Functional Evaluation of Prolactin Secretion in Patients with Hypothalamic-Pituitary Disorders

G. Tolis, M. Goldstein, and H. G. Friesen

From McGill University Clinic, Division of Endocrinology, Royal Victoria Hospital, Montreal 112, P.Q., Canada

Abstract Prolactin secretion was assessed in 23 patients with hypothalamic-pituitary disorders using L-Dopa suppression, chlorpromazine (CPZ), and thyrotropin-releasing hormone (TRH) stimulation tests. Based on the responses to these tests, three groups of patients were identified: those with panhypopituitarism (group I) and those with partial hypopituitarism either with (group II) or without (group III) evidence of hypothalamic involvement.

Panhypopituitary patients(group I) consistently had low serum prolactin values and failed to respond to all tests. Patients with hypothalamic involvement (group II) exhibited (*a*) elevated basal prolactin values, (*b*) an increase in serum prolactin after TRH stimulation, (*c*) blunted response to L-Dopa, and (*d*) lack of response to chlorpromazine stimulation. Patients with partial hypopituitarism but without hypothalamic involvement (group III) had normal serum prolactin levels and suppressed normally after L-Dopa; although the magnitude of response to both stimulatory agents was significantly lower than normally found the ratio of prolactin levels post-CPZ and TRH (Δ prolactin CPZ/Δ prolactin TRH) was similar to the ratio of normal individuals suggesting that these patients (group III) had a normal hypothalamic-pituitary prolactin axis.

In the 23 patients studied, the most consistent disorder of pituitary function proved to be an abnormal response to one or other of the three tests employed for the evaluation of prolactin secretion. Hence these tests have considerable potential as a sensitive screening procedure in the evaluation of patients suspected of having hypothalamic-pituitary disease.

INTRODUCTION

Functional tests have been proposed to investigate the hypothalamic-pituitary prolactin axis using thyrotropin-releasing hormone (TRH),[1] chlorpromazine (CPZ), and L-Dopa (1, 2). In normal individuals serum prolactin concentration is increased by the first two agents, whereas it is decreased by L-Dopa. Although the precise mechanism of action of each agent has not been clearly delineated in man, animal experiments suggest that TRH acts directly on the pituitary to stimulate prolactin secretion (3, 4), whereas CPZ and L-Dopa act on the hypothalamus (5) presumably decreasing or increasing the secretion of prolactin-inhibiting factor (PIF) respectively (5, 6); however, a direct effect of L-Dopa on the pituitary has not been excluded (7).

The application of all three tests in individual patients should allow one to distinguish an absolute deficiency of prolactin-secreting cells from defects in the control of prolactin secretion. A response to TRH or to CPZ would indicate the presence of functioning pituitary prolactin cells; on the other hand, a normal response to TRH but not to CPZ would suggest a hypothalamic disorder. Failure to decrease serum prolactin after L-Dopa would indicate that there is impaired secretion of PIF or that the prolactin cells have escaped from hypothalamic inhibition and are functioning autonomously.

Each of these agents has been used singly to stimulate or inhibit prolactin secretion in normal subjects (8–10) and in patients with hypothalamic-pituitary disorders (11, 12) but there has been no systematic analysis of the usefulness of all three agents in the evaluation of patients with hypothalamic-pituitary disorders. 23 of these patients were fully investigated using all three tests. On the basis of the data obtained, it is possible to classify patients with impairment of prolactin secretion into three categories: those with panhypopituitarism (group I); those with partial hypopituitarism with hypothalamic involvement (group II); those with partial

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[1] *Abbreviations used in this paper:* CPZ, chlorpromazine; GH, growth hormone; PIF, prolactin-inhibiting factor; PRF, prolactin-releasing hormone; TRH, thyrotropin-releasing hormone.

hypopituitarism without hypothalamic involvement (group III).

METHODS

Subjects. A total of 23 patients with clinical and laboratory evidence of abnormal hypothalamic-hypophyseal function were studied (Tables I–III) and divided into three groups.

Group I. Nine patients with panhypopituitarism.

Group II. Seven patients with impaired hypophyseal function with evidence of hypothalamic involvement.

Group III. Seven patients with partial hypopituitarism.

All patients underwent routine examinations including chest X ray, skull X ray, ECG (electrocardiogram), EEG (electroencephalogram), brain scan, standard biochemical and hematological tests, and complete opthalmological evaluation. All patients with an abnormal sella turcica had tomography, pneumoencephalography, and carotid angiography.

The hypothalamic-hypophyseal function was evaluated as follows: growth hormone (GH) was measured by radioimmunoassay in serum samples obtained in the fasting state under basal conditions and also 60–90 min after the onset of nocturnal sleep (13); during an arginine infusion and/or an insulin-induced hypoglycemia (14); and after 0.5 g L-Dopa (15–17). A response was considered normal if any GH value exceeded 5 ng/ml.

The pituitary-thyroid axis was evaluated by determining T_4 levels, thyroxine-binding index, 24 h ^{131}I uptake, and in most of the patients, serum thyroid-stimulating hormone (TSH) before and after TRH administration (18, 19). The normal range of serum TSH and T_4 under basal conditions in our laboratory is 0–8 μU/100 ml and 4–11 μg/100 ml, respectively.

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured in blood and in urine by specific radioimmunoassays (20, 21), as well as indirectly by the determination of urinary estriol and plasma testosterone. All measurements were done under basal conditions and in some patients after clomiphene citrate stimulation (50 mg twice daily × 7 days) (22, 23). Normal values in our laboratory are FSH: 10–30 μg/100 ml in adults, > 50 in midcycle or postmenopausally; LH: 1–20 μg/100 ml, > 20 in midcycle or postmenopausally; testosterone: 275–1100 ng/100 ml; estrogen: 18–100 μg/24 h. Normal responses to clomiphene are defined as a twofold increase of serum or urinary FSH-LH above base-line values.

The pituitary reserve of ACTH was assessed by measuring 17-ketogenic steroids (KGS) during the administration of oral Metopirone (24), (0.75 g at 4-hourly intervals for 24 h) and by the determination of plasma cortisol during the induction of hypoglycemia after intravenous insulin.

Serum prolactin was measured by radioimmunoassay (25), while fasting, after L-Dopa suppression test (0.5 g

TABLE I

Clinical and Laboratory Data on Patients with Panhypopituitarism (Group I)

Name	Age	Sex	Diagnosis	Abnormal: X ray	Abnormal: Ophthalmology		GH	E	FSH-LH	T	17-KGS	F	TSH	T_4	Prolactin, ng/ml: Basal $\bar{x}$	∇ L-dopa	Δ CPZ	ΔTRH
L. B.	45	F	Surgical hypophysectomy for diabetic retinopathy	+	+	B	0.5	<10	3.5	0.9	1.5	1.0	0	1.5	1.0			
						P	0.5				1.5	1.5	0			0	1.5	2.0
J. Y.	35	M	Surgical hypophysectomy for diabetic retinopathy	+	+	B	0.5		4.0	1.5	2.0	2.0	0	2.0	1.0			
						P	0.5				2.5	2.5	0			1	2.5	0
						B	0.8		1.8	75	2.0	1.8	0	2.0	7.0			
B. R.	65	M	Chromophobe adenoma	+	+	P	0.8				2.0	3.0	0			3	0	2
						B	0.8	<10	1.6	75	1.5	2.0	0	2.2	2.0			
L. J.	50	F	Sheehan's syndrome	−	−	P	2.0		1.8		1.5	2.0	0			1	1.5	0
						B	2.0		1.3	100	1.8	2.5	0	1.5	1.0			
C. R.	18	M	Pituitary tumor	+	+	P	3.0				1.8	2.5	0			1	0	0
						B	2.5		10.	3.0	84	*		0	3.0	4.0		
B. J.	24	M	Idiopathic hypopituitarism	−	−	P	4.0		10.	3.0		*		0		2	0	1
						B	1.0		4.5	1.5	120	1.5	2.0	0	1.0	1.0		
B. L.	68	M	Pituitary apoplexy	+	+	P	1.0		4.5	2.0		3.0	3.0	0		0	0	0
						B	0.5	<10		3.0		*		0	1.0	2.0		
B. S.	48	F	Pituitary apoplexy	+	+	P	0.5					*		0		0	0	0
						B	0.5	<10	3.0	1.6		3.0	2.5	0	1.8	2.0		
R. L.	68	F	Cavernous sinus thrombosis	+	+	P	1.5		3.0			4.5	4.0	0		0	0	0

* On replacement; ∇, decrease below basal; Δ, increase above basal; E, estrogens; T, testosterone; F, cortisol; $\bar{x}$, mean; B, basal; P, peak; 17-KGS, 17-ketogenic steroids.

orally) and during CPZ (25 mg intramuscularly) and TRH (400 μg intravenously) stimulation tests, as previously described (1). Blood samples during L-Dopa, CPZ, and TRH tests were taken at −15, 0, 30, 60, 120, 180 min, −15, 0, 30, 60, 90, 120 min, and −15, 0, 15, 30, 45, 60, 90-min intervals, respectively.

Serum prolactin values less than 4 ng/ml after L-Dopa administration or a twofold increase in serum prolactin after CPZ injection or a mean increase of 20 ng/ml in males and 40 ng/ml in females after TRH stimulation were considered to be normal responses (1).

RESULTS

Group I. (Table I). The patients in this group showed marked deficiencies of all the anterior pituitary hormones, including prolactin. The mean basal prolactin level (average of five fasting samples) was significantly lower than that of normal subjects (Table IV) and that of patients with hypothalamic disease (group II) or partial hypopituitarism (group III). Only patients with panhypopituitarism repeatedly had values less than 4 ng/ml. Both direct (TRH) and indirect (CPZ) stimulatory agents failed to increase serum prolactin, indicating a marked deficiency of functioning prolactin cells. In addition, serum TSH did not increase after TRH administration.

Group II. (Table II). Although the group was heterogeneous, it was quite homogeneous in so far as prolactin responses to the three tests were concerned. There are several points worth noting. (*a*) The mean basal prolactin was higher than in normals ($P < 0.005$) (Table IV) or panhypopituitary patients ($P < 0.001$). (*b*) The inhibitory response to L-Dopa was blunted. Although the absolute change in serum prolactin was a satisfactory one, percentage wise this response was significantly different than in normals ($P < 0.001$). Serum prolactin showed only a 44% decrease in contrast to the 80% decrease of the normal subjects. (*c*) CPZ administration failed to increase serum prolactin levels. This response was similar to that seen in the panhypopituitary patients, but differed significantly from the normals and from the partial hypopituitary patients without hypothalamic involvement ($P < 0.001$). (*d*) The increase in serum prolactin after TRH indicated the presence of functioning prolactin cells and differentiated this group from the panhypopituitary patients ($P < 0.001$).

Group III. (Table III). The patients in this group showed evidence of partial anterior pituitary deficiency due, in the majority (seven out of eight), to incomplete hypophyseal destruction by pituitary tumors. Mean basal prolactin levels did not differ from normals but were significantly higher ($P < 0.001$) than those of the panhypopituitary group (Table IV) L-Dopa administration effectively decreased serum prolactin levels. However, after CPZ stimulation, serum prolactin did not rise as much as in normal subjects but the increase was significantly greater than that noted in the panhypopitui-

TABLE II

Clinical and Laboratory Data on Patients with Hypothalamic Disease (Group II)

Name	Age	Sex	Diagnosis	Abnormal: X ray	Abnormal: Ophthalmology		GH	E	FSH-LH	T	17-KGS	F	TSH	T_4	Prolactin, ng/ml: Basal $\bar{x}$	∇ L-dopa	Δ CPZ	Δ TRH
L. J.	25	M	Idiopathic panhypopituitarism	−	−	B	0.5		7.0	1.6	90	2.0	1.0	0	4.0	9.0			
						P	0.5		9.0	2.3		2.5	1.0	14			6.0	1.0	19
						B	2.5	<10		3.0		3.0	1.5	0	3.5	7.0			
R. D.	27	F	Craniopharyngioma	+	−	P	4.0					4.5	3.3	27			5.0	1.5	10
						B	2.0	45	8.0			7.0	20	2	8.0	22			
O. E.	16	F	Perinatal trauma Mental retardation	−	−	P	8.0					7.0	20	18			4.0	1.0	15
						B	0.5		4.5	1.0	100	1.5	1.5	0	2.0	10			
O. J.	56	M	Suprasellar chromophobe adenoma	+	+	P	5.0					2.2	1.5	0			5.0	1.0	7
						B	1.5		1.5	120		5.0	6.0	0	1.8	10			
C. C.	43	M	Suprasellar chromophobe adenoma	+	+	P	6.8					16.0	12.0	0			5.0	1.5	9
						B	0.5	<10	2.6			6.5	5.0	0	6.0	27			
C. K.	50	F	Suprasellar chromophobe adenoma	+	+	P	0.5					18.0	13.0	0			6.0	2.0	7
						B	2.5		1.4	90		5.0	7.0	1.0	6.5	25			
A. E.	64	M	Olfactory neuroblastoma	+	+	P	7.7					5.0	7.0	9.0			6.0	1.0	8

* For explanation of abbreviations see Table I.

TABLE III

Clinical and Laboratory Data on Patients with Partial Hypopituitarism (Group III)

Name	Age	Sex	Diagnosis	Abnormal									Prolactin, *ng/ml*			
				X ray	Ophthalmology*		GH	E	FSH-LH	T	17-KGS	F	TSH	T_4	Basal $\bar{x}$	∇ L-dopa	Δ CPZ	Δ TRH
D. A.	43	M	Pituitary tumor	+	+	B	1.0		5.0	1.5	165	4.5	1.0	0	1.5	10.0			
						P	1.5			1.5		14.0	3.0	0			9.0	7.0	7.0
S. G.	40	M	Pituitary tumor	+	−	B	1.5		6.0	2.0	125	8.5		0	8.0	12.0			
						P	5.7			2.0		49		10			8.0	7.0	8.0
H. F.	66	M	Pituitary tumor	+	+	B	1.0		200	2.5	75	1.5	1.0	0	1.5	8.5			
						P	1.0					3.0	1.0	0			6.0	5.0	8.0
B. H.	58	M	Pituitary tumor	+	+	B	1.0		7.0	1.0	150	5.5	5.0	2.0	4.0	7.0			
						P	1.0			1.0		22.0	16.0	2.0			6.0	5.0	7.0
B. D.	19	M	Idiopathic GH deficiency	−	−	B	0.5		4.0	2.0	90	7.9	6.0	0	8.0	7.0			
						P	2.6		10.0	9.8	185	19.0	18.0	7.0			6.0	8.0	8.0
G. N.	60	M	Meningioma	+	+	B	1.0			6.6	189	7.0	9.0	0	7.5	12.0			
						P	1.0						27.0	9.0			7.0	6.0	9.0
L. L.	66	M	Pituitary tumor	+	+	B	1.5			1.0		6.5	7.0		6.5	5.0			
						P	1.5						17.0				5.0	6.0	8.0

* For explanation of abbreviations see Table I.

tary group or the patients with hypothalamic disorders. After TRH administration, serum prolactin concentrations were significantly higher than seen in the panhypopituitary patients but lower than that of the normal subjects or of the patients with hypothalamic involvement.

In the three groups of patients studied the most frequent abnormality of pituitary function was some impairment of prolactin secretion. The next most common deficiency observed was that of gonadotropin secretion followed by deficiencies of GH, ACTH, and TSH (Table V). Group I, as expected, was characterized by a deficiency of secretion of all pituitary hormones studied, whereas in group II, besides prolactin, deficiency of gonadotropin (86%) and ACTH (70%) secretion occurred frequently; in patients in group III, the most frequently observed deficiency, next to prolactin, was that of GH secretion (86%).

TABLE IV

*The Mean Serum Prolactin Concentrations Under Basal Conditions and the Change after Provocative Tests**

	Basal	∇ L-dopa	Δ CPZ	Δ TRH
Normal				
Males			20±9	18±4
Females	7±3	6±3	30±10	36±8
Hypopituitary patients				
I Panhypopituitary	2±2‡	1±1‡	1±1‡	1±1‡
II With hypothalamic involvement	16±8§	5±1	1±1‡	11±4‖
III Without hypothalamic involvement	9±2	7±1	6±1§	8±1§

* Values are compared between the hypopituitary patients and the normal males. Concentrations are expressed in nanograms per milliliter.
‡ $P < 0.001$.
§ $P < 0.005$.
‖ $P < 0.025$.

DISCUSSION

The prolactin cells of the pituitary and the hypothalamic mechanisms controlling prolactin secretion constitute the hypothalamic pituitary prolactin (h-p-p) axis. Therefore the complete investigation of the axis requires the evaluation of both the pituitary cells and their hypothalamic control mechanisms.

TABLE V

Distribution of Pituitary Hormone Deficiencies in Patients with Hypothalamic-Pituitary Disorders

Group	no.	Prolactin	Gonadotrophins	GH	ACTH	TSH
I	9	9	9	9	9	9
II	7	7	6	3	5	2
III	7	7	4	6	1	3
Total	23	23	19	18	15	14

Because TRH has a direct action on pituitary prolactin cells, the magnitude of the increase in serum prolactin values reflects the pituitary prolactin reserve. Failure to respond to TRH indicates an absolute prolactin deficiency, as observed in the panhypopituitary patients (group I). In all but one of these patients, serum prolactin was consistently less than 4 ng/ml, even after TRH stimulation. In one patient (B. R., Table I), the basal serum prolactin was normal, emphasizing the necessity of stimulatory tests to avoid diagnostic errors.

Prolactin secretion is regulated by the hypothalamus and mediated via two factors: an inhibitory one (prolactin-inhibiting factor, PIF) (26, 27) which decreases prolactin secretion and a stimulatory one (prolactin-releasing factor, PRF) (28–30) which increases it. Although little is known about the control of PRF, PIF secretion appears to be under dopaminergic control (31–33) and so agents which increase dopamine (e.g. L-Dopa) should increase PIF secretion thereby decreasing prolactin secretion. Experimentally and clinically this occurs after the administration of L-Dopa (1, 6, 11). Conversely, when PIF secretion is suppressed by agents such as CPZ then prolactin secretion should increase. Again, this is supported by experimental and clinical observations (1, 2, 11, 34). In patients with hypothalamic involvement, group II, the observed responses are predictable from the theoretical considerations of the physiologic and pharmacologic factors which are known to regulate prolactin secretion. The most significant feature in this group of patients is that despite the absence of any increase in serum prolactin after CPZ, an increase occurred after TRH. Therefore it is obvious that a diagnosis of isolated prolactin deficiency (35) cannot be entertained unless both stimulatory agents fail to increase serum prolactin concentrations.

Patients without hypothalamic disease (group III) had normal basal serum prolactin concentrations and suppressed normally with L-Dopa. In these patients the rise in serum prolactin after TRH and CPZ was lower than normally found, suggesting the existence of a decreased pituitary prolactin reserve. However, the increase in prolactin after CPZ and TRH was similar. Hence the ratio of the responses Δ prolactin post-CPZ/Δ prolactin post-TRH was the same as the ratio found in normal individuals (Fig. 1). This finding is the hallmark of the group III patients and it differentiates them from patients with hypothalamic involvement (group II).

One of the most fascinating findings was that in all patients studied with the three tests, an impairment of prolactin secretion was detected in each patient whereas no other clinical or laboratory test of pituitary function proved to be so consistently abnormal (Table V). Therefore we suggest that in all patients in whom a hypothalamic or pituitary disorder is suspected the complete functional evaluation of prolactin secretion is indicated.

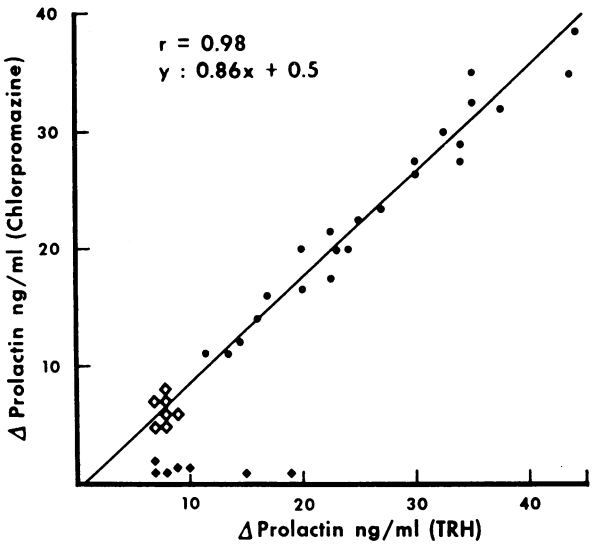

FIGURE 1 The increase in serum prolactin concentration after TRH and after CPZ is plotted on the abscissa and ordinate respectively in normal subjects (●) and patients with partial hypopituitarism either with (group II, ◆) or without (group III, ◇) hypothalamic disease. The regression line was determined by the method of least squares and the portion of the line below the normal values (●) was extrapolated to the intercept.

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