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SYNCHRONIZATION OF AUGMENTED LUTEINIZING HORMONE SECRETION WITH SLEEP DURING PUBERTY

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Abstract Luteinizing hormone (LH) was measured in plasma every 20 minutes for 24 hours in 14 children and adolescents in different stages of sexual maturation and in five adult men. Polygraphic monitoring of nocturnal sleep was carried out simultaneously to identify sleep onset, wakefulness and sleep stages precisely. Prepubertal children and adult men showed no consistent significant difference between mean LH concentrations with subjects asleep and awake. In all pubertal subjects, an increase in LH secretion was associated with sleep that resulted in significantly higher mean LH concentrations than with the subject awake. By experimental delay in sleep onset, synchronization of this LH secretory "program" with actual sleep was clearly demonstrated. The number of LH secretory episodes during night or day sleep corresponded to the number of sleep cycles of rapid and nonrapid eye movements. This finding of a sleep-associated increase in LH secretory activity provides a biologic index for the identification of puberty.

THE recent demonstration in man that the total daily production of cortisol occurs in a series of discrete secretory episodes, separated by periods of complete quiescence of the adrenal cortex,[1] prompted evaluation of the 24-hour secretory patterns of other hormones. Several groups of investigators have reported that luteinizing hormone (LH) secretion in women[2-4] and men[5,6] is characterized by abrupt increases in LH concentration followed by slower declines that approximate the half-life of LH. This behavior is consistent with an interval of glandular secretion followed by complete cessation of hormone production — a fact proved for cortisol secretion by the adrenal cortex.[1] In view of these findings, the 24-hour LH secretory pattern in children and adolescents was studied before and during sexual maturation in an attempt to clarify the sequential hormonal changes associated with the initiation and progression of puberty. The finding of a striking increase in LH secretion associated with sleep in all pubertal subjects of both sexes suggests an important biologic role of sleep in normal sexual development.

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MATERIALS AND METHODS

Subjects

The prepubertal and pubertal subjects were five to 16 years old and included nine boys and five girls. Pubertal stage was assigned according to the criteria of Tanner[7] from preadolescent (P1) to almost complete sexual maturity (P5). The intermediate stages are based on the progressive enlargement of the scrotum, testes, and penis in boys and increasing maturity of the breasts in girls. The five adult men were 22 to 40 years old. All subjects were separately hospitalized in a light-proofed and sound-proofed room on the Clinical Research Center. The subjects were adapted to the sleep laboratory for at least 24

Abbreviations Used	
HCG:	human chorionic gonadotropin
LH:	luteinizing hormone
NREM:	nonrapid eye movement
REM:	rapid eye movement
2d IRP-HMG:	Second International Reference Preparation of Human Menopausal Gonadotropin

hours before the 24-hour, 20-minute interval blood-sampling study. On the morning of the blood study, a catheter was inserted into an antecubital vein and attached to a longer connecting tube, which extended into an adjoining room. This made it possible to obtain blood samples around the clock without disturbing the subject. The precise details of obtaining and handling blood samples have previously been reported from this laboratory.[1] During all sleep periods, including the delayed sleep-onset study, the subject slept with scalp electroencephalogram, electro-oculogram and electromyogram electrodes. The polygraphic readings were scored for sleep stage in 30-second epochs according to the criteria of Rechtschaffen and Kales.[8]

Plasma LH Measurement

Plasma LH was measured by the double-antibody radioimmunoassay described by Midgley[9] as modified in our laboratory.[6] The highly purified LH (LER 960) used for radioiodination and the pituitary reference preparation (LER 907) were provided by the National Pituitary Agency–National Institutes of Arthritis and Metabolic Diseases. The anti-human chorionic gonadotropin (HCG) antibody used (rabbit) was shown to be specific for LH.[6] Results are expressed in terms of the Second International Reference Preparation of Human Menopausal Gonadotropin (2d IRP-HMG) provided by Dr. D.R. Bangham, Mill Hill, England. In terms of the pituitary reference preparation LER 907, 1 mIU of the 2d IRP-HMG is equivalent to 5 ng of LER 907. The coefficient of variation for duplicate samples is approximately 10 per cent. All plasma samples from each 24-hour study were assayed simultaneously.

Delayed Sleep-Onset Study

In Case 11, a repeat plasma sampling study was carried out as described above, with the modification that with continuous polygraphic monitoring, sleep onset was delayed until 5:25 a.m. The catheter had been inserted at 10 o'clock on the previous night, and 20-minute-interval sampling continued until 6 p.m. on the following day.

Results

Figure 1 shows the 24-hour LH secretory pattern of a representative boy in early puberty (Case 8) derived from 20-minute-interval blood sampling. A histogram has been constructed above the time of nocturnal sleep that portrays the sleep-waking pattern and sleep-stage sequence. The REM-NREM sleep cycle of rapid (REM) and nonrapid (NREM) eye movement averages 70 to 90 minutes and is repeated four to six times throughout the night, depending on the duration of sleep.[10] Figure 2 shows the LH secretory pattern and sleep histogram of another early pubertal boy (Case 11) during a delayed sleep-onset study. In the age group represented by these subjects the first REM period is frequently "missed," and the amount of sleep stages 3 and 4 may be greater than in the adult.[11]

An LH secretory episode was defined as an incremental rise in consecutive LH concentrations of more than 30 per cent followed by a plateau or fall

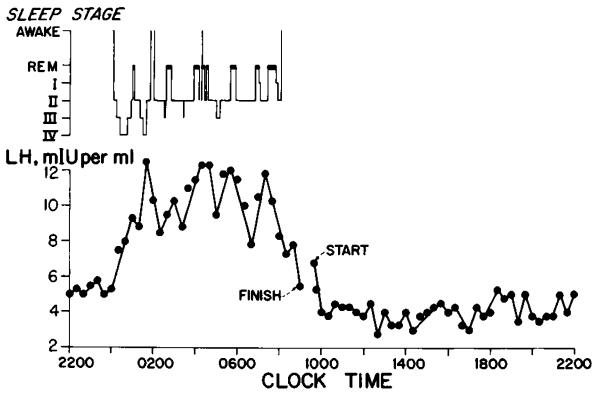

Figure 1. Plasma LH Concentration Sampled Every 20 Minutes around the Clock in Case 8, in Early Puberty.
The sleep histogram is shown above the eight-hour period of nocturnal sleep. Sleep stages are awake, REM=▬, stage I-IV by depth of line graph. Plasma LH concentration is expressed as mIU/ml 2d IRP-HMG.

in the plasma LH concentration. This conservative criterion was established to exclude changes in plasma LH that could have resulted from either assay variability or small secretory episodes of brief duration. It is our belief that these smaller increments in LH are the result of short secretory episodes.

Mean LH Concentration during Sleep and Awake Periods

The mean LH concentration during sleep and awake periods was calculated by averaging of all the LH values that fell within each period (Table 1). In the four preadolescent children (P1), there was no significant difference between the mean LH concentrations asleep and awake. In all seven early pubertal subjects (P2, P3) the mean sleep LH concentration was significantly (p less than 0.001) greater than the mean awake LH concentration. The increase in LH concentration was uniformly observed immediately after onset of sleep. It should be noted that except for Case 10, the mean awake LH concentrations were not significantly different from the

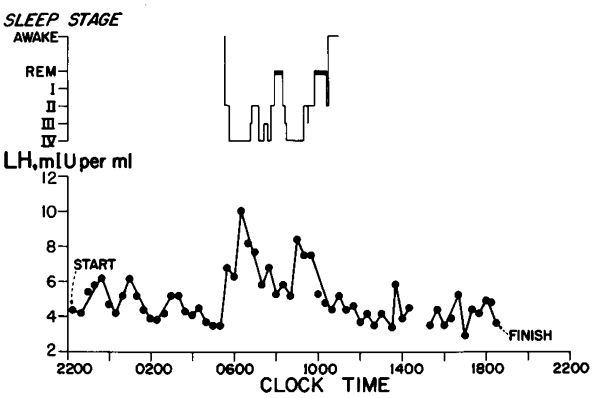

Figure 2. Plasma LH Concentration Sampled Every 20 Minutes in Case 11 during Delayed Sleep-onset Study.
The sleep histogram is shown above the period of sleep that began at 5:25 and ended at 10:25 a.m.

Table 1. Plasma LH Concentrations Asleep and Awake in Prepubertal, Early Pubertal and Late Pubertal Subjects.

Status	Case No.	Age (Yr)	Sex	LH (mIU/Ml)*	
				Sleep	Awake
Prepubertal (P1)†	1	6	F	4.2 ± .03	4.2 ± .07
	2	5	F	3.1 ± .03	2.9 ± .07
	3	8	M	3.4 ± .05	3.0 ± .07
	4	11	M	3.4 ± .10	3.3 ± .06
Early pubertal (P2, P3)‡	5	12	M	4.9 ± .06	3.4 ± .08
	6	9	F	5.5 ± .16	3.7 ± .11
	7	12	F	5.3 ± .07	3.6 ± .12
	8	15	M	10.1 ± .17	4.3 ± .08
	9	13	F	15.8 ± .20	5.2 ± .27
	10	10	M	8.9 ± .20	7.3 ± .16
	11	15	M	7.4 ± .18	4.1 ± .07
Late pubertal (P4, P5)‡	12	15	M	11.0 ± .50	8.2 ± .15
	13	13	M	12.5 ± .62	8.6 ± .25
	14	16	M	16.2 ± .42	13.0 ± .42

*Mean ± SE.
†Mean sleep LH concentration not significantly different from mean LH awake.
‡Mean sleep LH concentration significantly higher ($p < 0.001$) than mean LH awake.

prepubertal LH concentrations. In Case 8 (Fig. 1) not one LH sample obtained during wakefulness reached the lowest LH concentration of any sample obtained during sleep. In the three subjects in late puberty (P4, 5) daytime, waking LH secretory episodes begin to occur, resulting in a mean LH concentration in the adult range; however, there was still a significantly higher mean LH concentration during sleep. Only one of the five adult men (Table 2) showed a significantly higher mean LH concentration during sleep (Case 18). In five normal adult women studied during menstruation there was no significant difference between sleep and awake mean LH concentrations.[12]

Table 2. Plasma LH Concentrations Asleep and Awake in Adult Men.

Case No.	Age (Yr)	Sex	LH (mIU/Ml)*	
			Sleep	Awake
15	38	M	5.3 ± .09	5.7 ± .03
16	22	M	6.4 ± .36	7.9 ± .17†
17	40	M	7.5 ± .21	6.7 ± .26
18	24	M	13.0 ± .37	11.3 ± .31‡
19	21	M	7.3 ± .16	7.0 ± .18

*Mean ± SE.
†Mean LH awake significantly higher ($p < 0.05$) than mean LH asleep.
‡Mean LH asleep significantly higher ($p < 0.05$) than mean LH awake.

Intermittent LH Secretory Activity

The LH secretory patterns during sleep were characterized by regularly occurring secretory episodes with a periodicity of 70 to 90 minutes. In Figure 1, the interval between LH secretory episodes was 85 minutes. No such regularity was noted during the awake period in this or any of the other early pubertal subjects. In Figure 1, there are 11 secretory episodes during the 24-hour period. Five occurred during sleep, and six during wakefulness. Although the number of secretory episodes for the two periods was similar the amount of LH secreted during sleep was much greater. The mean and range for the incremental rise in plasma LH for the sleep and awake secretory episodes for the adolescent subjects are shown in Table 3. These data clearly show the enhanced secretion of LH associated with sleep. This augmentation of LH secretory activity associated with sleep was not found in prepubertal children, normal adult men[6] or adult women studied during menstruation.[12]

Table 3. LH Secretory Episodes and Their LH Increments Asleep and Awake in Early and Late Puberty.

Pubertal Stage	Case No.	Secretory Episodes		Mean LH Increment for Secretory Episodes (mIU/Ml)	
		Sleep	Awake	Sleep	Awake
P2, P3	5	6	3	1.8 (1.3- 2.3)*	1.5 (1.0- 2.0)
	6	4	5	4.0 (2.4- 5.6)	3.0 (1.7- 4.7)
	7	4	5	4.2 (2.0- 6.2)	1.8 (1.4- 2.3)
	8	5	6	3.5 (2.5- 4.0)	1.3 (1.2- 1.5)
	9	5	6	10.3 (6.8-14.5)	4.5 (3.2- 7.8)
	10	5	5	4.9 (3.0- 7.3)	4.0 (2.3- 7.0)
	11	5	1	2.9 (2.0- 3.8)	2.2†
P4, P5	12	5	8	9.1 (4.4-11.6)	6.8 (3.1-10.7)
	13	4	8	9.0 (4.5-11.7)	7.2 (5.0-10.8)
	14	5	5	11.1 (4.0-19.0)	11.6 (2.8-23.5)

*Figures in parentheses represent ranges of LH increments for secretory episodes.
†Only 1 statistically significant LH secretory episode.

Association of Augmented LH Secretion with Sleep

In Case 11, a delayed sleep-onset study was done to establish precisely the association of LH secretion with sleep during adolescence. The results are shown in Figure 2. The augmentation of LH secretion with actual sleep is clearly demonstrated as against the possibility of a circadian rhythm that is not immediately linked to sleep. The mean LH concentrations during sleep (6.8 mIU per milliliter) and awake (4.4 mIU per milliliter) periods were similar to those found in this subject's control 24-hour study (Case 11, Table 1). This effect was not due to darkness since blindfolding this subject while he was awake failed to cause increased LH secretion. A natural experiment of the relation of increased LH secretion to sleep occurred in a few of the subjects during periods of spontaneous arousal during the nocturnal sleep period. During these periods of arousal, the peak of an LH secretory episode was truncated, or the initiation of a secretory episode was delayed until the resumption of sleep. It is of interest that the LH secretory episodes between 10 p.m. and 4 a.m. in the delayed sleep-onset study (Fig. 2) were of greater magnitude and more regular than the LH secretory episodes during this subject's normal awake period (6 a.m. to 6 p.m.). When a comparison was made with the six-hour period before onset of sleep (5 to 11 p.m.) in this subject's control study a similar regularity was found, indicating, perhaps, a progressive buildup in LH secretory activity before onset of sleep. The subject in Figure 1 also shows a suggestion of this pre-sleep augmentation of LH secretory activity (6 to 12 p.m.). Further studies using delayed sleep onset, sleep reversal and short multiple sleep periods throughout the 24-hour period will be required to characterize this phenomenon more accurately. The sleep-associated increase in LH secretion, as well as sleep-associated growth-hormone secretion,[13] shifts immediately with sleep

irrespective of when sleep occurs. This phenomenon is in contrast to the cortisol secretory program, which remains unchanged for several weeks despite a 180° shift in the sleep-wake cycle.[14]

Periodicity of LH Secretory Activity during Sleep

In all pubertal subjects (P2-P5) there was a general relation between the number of LH secretory episodes occurring during sleep and the number of sleep cycles (Fig. 1 and 2). The LH secretory episode interval of 75 to 100 minutes is similar to the periodicity of the NREM-REM sleep cycle, which averages 70 to 90 minutes. In an attempt to correlate the initiation of LH secretory episodes with specific sleep stages it was noted that LH secretion was almost uniformly initiated during NREM sleep. The point of termination of LH secretory episodes was also noted to occur consistently in close proximity to or during REM sleep. These data suggest that REM sleep and wakefulness are associated with either a decrease or a cessation of LH secretory activity.

The mean sleep and awake LH concentrations for each of the 19 subjects studied from prepuberty to adulthood are shown in Figure 3.

Discussion

The association of increased LH secretion with sleep is consistently present only during adolescence (P2-P5). Before the initiation and after the completion of sexual maturation there is no consistent, significant augmentation of LH secretion during sleep. In later stages of puberty (P4, P5) the mean daytime, awake LH concentrations are increasing, and there is less distinction between the sleep and awake mean LH concentrations. Since this increase in LH secretion associated with sleep was found only during puberty, consideration must be given to the importance of this phenomenon in the initiation of puberty. Although LH and follicle-stimulating hormone (FSH) have been detected by bioassay[15] and radioimmunoassay[16] in the urine of prepubertal children it has not been established whether a sharp rise in either or both hormones coincident with the appearance of secondary sexual characteristics occurs. The present study demonstrates the existence of a central-nervous-system LH secretory program that is intimately linked to sleep and causes two to four times higher mean LH concentrations during sleep than during wakefulness. This would explain the finding of Leydig-cell stimulation[17] and increasing HCG responsiveness[18] during early puberty in the absence of a significant increase in the waking plasma LH concentration.

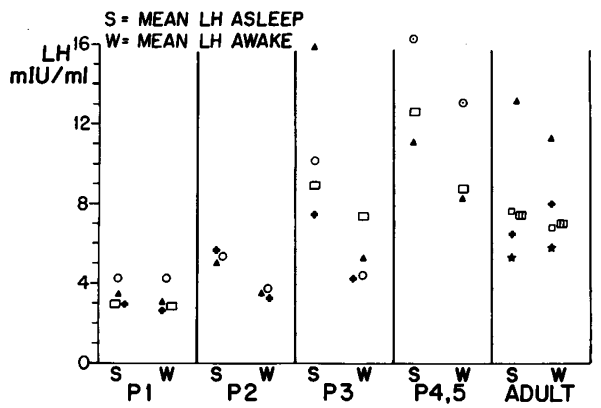

Figure 3. Mean Plasma LH Concentrations Asleep and Awake during the Stages of Sexual Maturation in Each of the 19 Subjects Studied.

Each pair of symbols within the same stage of maturation represents the concentration of LH during sleep or waking, in the same subject.

The finding of a similar periodicity between LH secretory activity during sleep and the recurrent REM-NREM sleep cycle suggests some inter-relation between these events; however, it remains to be established whether they are activated by a common mechanism. This study again underlines the importance of considering hormone secretion as a dynamic, 24-hour process characterized by widely fluctuating plasma concentrations and periods of episodic secretion. The importance of considering the effect of age as well as various stages of human development has also been demonstrated in this study as well as in a recent report for growth hormone.[19]

We are indebted to the National Pituitary Agency–NIAMD for providing the LH (LER 960) and pituitary reference preparation LER 907 used in this study, to Dr. D. R. Bangham, Mill Hill, London, England, who provided the second International Reference Preparation, and to Joanne Imperial, Margot Hartman, Henry Jeanette, Nate Katz, Mira Fein, Doris Mui and Hilda Denman for technical assistance.

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FERTILITY IN MALES WITH CYSTIC FIBROSIS

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Abstract Two unrelated males with cystic fibrosis had normal sperm counts and volume of ejaculate, and one of them fathered two children. Detailed chemical and morphologic analyses of the semen from the first patient were normal. These findings are in contrast to the aspermia and abnormal chemical values in semen previously reported for patients with cystic fibrosis.

In a survey of 105 cystic-fibrosis centers, 78 responded to a questionnaire and reported fertility data on 117 males; two (those reported in this paper) were fertile, and another six were believed to have fathered children but their semen was not studied. Normal fertility occurs in a small but appreciable number of males (in the range of 2 to 3 per cent) with this disease. The finding of such fertile males has genetic, social, and psychologic implications and makes it mandatory to evaluate the semen (at a minimum, sperm count and ejaculate volume measurement) in all postpubescent males with this disease before counseling.

SINCE the reports by Denning et al.[1] and Kaplan and his associates[2] it generally has been assumed that virtually all postpubescent males with cystic fibrosis are infertile, the sterility being due to aspermia secondary to maldevelopment of mesonephric derivatives. Feigelson and his co-workers reported a documented case of a fertile male with cystic fibrosis in the French literature in 1969.[3] Another reference to a fertile male patient has been made, but without documentation.[4] Both the unrelated males with cystic fibrosis described below had normal semen specimens, and one of them fathered two children.

CASE REPORTS

CASE 1. A 26-year-old white man was not diagnosed as having cystic fibrosis until the age of 21 years despite severe pulmonary symptoms for the previous 10 years. In childhood he was thought to have mild "asthma." Chest roentgenograms at the age of 10 years were interpreted as normal; x-rays 5 years later showed linear and nodular densities.

Since 17 years of age the patient had had numerous pulmonary exacerbations requiring hospitalization, and between the ages of 19 and 21 years, he was thought to have bronchiectasis and underwent thorough evaluation at several other institutions; the diagnosis of cystic fibrosis was considered but never made.

In 1966, at the age of 21 years, he was referred to the National Institutes of Health, where the diagnosis of cystic fibrosis was based on repeatedly abnormal sweat electrolyte levels obtained by pilocarpine iontophoresis (range, sodium, 91 to 98, and chloride, 79 to 84 mEq per liter), pancreatic insufficiency (absent trypsin, chymotrypsin and carboxypeptidase B activities on duodenal intubation), and chronic pulmonary disease. Despite the pancreatic deficiency, fecal fat excretion of 8 g per 24 hours on balance studies was only slightly elevated, and the patient had little symptomatology referable to the gastrointestinal tract, even though he was not taking supplemental pancreatic enzymes.

During the past 5 years he had had several small episodes of hemoptysis. In spring of 1971 a 30 to 40 per cent unilateral pneumothorax requiring hospitalization developed.

Currently, he weighs 71.5 kg, is 184 cm in height, and has a Shwachman score[5] of 73, with 2 to 3+ clubbing and persistent rales. Examination of the genitalia revealed normal testes, vasa deferentia, and prostate gland. The results of examination of his semen are shown in Table 1. He did not sleep in a mist tent, gave himself postural drainage intermittently, and required continuous antibiotic therapy. The most recent pulmonary-function tests revealed a normal vital capacity, but a forced expiratory volume at 1 second that was 49 per cent of the predicted value. Chest x-ray examination now showed moderate fibrosis and mild obstructive emphysema. The serum was positive for the cilia inhibitory factor* (Spock).[6]

There was no family history of cystic fibrosis, and 3 siblings were normal. The parents were not consanguineous.

CASE 2. A 24½-year-old white man was first diagnosed as having cystic fibrosis at the age of 19 years at the University of Wisconsin Medical Center, when a sibling was found to have the disease. At the age of 10 weeks he had had pneumonia and hospitalization was required. He had "whooping cough" at 12 weeks of age. X-ray examination at the time the diagnosis of cystic fibrosis was made revealed thickening of bronchi and prominent lung markings in the upper lobes, although an x-ray film taken at the age of 13 years had been described as normal; no history of a chronic cough could be obtained at the time of diagnosis. There also was no history of symptoms suggestive of malabsorption. Sweat tests done twice by pilocarpine iontophoresis revealed sodium concen-

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*Kindly performed by Dr. Alexander Spock, Duke University Medical Center, Durham, N.C.