Hypothalamic-Pituitary Function in Diverse Hyperprolactinemic States

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Abstract Prolactin secretion in normal adults is characterized by periods of episodic secretion which increase in magnitude during sleep. In this study, we report the 24-h mean prolactin concentrations, prolactin secretory patterns, and associated pituitary hormone function in nine patients (seven women and two men) with hyperprolactinemia of diverse etiologies. Four of the women and one of the men had clinically demonstrable pituitary tumors, one boy had a hypothalamic tumor, and the three other women had "functional" hyperprolactinemia. The 24-h mean prolactin concentrations derived from averaging the 20-min interval samples for 24 h ranged from 28.6 to 1,220 ng/ml. The plasma prolactin patterns in these patients showed persistence of episodic secretion in all and loss of the normal sleep-wake difference in plasma prolactin in seven of nine. Three of the patients with galactorrhea and comparable 24-h mean prolactin concentrations (58.3, 59.7, and 64.3 ng/ml) showed similar prolactin secretory patterns despite different etiologic mechanisms. Evaluation of the secretory patterns of luteinizing hormone (LH) in these patients showed loss of normal pulsatile LH release and a low 24-h mean LH concentration in the patient with the pituitary tumor, while the two patients without clinically demonstrable pituitary tumors ("post-pill" galactorrhea and "idiopathic" galactorrhea) showed normal LH secretory patterns and 24-h mean LH concentrations. The 24-h mean cortisol concentrations and secretory patterns were normal in five of the seven patients who had these parameters measured. The patient with the hypothalamic tumor had a low 24-h mean cortisol concentration and production rate and absent response to metyrapone. The patient with "idiopathic" galactorrhea had an elevated 24-h mean cortisol concentration but normal cortisol production rate and urinary 17-hydroxycorticoid excretion. Growth hormone secretion was abnormal in four of the patients (one with the hypothalamic tumor and three with pituitary tumors). Thyrotropin-releasing hormone (TRH) administration in four patients resulted in normal TSH release in two patients (one of whom developed galactorrhea after the test), an absent response in the patient with the hypothalamic tumor, and a blunted response in one of the women with a pituitary tumor. The two men had low 24-h mean plasma testosterone concentrations (69 and 30 ng/100 ml) and symptoms of impotence and loss of libido. Five of the women (four with pituitary tumors and one with Chiari-Frommel syndrome) had either low 24-h mean LH concentrations, abnormal LH secretory patterns, or both. These data indicate that patients with hyperprolactinemia encompassing a varied etiological range frequently show loss of the normal sleep-associated increase in prolactin secretion as well as abnormalities in the regulation of the other hypothalamic pituitary-regulated hormones. The finding that the abnormalities in LH, growth hormone, thyrotropin, and cortisol (adrenocorticotrophic) secretion were almost uniformly confined to the patients with the clinically demonstrable hypothalamic or pituitary tumors suggests that the size of the lesion is the critical factor.

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INTRODUCTION

Recent developments of sensitive and specific bioassays (1–5) and radioimmunoassays (5–8) for measurement of human prolactin (hPRL)[1] in plasma have led to an improved understanding of the pattern of secretion of this hormone in the normal (1–8) and in disease states (9–12). The demonstration that cortisol (22–24), ACTH (25), luteinizing hormone (hLH) (26), and growth hormone (hGH) (27, 28) are secreted episodic-

[1] *Abbreviations used in this paper:* BSA, bovine serum albumin; FSH, follicle-stimulating hormone; h, human; LH, luteinizing hormone; PRL, prolactin TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

ally throughout the day and night has greatly clarified and extended our knowledge of the physiological regulation of these hormones. Measurement of plasma hormone concentrations during sleep has proven to be especially important for hGH (29), LH (30), and follicle-stimulating hormone (FSH) during puberty (31) and most recently hPRL (32). In 1972, Nokin, Vekemans, L'Hermite, and Robyn (33) showed the episodicity of hPRL concentrations with peak values at 1 a.m. and 5 a.m. when sampling was carried out at 4-h intervals. Sassin, Frantz, Weitzman, and Kapen (32) showed the important role of sleep in the regulation of hPRL secretion in normal young adults of both sexes. The finding of episodicity and sleep-associated augmentation of hPRL secretion has been further clarified by recent studies (34, 35).

The present study concerns the 24-h pattern of hPRL secretion in some hyperprolactinemic patients. Plasma hPRL concentrations were measured at 20-min intervals for 24-h in nine patients with hyperprolactinemia from a variety of causes: five with pituitary tumors, one with a hypothalamic tumor, and three with "functional" [2] hyperprolactinemia (Table I). In order to evaluate the frequency and nature of associated disturbances in the hypothalamic-pituitary regulation of the secretion of other hormones, measurements were also made of LH, testosterone (in the two males), and cortisol levels (every 20 min for 24-h), control and thyrotropin-releasing hormone (TRH)-stimulated plasma thyroid-stimulating hormone (TSH) levels, control and metyrapone-stimulated urinary 17-hydroxycorticoid excretion, and control and stimulated (by insulin, arginine, and/or sleep) plasma hGH levels. The results of these studies show that: (*a*) seven of our nine patients with hyperprolactinemia had excessive diurnal hPRL secretion, disturbing the normal difference between preponderant sleep-related secretory episodes and those of wakefulness; (*b*) no differences were observed between the patterns of hPRL secretion in patients with hyperprolactinemia of "functional" origin to distinguish them from patients with pituitary or hypothalamic tumors; and (*c*) the normal pattern of secretion of hGH, LH, and TSH was more frequently affected in patients with clinically demonstrable tumors than in those patients with "functional" hyperprolactinemia.

METHODS

Subjects

Nine patients (seven women and two men) with hyperprolactinemia were studied (Table I). The seven women all had galactorrhea. Six had amenorrhea while the seventh had prolonged infertility. Four women and one man had pituitary tumors while the 17-yr-old boy had a hypothalamic tumor with diabetes insipidus. One woman had galactorrhea associated with the administration of oral contraceptives,[3] another developed galactorrhea during pregnancy, two had persistent postpartum galactorrhea-amenorrhea (Chiari-Frommel syndrome), and one patient with a pituitary tumor developed persistent galactorrhea after TRH administration.

24 h, 20-min sampling studies

All 9 patients had 20-min interval plasma sampling studies for 24 h according to protocols previously reported from this laboratory (23, 24). During the nocturnal sleep period (11 p.m. to 7 a.m.), polygraphic monitoring was carried out to identify precisely sleep onset, wakefulness, and specific sleep stages, scored according to standardized criteria (36).

Hormone assays

Plasma LH was assayed by radioimmunoassay as previously reported from this laboratory (26, 30, 31). GH (37), TSH (38), cortisol (39), and testosterone (40) were assayed by previously reported techniques. Cortisol production rate was estimated by isotope dilution (41), and urinary 17-hydroxycorticoids (42) and 17-ketosteroids (43) were measured by standard methods. Plasma hPRL was measured by a homologous radioimmunoassay utilizing reagents supplied by the NIAMD. 2 μg of highly purified human PRL (Lewis hPRL, 30 IU/mg) were iodinated with 400 μCi of ^{125}I (Union Carbide Corp., New York) according to the method of Hunter and Greenwood (44). Purification was achieved by passing the iodinated raw mixture over Sephadex G-100 (Pharmacia Fine Chemicals, Inc., Piscataway, N. J.). Three peaks were identified, and only the middle peak, which contained immunoreactive hPRL, was used for immunoassay. The anti-hPRL antibody (rabbit) was used at a dilution of 1:200,000. The hPRL was diluted with buffer to a concentration of 200 ng/ml, and standards were prepared by appropriate dilution to concentrations of 0.25, 0.50, 1.0, 1.5, 2.5, 3.75, and 5.0 ng/ml. Parallel standard curves were obtained with the hPRL standard and multiple dilutions of plasma from a patient with galactorrhea. Known quantities of standard hPRL were recovered quantitatively. Specificity studies of the anti-hPRL antibody were previously reported (8).

The anti-hPRL antibody was diluted in 0.01 M Na phosphate buffer, pH 7.6, containing 0.14 M NaCl, 0.05 M EDTA, and 3% normal rabbit serum at a final dilution of 1:200,000 in each assay tube. The [^{125}I]hPRL (10,000 cpm) was diluted in 0.01 M Na phosphate buffer, pH 7.6, containing 0.14 M NaCl and 0.1% bovine serum albumin (BSA). Plasma samples in normal subjects were assayed at 100 μl in duplicate and at 25 μl in duplicate in the patients with moderately elevated plasma hPRL concentrations (50–100 ng/ml). In the patients with marked elevations of plasma hPRL, plasma was diluted 1:10 with 1% BSA

[2] "Functional" hyperprolactinemia refers to those patients with elevated hPRL levels who have no evidence of a hypothalamic or pituitary tumor. It is readily accepted that some of these patients may have pituitary microadenomata which at the time of study are not clinically demonstrable.

[3] "Post-pill" or "post contraceptive amenorrhea-galactorrhea" refers to those women in whom amenorrhea galactorrhea occurred in close temporal association to the withdrawal of oral contraceptives. The authors recognize that no pathogenetic relationship between the withdrawal from oral contraceptives and the onset of galactorrhea has been proved.

TABLE I

Clinical Data on Patients with Hyperprolactinemia

Case no.	Age	Sex	Diagnosis	Symptoms	Visual fields	Tomograms of the sella turcica	EEG	Arteriogram	Pneumoencephalogram
1 (M. B.)	38	M	Pituitary tumor	Gynecomastia, impotence, and loss of libido	Normal	Double floor with erosion into sphenoid sinus	Normal	Normal	Intrasellar mass
2 (Z. A.)	28	F	"Post-pill" galactorrhea (amenorrhea)	Infertility, galactorrhea	Normal	Normal	Normal	—	—
3 (G. D.)	21	F	"Idiopathic" galactorrhea (oligomenorrhea)	Infertility, galactorrhea	Normal	Normal	Normal	—	—
4 (C. D.)	43	F	Pituitary tumor	Amenorrhea, galactorrhea	Normal	Enlarged sella turcica with erosion of posterior clinoids	Normal	Intrasellar mass	—
5 (S. M.)	30	F	Pituitary tumor, galactorrhea-post TRH-test	Visual difficulty, loss of visual acuity	Bitemporal hemianopsia	Enlarged sella with erosion into sphenoid sinus	Normal	Suprasellar, retrosellar, and intrasellar mass	—
6 (M. M.)	23	F	Chiari-Frommel (pituitary tumor)	Headaches, amenorrhea, galactorrhea	Normal	Enlarged sella with erosion into sphenoid sinus	Diffusely abnormal record with increase in slow wave activity	Intrasellar mass with lateral and suprasellar extension	—
7 (M. N.)	17	M	Hypothalamic tumor	Diabetes insipidus, loss of libido	Normal	Normal sella	Temporal lobe abnormality	Masses in thalamus and hypothalamic region	Multiple lesions in left lateral ventricle, anterior, posterior, and floor of third ventricle
8 (G. L.)	20	F	"Post-pill" galactorrhea-amenorrhea (pituitary tumor)	Amenorrhea, galactorrhea	Normal	Enlarged sella with erosion of anterior clinoid and thinning of dorsum sella	—	—	Intrasellar mass with bulging above pituitary fossa
9 (F. L.)	28	F	Chiari-Frommel	Persistent postpartum amenorrhea-galactorrhea	Normal	Normal	Normal	—	—

TABLE II

Mean (SD) 24-h Asleep and Awake hPRL Levels

Case no.	Diagnosis	24-h hPRL	hPRL	
			Asleep	Awake
		ng/ml	*ng/ml*	
Normal (eight studies)		9.6 (4.3)	11.9 (5.3)	8.5 (4.1)
1	Pituitary tumor	657 (137)	668 (136)	652 (138)
2	"Post-pill" galactorrhea	58.3 (10.5)	55.3 (6.5)	59.4 (8.2)
3	"Idiopathic" galactorrhea	59.7 (9.1)	62.9 (11)	58.8 (8.3)
4	Pituitary tumor	64.3 (16.3)	63.7 (17)	64.6 (15.4)
5	Pituitary tumor	595 (102)	607 (84)	590 (109)
6	Chiari-Frommel → pituitary tumor	1,220 (219)	1,350 (178)*	1,210 (169)
7	Hypothalamic tumor	28.6 (5.8)	28.4 (4.1)	28.8 (6.8)
8	"Post-pill" galactorrhea → pituitary tumor	75.1 (15.1)	77.8 (14.1)	72.6 (16.1)
9	Chiari-Frommel	78.5 (17.6)	92.5 (12.1)*	71.9 (15.8)

* Mean prolactin asleep significantly ($P < 0.001$) higher than mean prolactin awake.

buffer, and 50-μl aliquots of the diluted material were assayed. This dilution permitted the most sensitive part of the standard curve to be used for the assay and produced results indistinguishable when compared with results obtained by dilution using plasma from a hypophysectomized patient. The total volume in each reaction tube was adjusted to 500 μl by the appropriate addition of 0.01 M Na phosphate buffer, pH 7.6, containing 0.14 M NaCl and 1% BSA. After 72 h incubation at 4°C, 200 μl of goat-antirabbit gamma globulin appropriately diluted in buffer was added to precipitate maximally the antigen-antibody complex in each reaction tube. 24 h later, the tubes were centrifuged at 1,000 *g* for 30 min, the supernates were decanted, and the precipitates were counted in an automatic gamma counter. Total counts were checked for consistency in tubes throughout the assay. Results were calculated from dose interpolation of the standards by using logit-log transformation. The interassay precision for a plasma assayed in nine different assays was 11.1±2.1 (SD) ng/ml. All samples from each 24-h study were assayed simultaneously to negate interassay variability.

Special studies

L-Dopa test. L-Dopa (0.5 g) was given orally between 9 and 11 a.m., and plasma hPRL concentrations were measured at 30-min intervals for 2 h.

Thyrotropin reserve test. 500 μg of TRH was administered as a single intravenous injection, and plasma samples for TSH were measured at 20-min intervals for 2 h.

Insulin tolerance test. Crystalline insulin was injected intravenously at a dose of 0.1 U/kg, and plasma samples were obtained at 15-min intervals for 2 h for measurement of GH.

Arginine tolerance test. Arginine HCl, 0.5 g/kg (max 30 g) was administered intravenously, and plasma samples were obtained at 30-min intervals for 2 h for measurement of GH.

Metyrapone test. After two base-line 24-h urine collections, 750 mg metyrapone was given orally every 4 h for six doses, and urine 17-hydroxycorticoids and 17-ketosteroids were measured on the base-line days, day of metyrapone administration, and day after metyrapone administration.

Cortisol metabolism. [^{14}C]cortisol was injected intravenously to determine production rate, half-life, and metabolic clearance rate of cortisol by methods previously reported from this laboratory (23, 41).

Mean hormone concentrations. By averaging all 72 results obtained during the course of a 20-min interval 24-h study for hPRL, LH, cortisol, and testosterone in the males, the 24-h mean hormone concentrations were obtained. The mean cortisol concentration obtained by this method compares favorably with that obtained with the constant withdrawal pump (45). Mean plasma hPRL concentrations during sleep and awake periods were calculated by averaging the results which fell within these respective periods. Comparison of the mean plasma hPRL concentrations calculated from plasmas obtained from patients asleep and awake were used to assess the presence of the normal sleep-associated augmentation of hPRL secretion. Statistical analyses were performed by using Student's *t* test, to establish the loss of the sleep-associated augmented hPRL secretion.

RESULTS

Plasma prolactin concentrations (Table II). All nine patients had significantly elevated 24-h mean plasma hPRL concentrations, ranging from 28.6±5.8 (SD) ng/ml to 1,220±219 (SD) ng/ml. Every patient continued to show episodic secretion of hPRL throughout the 24-h period (Figs. 1–3). However, the normal increase of hPRL concentrations during sleep was lost in seven of the nine patients; levels were elevated and equal during the sleeping and waking periods. The two women with Chiari-Frommel syndrome,[4] like normal subjects, had

[4] Case 6, who initially presented as a case of the Chiari-Frommel syndrome and later developed a pituitary tumor, showed a significant statistical difference between the mean hPRL asleep compared with waking; however, the high

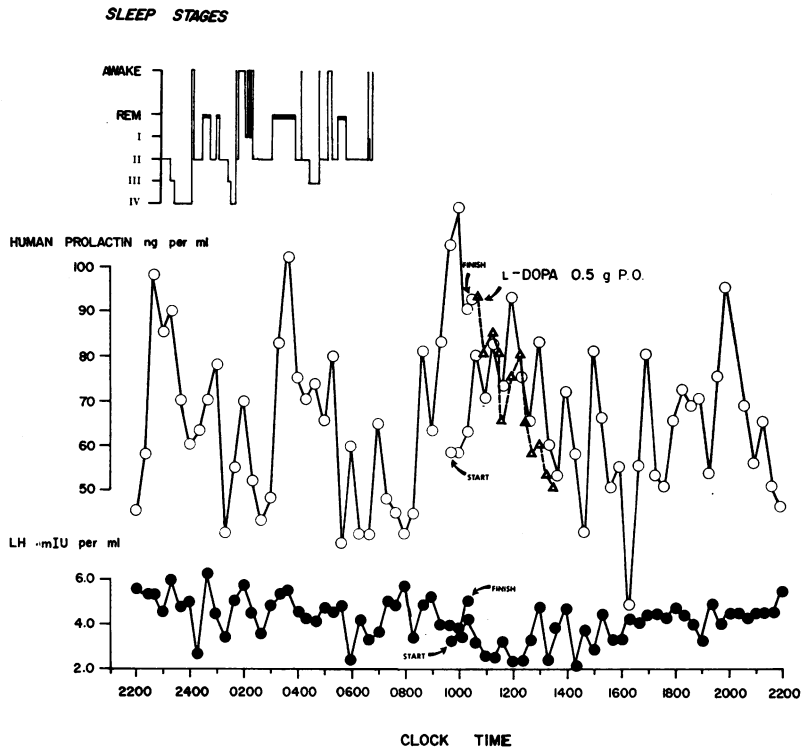

FIGURE 1 20-min interval plasma hPRL (○) and LH (●) concentrations in case 4 (C. D.) with amenorrhea-galactorrhea associated with a pituitary tumor. The effect of 0.5 g L-dopa p.o. on plasma PRL is shown from 1100–1330 h △ - - - △. The sleep histogram displaying sleep-stage sequence is shown above the period of nocturnal sleep.

significantly higher mean hPRL concentrations during sleep than while awake. Comparison of the 24-h pattern of hPRL secretion in the tumor patients with those of patients with "functional" hyperprolactinemia showed no specific characteristics that could be used to distinguish one group from the other.

LH concentration (*Table III*). The 24-h mean LH concentration was somewhat low in four of the patients with pituitary tumors (3.5–5.6 mIU/ml; normal, 10.2± 3.8 in women and 7.2±3.2 in men). Both men (cases 1 and 7) had low LH concentrations in relation to their prepubertal plasma testosterone concentrations. Clomiphene citrate, 50 mg twice daily, given orally for 6 wk in case 1 and 7 days in case 7, resulted in a normal rise in LH and testosterone in case 1 but no response in case 7. The three women with "functional" hyperprolactinemia had normal mean LH concentrations (7.5–10.3 mIU/ml). Cases 2 and 3 with "functional" hyperprolactinemia (Figs. 2, 3) also showed normal LH secretory patterns compared with normal women (46); however, in case 9 with the Chiari-Frommel syndrome there was abnormal suppression of LH secretion during sleep.

Thyroid function (*Table IV*). All nine patients were clinically euthyroid and had normal plasma thyroxine concentrations by radioassay. Three of the four who were tested had normal 24-h ^{131}I uptakes; the fourth (with the hypothalamic tumor) had a slightly low uptake of 10% (47). Administration of TRH (500 μg i.v.) to four patients showed a normal TSH rise in two (one with a pituitary tumor and one with "functional" hyperprolactinema), a blunted TSH response in one (with a pituitary tumor), and no response in one (with the hypothalamic tumor). In the patient with the pituitary tumor who showed a normal response (case 5), the test precipitated persistent galactorrhea which eventually remitted after radiotherapy. This side effect of the TRH test has been unusual in our experience, although others (48) have reported resumption of lactation in women who had stopped nursing for several days after TRH administration.

GH reserve (*Table IV*). Four of the nine patients (three with pituitary tumors and the one with a hypothalamic tumor) showed subnormal hGH reserve, i.e. failure of hGH to rise above 7 ng/ml either during

hPRL levels and large standard deviations suggest cautious interpretation of this difference.

stage III, IV sleep, in response to arginine infusion, in response to insulin hypoglycemia, or all three.

ACTH-cortisol function (*Table IV*). The 24-h mean cortisol concentration was measured in seven of the nine patients. It was very low (1.6 μg/100 ml) in the patient with the hypothalamic tumor but was essentially normal in the other six patients, (perhaps slightly high, 9.5 μg/100 ml in one patient with "functional" hyperprolactinemia). Cortisol production rates were measured in six of these seven patients and one other patient; they were normal in every case except the hypothalamic tumor patient in whom it was very low (2.4 mg g creatinine 24 h). This patient also had very low 17-hydroxycorticoids which failed to rise sufficiently in response to metyrapone (but did respond to ACTH). The other eight patients had normal 17-hydroxycorticoids. The five patients with pituitary tumors tested with metyrapone had normal responses.

Interrelation of LH and hPRL secretory activity (*Figs. 2 and 3*). In the three women with "functional" hyperprolactinemia and normal 24-h mean LH concentrations, a suggestive reciprocal relationship could be identified between the initiation of LH and hPRL secretory episodes. Fig. 2 shows that the peaks of the three major LH secretory episodes occurring during the night coincided with nadirs of the corresponding hPRL concentrations or cessation of secretory activity. For example, when LH secretory activity is quiescent (Fig. 2, 0900–1400 h) hPRL secretion occurs. In Fig. 3, this reciprocal relationship between hPRL and LH is evident at 0300, 0500, and 0700 h; when hPRL secretion begins, LH secretion begins to decrease or is at a low secretory rate. One of the patients with the Chiari-Frommel syndrome (case 9) had marked suppression of LH secretory activity during sleep when hPRL secretion was maximal. This subject's hPRL and gonadotropin secretory patterns before and after clomiphene administration are the subject of a separate report.[5]

L-*Dopa suppression test.* The three women with galactorrhea and moderate hyperprolactinemia (cases 2, 3, and 4) also had L-dopa suppression tests. All three showed significant decrements in plasma hPRL after L-dopa. The two patients (cases 2 and 3) with "functional" hyperprolactinemia showed hPRL decrements of 29.4 ng/ml (75.4 → 46) and 70 ng/ml (93 → 23). The patient with the pituitary tumor (case 4) had a fall in

[5] Kapen, S., R. Boyar, R. Freeman, A. G. Frantz, L. D. Hellman, and E. D. Weitzman. 1974. Twenty-four hour secretory patterns of gonadotropins and prolactin in a case of Chiari-Frommel syndrome. Submitted for publication.

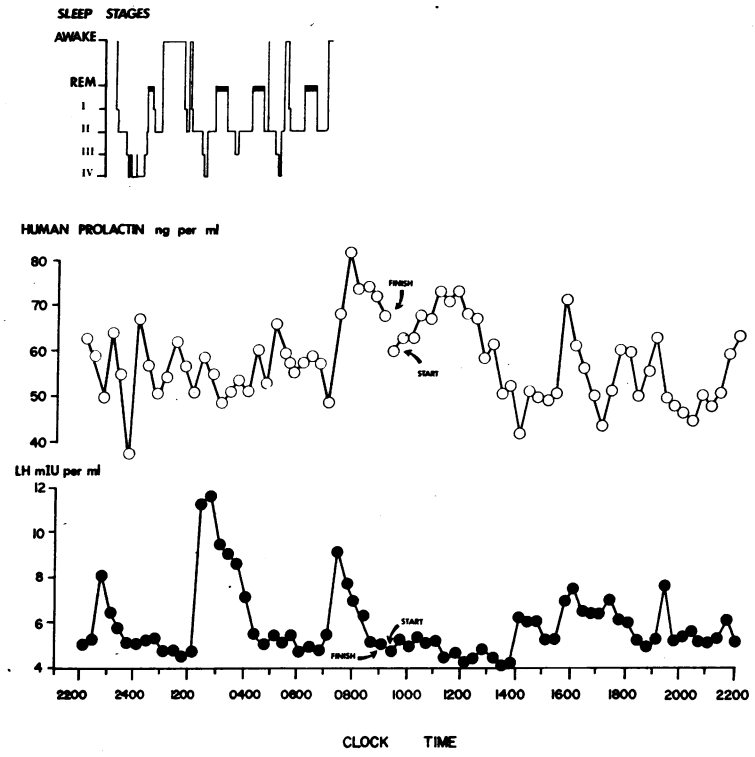

FIGURE 2 20-min interval plasma hPRL (○) and LH (●) concentrations in case 2 (Z. A.) with "post-pill" amenorrhea-galactorrhea. The sleep-stage sequence is shown above the period of nocturnal sleep.

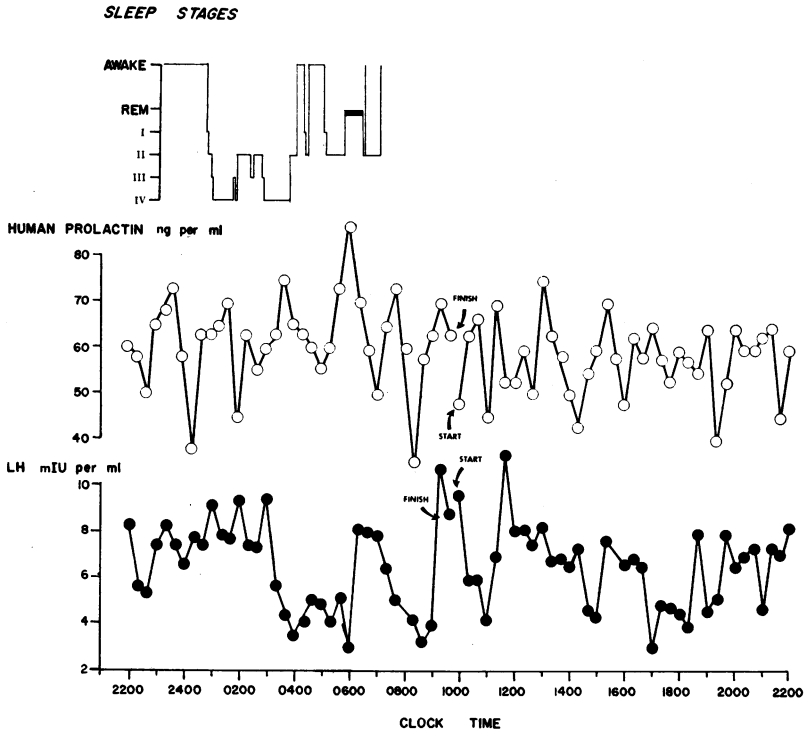

FIGURE 3 20-min interval plasma hPRL (○) and LH (●) concentrations in case 3 (G. D.) with "idiopathic" galactorrhea. The sleep histogram is depicted above the period of nocturnal sleep.

plasma hPRL from 93 to 50 ng/ml, a decrement of 43 ng/ml. The individual values for hPRL during the L-dopa test in case 4 with the pituitary tumor (performed at the termination of her 24-h study) are shown in Fig. 1. Although episodic release persists after the administration of L-dopa, the amplitude of the hPRL secretory episodes appears to decrease when compared to the corresponding clocktimes during the preceding day. These three patients with galactorrhea of diverse etiologies all showed significant suppression of the plasma hPRL concentration after L-dopa administration.

TABLE III
24-h Mean (SD) LH and Testosterone Concentrations

Case no.	LH	Testosterone
	mIU/ml	*ng/100 ml*
Normal		
Male	7.2 (3.2)	466 (149)
Female	10.2 (3.8)	
1	4.0* → 22.8	69* → 680
2	10.3	
3	7.5	
4	4.3	
5	6.3	
6	3.5	
7	8.3‡ → 7.2	30‡ → 38
8	5.6	
9	8.0§	

* LH and testosterone after 6 wk clomiphene citrate administration.
‡ LH and testosterone after 7 days clomiphene citrate administration.
§ Marked suppression of LH secretory activity during sleep.

DISCUSSION

The hyperprolactinemic patients studied comprised six with tumors (five pituitary and one hypothalamic) and three with "functional" disorders (one with the Chiari-Frommel syndrome, one with "post-contraceptive" amenorrhea-galactorrhea, and one with "idopathic" galactorrhea). Five of the six patients with clinically demonstrable tumors and two of the three patients with "functional" hyperprolactinemia (the one with "post-contraceptive" amenorrhea-galactorrhea and the one with "idiopathic" galactorrhea) showed a loss of the normal sleep augmentation of hPRL secretion; hPRL levels were elevated but equal during the sleeping and waking periods. The two hyperprolactinemic patients with the Chiari-Frommel syndrome (one with a pituitary tumor and one without a clinically demonstrable pituitary tumor) showed comparable elevation of the 24-h mean

TABLE IV

Laboratory Evaluation of Endocrine Function in Patients with Hyperprolactinemia

Case no.	Thyroxine as iodine	I^{131} uptake for 24 h	TSH basal → TRH max post	Urinary 17-hydroxycorticoids basal → metyrapone	Urinary 17-keto-steroids	24-h Mean plasma cortisol	Cortisol production rate	GH
	μg/100 ml	%	*μU/ml*	*mg/24 h*	*mg/24 h*	*μg/100 ml*	*mg/g creatinine/24 h*	*ng/ml*
Normal	2.9–6.5	15–40	basal < 2–10 TSH Δ 19±7	3–12 → > 2.5 × basal	8–22	3.5–6.0	10–20	>7
1	5.5	12	5.6	6.7 → 28.2	20	—	17	17.6 (I)
2	3.2	—	2.6	5.9	12.9	4.7	13	8.4 (S)
3	4.8	—	<2.0 → 28	6.9 → 38.0	12.7	9.5	19	20.0 (S) 26.0 (I)
4	5.2	—	<2.0	7.8 → 38.8	15.3	4.4	13	4.5 (S)
5	3.5	22	7.8 → 46	5.9 → 46.1	20.8	5.8	17	0 (S)
6	4.2	23	3.0 → 10	5.1 → 18.1	11.1	4.0	22	2.2 (A) 1.3 (I) 1.6 (S)
7	4.0	10	<2 → < 2	0 → 0.9	4.0	1.6	2.4	0 (A) 0 (I) 0 (S)
8	5.3	15	10	5.0 → 17.6	12.9	—	—	7.9 (A) 14.0 (I)
9	4.2		<2	4.5	10.5	4.4	—	13.5 (S)

A, arginine; I, insulin; S, sleep.

hPRL concentration but retained the normal sleep associated augmentation of plasma concentrations. Episodic secretion "but at a higher level" was present in all nine patients.

This abnormality of hPRL secretion, viz. elevated 24-h mean, peak, and minimal plasma concentrations and loss of sleep augmentation, is very reminiscent of the abnormality of the cortisol secretory pattern that is seen in Cushing's disease[6] (50). Krieger and Glick (51) suggested, on the basis of the latter findings, that Cushing's disease is a disorder of hypothalamic regulation of hormonal secretion. They found confirmation of the postulated hypothalamic dysfunction by demonstrating strikingly subnormal GH secretory reserve in patients with Cushing's disease, whether or not a clinically demonstrable pituitary adenoma was present. The present study of patients with hyperprolactinemia also shows a high frequency (Table V) of deficient secretory reserve for the other hypothalamic-pituitary-regulated hormones (7/9 for LH, 4/9 for GH, 2/9 for TSH, and 1/9 for ACTH-cortisol function). In contrast with Krieger's findings in Cushing's disease, however, the associated hormonal secretory defects in hyperprolactinemia were almost uniformly found in the patients with tumors and were essentially absent in patients with "functional" hyperprolactinemia. This distinction may be much less meaningful than it appears: in Cushing's disease, pituitary microadenomata are often present in what appears to be ordinary bilateral adrenocortical hyperplasia, and these frequently progress to gross pituitary tumors after bilateral adrenalectomy (Nelson's syndrome). In hyperprolactinemia, progression from "functional" hyperprolactinemic disorders (e.g. Chiari-Frommel syndrome) to grossly apparent pituitary tumors also occurs; indeed, we noted this sequence of events in two of our patients. It may be either that long-continued "functional" hyperprolactinemia that originates as a hypothalamic regulatory abnormality can lead to pituitary tumor formation or that pituitary microadenomata are present from the start in "functional" hyperprolactinemia and simply grow larger with time. Available data do not permit us to judge between these two possibilities; the analogous problem in Cushing's disease has not yet been resolved either.

Our findings and those of others (9–12) that L-dopa can acutely suppress elevated hPRL levels in hyperprolactinemic patients even when associated with a pituitary tumor suggest that pituitary tumors in such patients remain under some degree of hypothalamic control. The persistence of episodic secretion of hPRL in our patients with hypothalamic or pituitary tumors is further evidence that the hypothalamus may inhibit hPRL secretion intermittently. These findings emphasize the im-

[6] "Cushing's disease" is the term suggested by Liddle's group (49) for hypercortisolism associated with adrenocortical hyperplasia and an excess of pituitary ACTH, whether or not a grossly apparent pituitary adenoma is present.

TABLE V

Summary of Hypothalamic Pituitary Function in Patients with Hyperprolactinemia

Case no.	Diagnosis	hPRL sleep >waking*	hGH	hLH	hTSH	ACTH-cortisol
1	Pituitary tumor	−	+	−	+	+
2	"Post-pill" galactorrhea	−	+	+	+	+
3	"Idiopathic" galactorrhea	−	+	+	+	+
4	Pituitary tumor	−	−	−	+	+
5	Pituitary tumor	−	−	−	+	+
6	Chiari-Frommel (pituitary tumor)	+	−	−	±	+
7	Hypothalamic tumor	−	−	−	−	−
8	"Post-pill" galactorrhea (pituitary tumor)	−	+	−	+	+
9	Chiari-Frommel	+	+	−	+	+

+, normal; ±, borderline; −, defective.

Mean hPRL asleep significantly greater ($P < 0.001$) than mean hPRL awake.

portance of early medical diagnosis of hyperprolactinemic states, since it is possible that early treatment may prevent "functional" hyperprolactinemic disorders, whether or not they are associated with pituitary microadenomata, from progressing to clinically demonstrable pituitary tumors. The findings of episodic secretion of hPRL as well as L-dopa responsiveness in patients with clinically demonstrable pituitary tumors suggest that medical therapy may also be effective in these patients.

The observation of a temporal reciprocal relationship between the initiation of hPRL secretion and cessation or a decrease in the pulsatile secretion of LH in some of our hyperprolactinemic patients supports the conclusion from experiments in rats that a dopaminergic mechanism controls the secretion of these two hormones. Kamberi, Mical, and Porter (52, 53) showed that dopamine injected into the third ventricle causes a rise in LH-releasing factor and a rise in PRL-inhibiting factor in the hypophyseal portal circulation. The finding of complete cessation of pulsatile LH secretion during the nocturnal hours when hPRL secretion was maximal in case 9 with the Chiari-Frommel syndrome suggests that a similar mechanism may be operative in man (48). These results as well as the frequency with which amenorrhea is associated with galactorrhea suggests that the elevated hPRL levels per se may exert a direct effect on the normal hypothalamic regulation of LH and FSH secretion. The finding that hyperprolactinemic patients show normal LH and FSH responses to the gonadotropin-releasing hormone (54) and clomiphene citrate (case 1) supports this view. The clinical observations that suppression of elevated hPRL levels medically with 2-bromo-α-ergocryptine (CB 154) results in suppression of galactorrhea and concomitant resumption of normal menses (55) provide additional evidence that elevated hPRL levels may exert a direct effect on the normal secretion of LH and FSH. Since all three of our patients with "functional" hyperprolactinemia had normal TSH, hGH, and ACTH-cortisol function, an important direct effect of elevated hPRL levels on the hypothalamic regulation of these hormones appears unlikely.

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