

Differential Control of Luteinizing Hormone and Follicle-Stimulating Hormone Secretion by Luteinizing Hormone-Releasing Hormone Pulse Frequency in Man*

KENNETH M. GROSS, ALVIN M. MATSUMOTO, AND WILLIAM J. BREMNER

Endocrinology Section and Geriatric Research, Education, and Clinical Center, Veterans Administration Medical Center; Population Center for Research in Reproduction; and the Divisions of Endocrinology, Gerontology and Geriatric Medicine, Department of Medicine, University of Washington School of Medicine, Seattle Washington 98108

ABSTRACT. To test the hypothesis that the frequency of pulsatile LHRH stimulation can differentially control LH and FSH secretion in man, we administered low doses of LHRH in pulsatile fashion in several different regimens to men with idiopathic hypogonadotropic hypogonadism (IHH) and presumed endogenous LHRH deficiency. In study 1, four men with IHH received a constant amount of LHRH per day in three different frequencies. After an initial 7-day period of LHRH (5.0 μ g every 2 h), the men received 2.5 μ g every 1 h and 7.5 μ g every 3 h, each for 4 days, in varying order. Frequent blood samples were obtained before LHRH administration and at the end of each regimen. Before LHRH administration, mean serum FSH and LH levels were low [28 ± 3 (\pm SEM) and 6 ± 2 ng/mL, respectively], and they increased into the normal adult male range during LHRH treatment. As the frequency of LHRH administration decreased from every 1 to 2 to 3 h, serum FSH levels progressively increased from 99 ± 33 to 133 ± 34 to 181 ± 58 ng/mL ($P < 0.05$). Serum LH levels (34 ± 6 , 33 ± 6 , and 34

± 5 ng/mL) were significantly higher than those before LHRH administration and did not differ significantly among the three regimens. Total serum testosterone (T), estradiol, and free T levels were increased by LHRH, but were not significantly different during the three regimens of LHRH administration. In study 2, three men with IHH received the same amount of LHRH per dose, given in two different pulse frequencies; 2.5 μ g LHRH were administered in frequencies of every 0.5 h and every 1.5 h, each for 4 days, in varying order. During the 0.5 h frequency, the mean serum FSH level was 42 ± 13 ng/mL, and it rose to 80 ± 19 ng/mL during the 1.5 h frequency ($P < 0.05$). Corresponding mean serum LH levels were 25 ± 5 and 27 ± 4 ng/mL. Serum T and estradiol levels were not significantly different during the two LHRH regimens. We conclude that 1) the frequency of LHRH stimulation can differentially control FSH and LH secretion by the human pituitary gland, and 2) the pattern of hormonal stimulation may be a determinant of target organ response. (*J Clin Endocrinol Metab* 64: 675, 1987)

THE ACTION of a hormone at its target organ is determined by the molecular structure of the hormone, its mean level in the circulation, the interaction of the hormone with its receptor, and postreceptor mechanisms within target cells. Most hormones are secreted in a pulsatile manner (1), so that the amount of hormone present in the circulation and available for target organ stimulation is not constant over time, but, rather, rises and falls episodically over minutes to hours.

The physiological significance of this pulsatile stimu-

lation of target organs is poorly understood. The work of Knobil (2) suggested that the pattern of hormonal stimulation may itself be an important signal modulating target organ response. In ovariectomized rhesus monkeys with arcuate nucleus lesions resulting in LHRH deficiency, Belchetz *et al.* (3) demonstrated that continuous LHRH administration was incapable of sustaining gonadotropin secretion, whereas both LH and FSH secretion were restored and maintained when LHRH was given in a pulsatile fashion. Subsequently, Wildt *et al.* (4) found that the frequency of administered LHRH pulses in the same animal model modulated the relative secretion of LH and FSH by the pituitary. A slower pulse frequency of administered LHRH favored the secretion of FSH relative to LH (4).

We investigated the potential physiological significance of pulsatile hormone stimulation in man. Specifically, we tested the hypothesis that the frequency of LHRH stimulation can differentially alter pituitary LH and FSH secretion. Several different frequencies of

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Address reprint requests to: Dr. William J. Bremner, Veterans Administration Medical Center (111), 1660 South Columbian Way, Seattle, Washington 98108.

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LHRH were administered to men with idiopathic hypogonadotropic hypogonadism (IHH) with presumed endogenous LHRH deficiency, and the LH and FSH responses to each frequency were assessed after several days. The effect of LHRH pulse frequency on gonadotropin secretion was tested in the presence of both a constant total daily dose (study 1) and a constant bolus dose (study 2) of LHRH.

Materials and Methods

Subjects

Six men, aged 19–38 yr, with well documented IHH (*i.e.* presumed endogenous LHRH deficiency) volunteered to take part in these studies. In all men the diagnosis of IHH was established by the absence of spontaneous puberty, low serum gonadotropin and gonadal steroid concentrations, otherwise normal pituitary function, and normal skull roentgenograms and/or computerized axial tomography. One man took part in both studies; the others participated in only one study.

Protocols

Study 1. Four men with IHH were studied. Before starting the protocol, all had testosterone (T) enanthate replacement treatment discontinued for at least 5 weeks. Before LHRH administration, blood was sampled every 20 min for 4 h. Then, each man was instructed in the use of a portable infusion pump (Auto Syringe, AS 2BH, Travenol Laboratories, Hooksett, NH) for LHRH administration and insertion of needles into the abdominal sc tissue using antiseptic technique.

Fifteen days of pulsatile LHRH (Ayerst, Rouses Point, NY) administration, employing three different regimens, was then begun. The total amount of LHRH per day (60 μg) was constant among the regimens, while the dosing interval (*i.e.* LHRH pulse frequency) was varied. During the first 7 days, each man received a 5.0- μg bolus dose of LHRH every 2 h. During the next 4 days, each man received either 2.5 μg LHRH every 1 h or 7.5 μg LHRH every 3 h, followed by a final 4 days of the LHRH regimen (either 2.5 μg every 1 h or 7.5 μg every 3 h) that he had not received in the preceding 4 days. Therefore, each man received all three LHRH regimens, the last two in varying order. The interpulse intervals were chosen to include the physiological range of LHRH pulse frequencies (5) and were based on the responsiveness of gonadotropins to LHRH administration in pilot studies of men with hypogonadotropic hypogonadism (Gross, K. M., A. M. Matsumoto, and W. J. Bremner, unpublished observations).

Blood was sampled every 10 min after the last two LHRH doses of each regimen. All blood drawing was performed through an indwelling iv catheter inserted into an arm vein. LH and FSH levels were measured in each sample. Total T, estradiol (E_2), sex hormone-binding globulin (SHBG), and free T levels were determined in the first sample from each sampling period.

Study 2. Three men with IHH were studied using a protocol in which the bolus dose of LHRH administered per pulse was

constant (2.5 μg), while LHRH pulse frequency was varied. All three men had received LHRH therapy in a dose of 2.5 μg every 2 h for from 1 week to several months immediately before participating in the study. In these men, 2.5 μg LHRH were administered every 0.5 h for 4 days and every 1.5 h for 4 days in random order. Blood was sampled every 10 min for 1 h before the initiation of LHRH therapy (control) and again every 10 min after the last three LHRH doses of the every 0.5 h regimen and every 10 min after the last dose of the every 1.5 h regimen. LH and FSH levels were measured in each sample, and T and E_2 levels were measured in the first sample from each sampling period.

The study protocols were reviewed and approved by the Human Subjects Review Committee of the University of Washington. Informed consent was obtained from each man before his participation in the study.

Hormone assays

LH and FSH RIA. The RIA for LH (6, 7) used a reference standard (LER 907) and first antibody (antihuman LH batch 2) supplied by the National Pituitary Agency. The tracer was purified hCG (supplied courtesy of Dr. C. Alvin Paulsen) radioiodinated with ^{125}I using chloramine-T (8). The limit of detectability was 6 ng/ml, and the intra- and interassay coefficients of variation were 5.5% and 8.4%, respectively.

The RIA for serum FSH (6, 7) used reagents distributed by the National Pituitary Agency. The reference standard was LER 907, the first antibody was antihuman FSH batch 5, and the tracer was HS-1 radioiodinated with ^{125}I using chloramine-T (8). The limit of detectability of FSH was 25 ng/mL. The intraassay variability was 7.3%, and the interassay variability was 9.7%. All samples from each man were analyzed in the same assay. Serum LH and FSH results were calculated using the computer program of Burger *et al.* (9).

T and E_2 RIA. The RIA for serum T and E_2 used reagents supplied by the WHO Matched Reagent Programme (10). The antisera were raised in rabbits against BSA conjugates of T and E_2 . The anti-T antiserum had 14% cross-reactivity with 5 α -dihydrotestosterone, 6% with 5 α -androstanediol, and less than 2% with the other steroids tested. The anti- E_2 antiserum had 17% cross-reactivity with estrone. Both T and E_2 were extracted from serum with ether. Separation of bound from free hormone in these assays was accomplished by dextran-coated charcoal. The assay sensitivity was 0.1 ng/ml for T and 8 pg/ml for E_2 . The intra- and interassay variabilities were 5.1% and 9.8%, respectively, for T, and 8.2% and 8.8%, respectively, for E_2 .

SHBG and free T calculation. SHBG determinations were performed courtesy of Dr. Stephen R. Plymate, Madigan Army Medical Center (Tacoma, WA), using a modification (11) of procedures for measuring androgen-binding protein described by Musto and Bardin (12). Serum samples were incubated with charcoal for 16 h at 4 C so as to remove circulating steroids before dihydrotestosterone saturation analysis. Free T levels were calculated by the formula of Pearlman (13) using the equilibrium association constant of T for SHBG of Moll *et al.* (14).

Statistical analysis. Results between different LHRH regimens in each study were compared using a two-way analysis of variance. In determining mean results, the limit of detectability for the particular assay was used for individual results that were below assay sensitivity.

Results

Study 1

Figure 1 shows the mean serum FSH and LH levels at 10-min intervals before LHRH and after the last two doses of LHRH in each of the three periods. FSH and LH levels before LHRH administration were below or at the lower limit of the normal adult male range (FSH, 30–230 ng/mL; LH, 8–50 ng/mL) in all IHH men. During LHRH administration, FSH levels rose to within the normal range. Serum FSH levels progressively increased as the LHRH regimen changed from 2.5 μ g every 1 h to 5.0 μ g every 2 h to 7.5 μ g every 3 h (*i.e.* as the LHRH pulse frequency decreased, while the total daily dose of LHRH was constant). Serum LH levels also rose to

within the normal adult male range during LHRH administration. However, in contrast to the progressive increase in FSH levels with decreasing LHRH pulse frequency, mean LH levels were similar during the three regimens.

Figure 2 shows the mean serum FSH and LH levels for all samples obtained at the end of each LHRH regimen (10-min sampling after the last two LHRH doses). During the control period, the mean FSH level was 28 ± 3 ng/mL. As the LHRH pulse frequency decreased from every 1 to every 2 to every 3 h, mean FSH levels progressively increased from 99 ± 33 (\pm SEM) to 133 ± 34 to 181 ± 58 ng/mL ($P < 0.05$). During the control period, the mean LH level was 6 ± 2 ng/mL. During LHRH administration, LH levels were not significantly different among the regimens. As the LHRH regimen changed from 2.5 μ g every 1 h to 5.0 μ g every 2 h to 7.5 μ g every 3 h, the mean LH level remained nearly constant at 34 ± 6 , 33 ± 7 , and 34 ± 5 ng/mL, respectively.

Steroids and SHBG

Steroid results are shown in Fig. 2 and Table 1. Initially, serum total and free T levels were in the prepu-

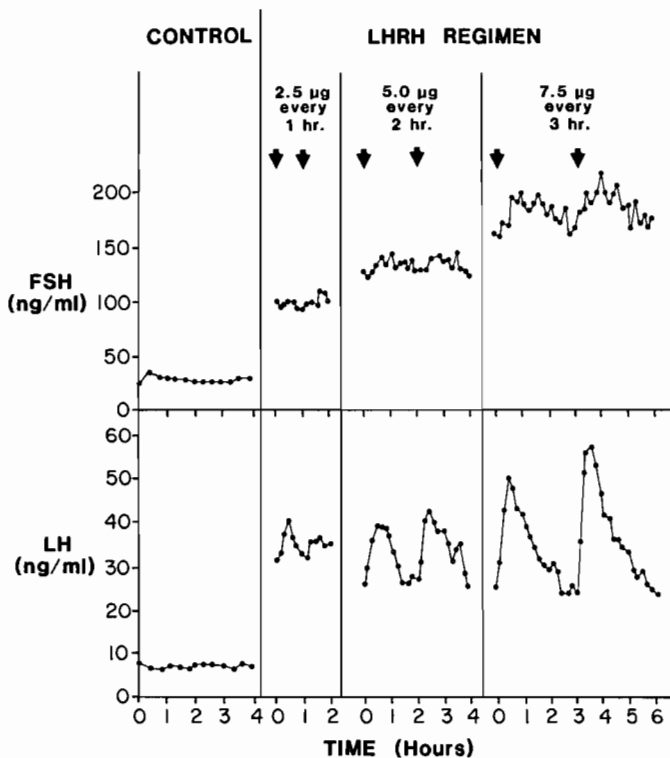


FIG. 1. Mean serum FSH and LH levels at each individual time point during frequent blood sampling in four men with IHH before and during the pulsatile administration of the same total daily dose of LHRH in three different pulse frequencies. LHRH regimens are arranged in order of decreasing frequency, although the order of administration differed in each man (see *Materials and Methods*). Arrows denote the time of LHRH pulses. Note the progressive increase in FSH levels and unchanging LH levels with decreasing LHRH pulse frequency.

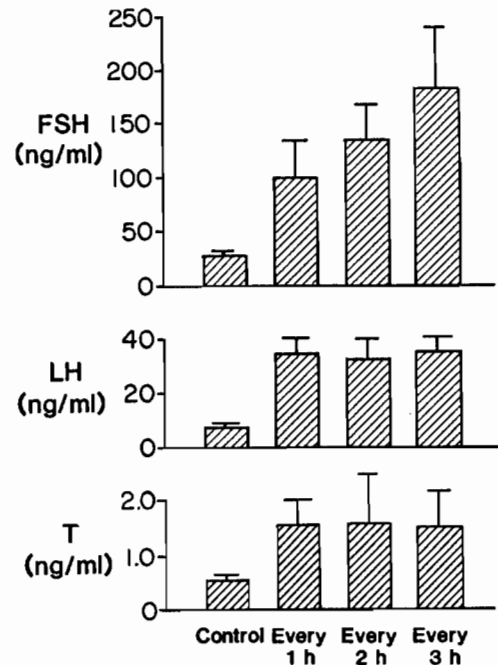


FIG. 2. Mean (\pm SEM) serum FSH, LH, and T levels during frequent blood sampling during the pulsatile administration of the same daily dose of LHRH in three different pulse frequencies to four men with IHH. The increase in FSH levels with decreasing LHRH pulse frequency was statistically significant by analysis of variance ($P < 0.05$). There were no significant differences in LH and T levels with decreasing LHRH frequency, although both were increased by LHRH compared to control values.

TABLE 1. Serum SHBG, free T, and E₂ values in study 1

	E ₂ (pg/mL)	SHBG (ng DHT bound/ml)	Free T (pg/mL)
Control	<8	10.2 ± 5.1	12 ± 4
LHRH regimen			
2.5 µg every h	9 ± 1	9.0 ± 3.8	45 ± 20
5.0 µg every 2 h	12 ± 3	8.8 ± 2.9	47 ± 20
7.5 µg every 3 h	12 ± 2	8.8 ± 3.0	44 ± 20

All values are the mean ± SEM (n = 4) of single blood samples drawn during the control period and at the end of each LHRH treatment regimen. DHT, Dihydrotestosterone.

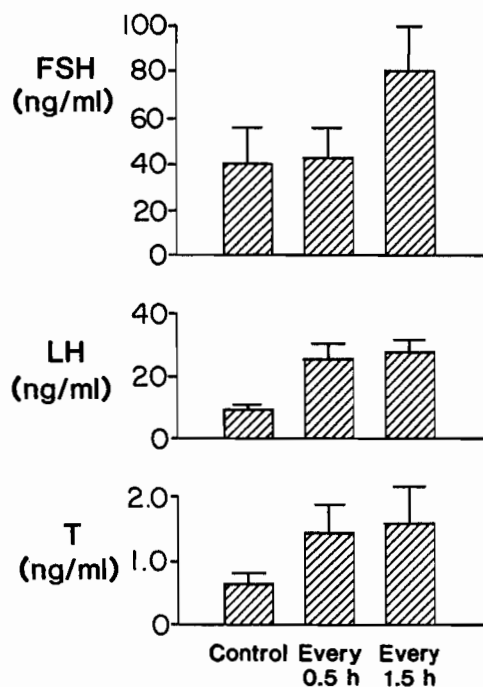


FIG. 3. Mean (±SEM) FSH, LH, and T levels during frequent blood sampling before and during pulsatile LHRH administration of a constant bolus dose of LHRH in two different pulse frequencies to three men with IHH. Compared to control levels, FSH, LH, and T levels increased during LHRH administration. Note the increase in FSH levels and unchanging LH and T levels during the less frequent schedule of pulsatile LHRH administration (every 1.5 h).

beral range, and E₂ levels were undetectable in all men. All had increased T and E₂ levels during LHRH administration, although the mean T and E₂ levels remained below the normal adult male range throughout the study. There were no statistically significant differences in total T, free T, E₂, or SHBG levels among the LHRH regimens.

Study 2 (Fig. 3)

Control serum FSH and LH levels were at or below the lower limit of the normal adult range. When LHRH was administered at a dosage of 2.5 µg every 0.5 h, there was a significant increase in LH, but no change in FSH

levels. With slowing of the LHRH pulse frequency from every 0.5 h to every 1.5 h, FSH levels increased significantly (42 ± 13 to 80 ± 19 ng/mL; *P* < 0.05), while LH did not change.

The mean control serum T levels (Fig. 3) and E₂ levels (9 ± 1 pg/mL) were in the prepubertal range. During both regimens of LHRH administration, mean T levels increased to approximately 1.5 ng/mL (Fig. 3). E₂ levels also increased to a similar extent during the every 0.5 h (14 ± 3 pg/mL) and every 1.5 h (17 ± 1 pg/mL) regimens.

Discussion

To explore the potential physiological significance of pulsatile hormone stimulation to target organ response, we determined the effect of administering LHRH in a pulsatile manner at several different frequencies on gonadotropin secretion in men with IHH and presumed endogenous LHRH deficiency. As the frequency of LHRH administration decreased, serum FSH levels increased progressively relative to LH levels when either the total daily LHRH dose or the individual LHRH dose was held constant. These results demonstrate that in man, the frequency of LHRH stimulation can differentially alter FSH and LH secretion by the pituitary gland.

In designing studies of this type, there are three relevant interrelated parameters for LHRH administration. These are the dose per pulse, the frequency of the pulse, and the total amount of hormone administered. It is not possible to alter only one of these parameters at a time; at least two must be altered. This is the reason that we performed the two studies reported here. The frequency of LHRH administration was varied in both studies, while the total amount of LHRH administered was held constant in study 1, and the dose per pulse was held constant in study 2.

In study 1, four patients with IHH were given LHRH in three different pulse frequencies, with the amount of LHRH per day being held constant. Mean serum FSH levels progressively increased as pulse frequency decreased. Because the every 1 and every 3 h regimens were administered in different orders, the increase in FSH levels with decreasing frequency of LHRH administration was not related to the duration of LHRH administration. Unlike the progressive increase in FSH, mean LH levels, although increased above control levels, were not significantly affected by changes in the frequency of LHRH stimulation. Therefore, changing the pattern of LHRH stimulation can separately alter LH and FSH secretion.

In study 2, the amount of LHRH administered per dose was held constant, while the dosing frequencies of LHRH were varied from every 0.5 to every 1.5 h. FSH levels increased as the LHRH pulse frequency decreased,

whereas LH levels did not change. FSH levels rose despite the fact that the total amount of LHRH administered per day was less at the lower pulse frequency.

Mean T and E₂ levels increased to a similar extent despite the changes in LHRH pulse frequency in both studies, but were still in the hypogonadal range. The increases probably reflect the similar amount of LH stimulation of the testes achieved by the various LHRH regimens. The lack of increase to within the normal range allowed us to assess pituitary responsiveness to the different frequencies of LHRH administration with minimal influence of testicular steroids. Because the sex steroid levels were stable, changes in steroid feedback are highly unlikely to account for the selective increase in FSH.

Finkelstein *et al.* (15) recently reported that low dose pulsatile LHRH administration in decreasing pulse frequencies did not lead to a selective increase in FSH levels in IHH men. However, these investigators studied IHH men only after serum T levels were normalized for at least 6 months. As stated above, we studied IHH men at a time when serum T and E₂ levels were not normal to minimize the influence of testicular steroids. The importance of steroid hormone milieu on differential modulation of FSH and LH secretion by alterations in LHRH pulse frequency has been demonstrated by Adams *et al.* (16). In orchidectomized juvenile monkeys, these investigators found that slower pulse frequencies of LHRH favored selective secretion of FSH over LH. However, when T levels were restored to adult levels using T-containing Silastic capsules, differential regulation of FSH and LH secretion by LHRH pulse frequency was not found. Therefore, the apparently conflicting results of our studies with those of others may be explained by differences in steroid hormone milieu.

Another difference between the study of Finkelstein *et al.* (15) and this study is that they administered LHRH iv, while we used the sc route. It seems unlikely that this is a critical difference, since both routes induce prompt serum LHRH pulses (Gross, K. M., A. M. Matsumoto, and W. J. Bremner, unpublished observations) and gonadotropin release.

Our studies demonstrate that when either the total amount of LHRH per day or the amount of LHRH per dose is held constant, the frequency of LHRH administration can alter the ratio of FSH to LH secretion. The mechanism for such frequency modulation is at present unknown. Because the action of LHRH is mediated by cellular receptors located on the gonadotropin-producing cells, the pattern of LHRH stimulation of these receptors may alter their function or number. Recent studies suggest that LHRH receptor number is dependent on the frequency of pulsatile LHRH stimulation (17). It is possible that the differential control of LH and FSH secre-

tion by LHRH pulse frequency is mediated by a mechanism that employs two populations of receptors with different regeneration times. In fact, there is evidence for more than one population of LHRH receptors (18, 19). Alternatively, postreceptor mechanisms may be involved in the frequency modulation of LH and FSH secretion.

Elevations of FSH levels relative to LH levels occur in several clinical and physiological situations, including peripuberty, perimenopause, idiopathic oligospermia, and gonadal dysgenesis. Explanations for this hormonal pattern have included decreased gonadal steroid feedback (20), decreased inhibin levels (21), and increased activity of a separate FSH-releasing hormone (22). Although not excluding any of these proposed mechanisms, our results provide an alternative mechanism for elevation of FSH relative to LH levels, namely diminished LHRH pulse frequency. We have reported that men with selective elevations of FSH have a slowed LH pulse frequency compared to normal men, providing evidence for decreased LHRH pulse frequency in these men (23). In study 1, administration of LHRH at a dosage of 7.5 µg every 3.0 h produced a gonadotropin secretory pattern similar to that found in men with selective FSH elevation (23), *i.e.* elevated FSH and normal LH levels with a slowed LH pulse frequency and increased LH pulse amplitude. These findings suggest that decreased LHRH pulse frequency in these men is at least partly responsible for their elevated FSH levels.

Our results demonstrate the potential importance of the frequency of LHRH stimulation on anterior pituitary function in man. Knobil and his colleagues (2-4) demonstrated similar effects of the pattern of LHRH stimulation in nonhuman primates. Recently, studies examining the importance of the pattern of hormonal stimulation on target organ response in several other hormonal systems have been reported. In perfused rat ovarian tissue, continuous administration of LH was less effective than pulsatile administration for supporting E₂ production (24). In humans treated with somatostatin to suppress endogenous insulin production, the hypoglycemic effect of administered insulin was greater during pulsatile compared to continuous delivery (25). Weigle *et al.* (26) found that glucose production by perfused rat hepatocytes was greater during pulsatile compared to continuous glucagon administration. Clark *et al.* (27) demonstrated that pulsatile GH administration to hypophysectomized immature rats resulted in greater body weight and growth rate than continuous GH infusions at the same daily dose. This increasing body of evidence suggests that the pattern of hormonal stimulation is a part of the endocrine signal conveying information to target organs and, therefore, is an important component of physiological control mechanisms.

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