approved by the Human Investigation Committee of The University of Virginia and written informed consent was obtained from all participants.

Test Procedure

The endurance-trained athletes completed a 10–15 mile run on each of two days 1 hour before an indwelling heparin-lock needle was inserted into a forearm vein. Blood samples were withdrawn every 20 minutes for 8 hours beginning 20 to 30 minutes after

placement of the heparin lock. Subjects were permitted to ambulate freely. Due to the very long half-life of naltrexone (eg, 100 mg naltrexone blocks the effect of 25 mg heroin IV for at least 48 hrs [Verebey et al, 1976]), the placebo elixir was given orally on the first day and naltrexone (Endo laboratories) 1.0 mg/kg as a 10 mg/ml elixir, was administered on the second day, both being given 30 minutes prior to the withdrawal of the first blood sample. Some subjects noted mildly dysphoric side effects following naltrexone administration (Mendelson et al, 1979).

Sample Processing and Radioimmunoassays

Blood samples were withdrawn through the indwelling needle after first removing the heparin solution with a separate syringe. All samples were allowed to clot at room temperature prior to centrifugation to separate the serum from the formed elements. Serum was removed and stored at -20°C before assay. All samples from an individual were analyzed in the same assay to avoid interassay variability.

Serum PRL, T_4 , TSH, testosterone and estradiol were determined as previously described (Evans et al, 1980). Luteinizing hormone concentrations were assayed in triplicate using a modification of the method of Odell et al (1967). The reagents were those described previously (Evans et al, 1980). Seven additional pools of serum were assayed nine times each to define the intra-assay variability more precisely at multiple points along the displacement curve. Our analysis of pulsatile secretion employed assay specific variance at the relevant level of displacement (see below). The intra-assay coefficients of variation were between 6.5% and 9.0% in the range of the measured LH concentrations in the present study.

Follicle stimulating hormone was assayed according to the method of Cargille et al (1969), with minor modifications.

Quantitative Analysis of Pulsatile Hormone Secretion

Quantitative analysis of pulsatile hormone secretion employed the computerized methods of Santen and Bardin (1973), and Steiner et al (1982). We used the algorithm of Santen and Bardin to calculate individual pulse amplitudes (expressed as a percent increase above preceding nadir), and area under the 8-hour time-concentration curve. To identify individually significant hormone fluctuations (pulses) that exceeded intrinsic variance associated with procedural and assay noise, we applied the program of Steiner et al (1982). This program will identify individual peaks, compute mean pulse frequency (or periodicity), and define mean incremental pulse amplitude. In this algorithm, LH pulses are characterized by applying the pertinent within-assay coefficients of variation as initial estimators for subsequent iterative detection of significant gonadotropin pulses by sequential scanning with an adaptive threshold. This procedure is effective at signal-to-noise ratios of 1.5 or greater. In the present study, LH pulses exhibited a signal-to-noise ratio of at least 2.5. Discrete pulses detected by the method of Steiner et al (1982) were 83%

concordant with those defined by the method of Santen and Bardin (1973), (JDV, unpublished data). Significant fluctuations at either extreme of the sampling interval are scored as one-half pulses, since the completed pulses are assumed to occur outside of the range of sample withdrawal.

When a single prominent LH pulse was apparent (amplitude exceeding that of other LH pulses by $>50\%$), the data were rescanned after omission of the dominant pulse in order to obviate damping of the residual pulse signals. In addition, the program was modified to display the individual significant increases and decreases (pulses) detected, which were then enumerated.

Statistical Analyses

Data are presented as mean \pm SD. Paired, two-tailed Student's *t* testing was utilized to assess within-subject effects (placebo vs. naltrexone), while unpaired testing was employed to estimate between-group effects (runners vs. controls). Exact *P* values were computed with the aid of the general statistics library module of a Texas Instruments (TI-59) desk calculator.

Results

Luteinizing Hormone

There were no differences in any parameters of basal pulsatile LH release between the marathon runners and the control group of 11 nonendurance-trained volunteers (Table 1). In particular, the mean LH concentration, area under the 8-hour time-concentration curve, pulse frequency, pulse amplitude (absolute, incremental or fractional) were not distinguishable from normal. Thus, physiologically pulsatile patterns of LH secretion were preserved in athletes. Moreover, both athletes and controls exhibited approximately a 30% rise in mean LH concentration following naltrexone administration. There were similar statistically significant increases in both groups in the mean number of LH peaks in 8 hours, the mean absolute peak LH concentrations, and the area under the LH concentration vs. time curve (Table 1). In addition, the incremental rise (in mIU/ml) and the mean percent rise for LH peaks were similar following placebo or naltrexone administration. The latter data suggest that the increase in mean absolute peak LH values is associated with an increase in the inter-pulse LH base line following naltrexone administration and thus the apparently greater peak LH values represent a similar amount of gonadotropin secretion, but start from a greater absolute baseline.

Our detailed LH analysis indicated that both the basal physiologically pulsatile pattern of LH secre-

TABLE 1. Luteinizing Hormone Pulse Analysis

Subjects Endurance-Trained Men*	Mean LH \pm SD [†] (mIU/ml)	Area Under LH Curve (mIU/ml \times min)	Peaks/8 Hr	Mean Absolute Peak LH Levels (mIU/ml)	Incremental LH Amplitude (mIU/ml \times 8 hr)	Mean % LH Rise	Periodicity (min)
1-Placebo	18.90 \pm 1.48	9058	3.5	20.4	3.06	26	150
-Naltrexone [‡]	19.86 \pm 2.11	9496	4.5	21.6	3.47	18	110
2-Placebo	11.88 \pm 1.59	5718	2.0	13.75	4.05	45	116
-Naltrexone	14.03 \pm 1.88	6734	4.0	15.8	3.93	46	107
3-Placebo	11.44 \pm 2.78	5534	3.0	15.2	3.97	66	120
-Naltrexone	16.40 \pm 1.78	7886	6.5	17.7	3.06	30	64
4-Placebo	3.84 \pm 0.96	1814	2.0	6.20	4.80	80	—
-Naltrexone	5.81 \pm 1.38	2756	4.0	7.64	2.65	70	113
5-Placebo	8.62 \pm 2.63	4176	3.5	11.4	5.91	94	167
-Naltrexone	11.84 \pm 3.61	5684	5.5	15.9	9.15	128	83
Means-Placebo (\pm SD)-Naltrexone	10.94 \pm 4.90 13.58 \pm 4.71	5368 \pm 2316 6511 \pm 2264	2.80 \pm 0.68 4.90 \pm 0.74	13.39 \pm 4.65 15.73 \pm 4.56	4.36 \pm 0.95 4.45 \pm 2.39	62 \pm 24 58 \pm 39	144 \pm 17 93.3 \pm 20
Significance (<i>P</i> values) Placebo vs. Naltrexone	0.007	0.05	0.01	0.006	NS	NS	0.05
Normal Men (N = 11) [§]							
-Placebo	10.53 \pm 3.39	4098 \pm 1072	3.18 \pm 1.03	11.89 \pm 3.29	5.75 \pm 3.49	72 \pm 20	167 \pm 87
-Naltrexone	14.26 \pm 4.81	5892 \pm 1601	4.64 \pm 0.93	15.47 \pm 4.23	8.23 \pm 3.59	63 \pm 28	98.5 \pm 28
Significance (<i>P</i> values) Placebo vs. Naltrexone	<0.01	<0.01	<0.01	<0.01	NS	NS	<0.01

* Completed 10–15 mile run on each of two days.

[†] N = 25 samples drawn at 20-minute intervals over 8 hours.

[‡] 1.0 mg/kg given as a 10 mg/ml elixir 30 minutes prior to withdrawing the first blood sample.

[§] Controls: did not run.

tion and the response to naltrexone are indistinguishable in these male volunteers, whether or not they are endurance-trained.

Follicle Stimulating Hormone

A similar analytic approach was taken for the secretion of FSH. We found no differences between runners and controls in terms of mean FSH concentration, area under the FSH concentration vs. time curve, number of peaks in 8 hours, peak amplitude and percent FSH rise. For this analysis the control group consisted of five nonendurance-trained normal volunteers since serum was not available from the other six men (Table 2). After naltrexone administration, only FSH pulse frequency changed in the endurance-trained athletes. There were small, but statistically significant, increases in mean FSH concentration, area under the FSH concentration vs. time curve, and FSH pulse frequency for the control, but not the athlete, group. Thus, in the basal state these two groups are indistinguishable, but the endurance-trained athletes did not increase their mean FSH concentration to the same degree as our normal volunteers after naltrexone administration.

Prolactin

Mean, multiply-sampled basal serum prolactin concentrations were not significantly increased in marathon runners. Naltrexone administration did not affect mean serum PRL concentration, or the area under the PRL concentration vs. time curve in either the endurance-trained athletes or the normal volunteers. However, after naltrexone, the group mean serum PRL concentration and group mean area under the concentration vs. time curve were somewhat greater in the endurance-trained athletes than in the normal volunteers (Table 3). The prolactin concentrations fluctuated more widely than the LH or FSH levels. The three men with highest PRL concentrations ran at a rapid pace under adverse (–20 F) weather conditions before the testing procedure (Table 3, subjects 1, 2, and 3).

Discussion

We have characterized pulsatile patterns of LH release in male marathon runners, and compared their patterns with those of nonendurance-trained

TABLE 2. Follicle Stimulating Hormone Pulse Analysis

Subjects Endurance-Trained Men†	Mean ± SD (mIU/ml)	Basal				Mean ± SD (mIU/ml)	Naltrexone*			
		Area‡	Peaks per 8 Hr	Ampli- tude§	%¶		Area‡	Peaks per 8 Hr	Ampli- tude§	%¶
1	3.64 ± 0.63	1735	4	1.37	56.7	3.13 ± 0.90	1499	6	1.35	44.4
2	4.23 ± 0.51	2024	2	0.81	27.1	3.67 ± 1.60	1785	4	2.37	18.
3	7.5 ± 1.32	3548	2	2.43	51.2	7.45 ± 1.02	3594	5	2.70	38.7
4	6.42 ± 0.60	3083	4	1.47	23.5	6.98 ± 1.00	3242	6	1.33	26.0
5	4.50 ± 0.65	2152	5	1.32	41.7	4.94 ± 0.66	2364	6	1.30	51.9
Mean	5.29	2508	3.4	1.48	40.0	5.23	2497	5.4	1.81	35.9
± SD	± 1.50	± 689	± 1.2	± 0.53	± 13	± 1.72	± 810	± 0.8	± 0.60	± 12
Significance	—	—	—	—	—	NS	NS	P = 0.009	NS	NS
Normal Men¶										
1	2.53 ± 0.54	1151	4	1.43	87.4	3.45 ± 0.54	1657	5	0.90	36.3
2	4.06 ± 0.47	1946	4	0.92	31.8	4.88 ± 0.43	2347	4	0.80	52.7
3	1.98 ± 0.37	947	5	0.95	62.4	2.52 ± 0.45	1205	6	1.03	47.7
4	4.54 ± 0.61	2273	2	1.28	51.9	5.45 ± 0.52	2625	4	1.47	23.7
5	3.55 ± 0.46	1705	4	1.13	42.2	4.03 ± 0.75	1934	6	0.85	40.1
Mean	3.22	1604	3.8	1.14	55.1	4.07	1954	5.0	1.04	40.2
± SD	± 0.95	± 492	± 0.98	± 0.19	± 19	± 1.03	± 508	± 0.89	± 0.24	± 10.
Significance	—	—	—	—	—	P = 0.003	P = 0.006	P = 0.016	NS	NS

* 1.0 mg/kg given as a 10 mg/ml elixir 30 minutes before withdrawing the first blood sample.

† Completed 10–15 mile run on each of two days.

‡ mIU/ml × minutes (over 8 hours, for N = 25 samples).

§ Incremental, mIU/ml.

¶ Mean % FSH rise.

¶ Controls: did not run.

men. We chose to study marathon-class runners, because they may represent an extreme end of the spectrum of physical exertion, against which sparingly exercising normal men could be compared.

Quantitative parameters of spontaneous pulsatile LH secretion in heavily training marathon men, even under conditions of recent (within an hour) sustained, vigorous exertion were normal, indi-

TABLE 3. Serum Prolactin Concentrations in Endurance-Trained and Normal Men

Subjects Endurance-Trained Men†	Placebo		Naltrexone*	
	Mean ± SD (ng/ml)	Area‡	Mean ± SD (ng/ml)	Area‡
1	22.98 ± 4.85	11025	16.24 ± 4.50	7690
2	21.58 ± 3.65	10433	24.03 ± 6.32	11646
3	23.40 ± 3.11	11223	24.93 ± 6.89	11914
4	10.32 ± 4.61	4856	13.91 ± 4.72	6552
5	6.39 ± 1.61	2941	7.04 ± 2.10	3402
Means ± SD	16.93 ± 7.98	8096 ± 3901	17.23 ± 7.44	8240 ± 3594
Normal Men§				
1	13.5 ± 2.41	6491	11.84 ± 4.80	5711
2	8.47 ± 1.88	4065	8.63 ± 1.90	4111
3	11.47 ± 1.34	5485	9.98 ± 1.28	4752
4	9.23 ± 2.01	4262	8.55 ± 0.87	4271
5	7.22 ± 3.00	3365	7.76 ± 1.67	3705
Means ± SD	9.97 ± 2.51	4734 ± 1245	9.35 ± 1.60	4510 ± 769
Significance (Endurance-trained vs. control)				
	P = 0.077	P = 0.079	P = 0.038	P = 0.041

* 1.0 mg/kg given as a 10 mg/ml elixir 30 minutes prior to drawing the first blood sample.

† Ran 10–15 miles on each of two days.

‡ ng/ml × minutes (over 8 hours, for N = 25 samples).

§ Controls: did not run.

cating unimpaired dynamics of gonadotropin secretion in these endurance-trained athletes. In particular, our observed LH pulse periodicity of 144 ± 17 minutes in these athletes is similar to that in our control group (167 ± 87 minutes), as well as in normal men studied by Winters and Troen, 1983 (151 ± 34 minutes) and in another independent control group we recently investigated (166 ± 37 minutes, Veldhuis et al 1983). Each subject also had normal serum concentrations of testosterone and estradiol. Our observations in men contrast with recent reports of clinical hypogonadism in either similarly trained or less strenuously trained female athletes (Warren 1980, Speroff and Redwine, 1980), and impaired mean and pulsatile gonadotropin secretion in women distance runners (McArthur et al, 1980; Wakat et al, 1982).

Our studies further indicate that the endogenous opiate system clearly impinges on gonadotropin secretion in male distance runners, because the opiate-receptor antagonist, naltrexone, elicited highly significant increases in LH pulse frequency, mean serum LH concentrations, peak pulse amplitude and area under the LH concentrations vs. time curve in these men. However, the magnitude of these increases did not differ between endurance-trained male athletes and sedentary controls. Thus, we infer that LH release in both groups is under a similar degree of tonic inhibitory control by endogenous opiate systems. Our data in the control group are in agreement of those of Morley and coworkers (1980) and Ellingboe et al (1982), who determined circulating LH concentrations after naloxone infusion and naltrexone administration, respectively. However, our results in endurance-trained men contrast with those in a preliminary study of female athletes, which described an exaggerated rise in serum LH concentrations after naloxone infusion (McArthur et al, 1980).

The pulsatile pattern of FSH secretion is not so well defined as that for LH. Using objective numerical criteria to delineate significant fluctuations in serum FSH levels, we found similar patterns of FSH release demonstrated in marathon runners and controls. We cannot, however, state whether these objectively defined pulses reflect a biologically relevant hormonal signal. In addition, the completely normal mean FSH concentration and area under the FSH concentration vs. time curve in endurance-trained men would argue against major abnormalities of seminiferous-tubule function. To our knowledge, actual semen analyses have not yet been described in marathon runners.

The mean basal serum PRL concentrations and the areas under the prolactin concentration-time curves were not significantly increased in marathon runners. Thus, in conjunction with normal patterns of gonadotropin secretion, we cannot implicate any functionally significant disturbance in PRL secretion in these endurance-trained male athletes studied soon after a long run. Neither the sedentary controls nor the marathon runners exhibited any alteration in mean prolactin concentrations or area under the concentration vs. time curve in response to naltrexone administration. These data confirm and extend those of Morley and coworkers (1980) using naloxone infusion in normal subjects and those of Ellingboe et al (1980) who administered naltrexone to three young men with a history of heroin addiction. These endurance-trained athletes were studied within 1 hour of a relatively normal training run. It is conceivable that the acute effects of exercise were dampened or lost by this protocol. Moretti and coworkers (1983) have noted attenuated GH and PRL concentration increases when professional athletes, who exercise to 80% of their maximal heart rate, received infusions of naloxone.

The absence of demonstrable abnormalities in gonadotropin and prolactin secretion in marathon-level runners in active training should not be taken to completely exclude possible abnormalities in less strenuously training men, men just beginning endurance training, or even those at a "steady state" or plateau of training. Nonetheless, our results clearly indicate that sustained high-level training per se does not influence prolactin and gonadotropin secretion adversely.

In summary, parameters of physiologically pulsatile LH and FSH secretion in marathon men are not distinguishable from those of sparsely exercising normal male controls. In addition, no significant alterations in PRL secretion can be discerned basally or in response to opiate-receptor blockade. Finally, LH release in endurance-trained male athletes as in normal men appears to be under tonic inhibitory control by endogenous opioid systems, but the inhibitory influence of opiates is not exerted to an accentuated degree.

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