

**Functional Evaluation of Prolactin Secretion: a Guide to Therapy**

H. Friesen, ... , J. E. Tyson, A. Barbeau

*J Clin Invest.* 1972;**51**(3):706-709. <https://doi.org/10.1172/JCI106859>.**Concise Publication**

Stimulation and inhibition tests are proposed for evaluating prolactin secretion. Thyrotropin-releasing hormone (TRH) stimulates the release of prolactin from the pituitary. Chlorpromazine acts presumably at the hypothalamic level to increase prolactin secretion. L-Dopa (D,L- $\alpha$ -hydrazino- $\alpha$ -methyl- $\beta$ -[3,4-di-hydroxyphenyl]) has the opposite effect; it inhibits prolactin secretion and may be effective in suppressing galactorrhea.

**Find the latest version:**<https://jci.me/106859/pdf>

# Functional Evaluation of Prolactin Secretion: a Guide to Therapy

H. FRIESEN, H. GUYDA, P. HWANG, J. E. TYSON, and A. BARBEAU

*From McGill University Clinic, Royal Victoria Hospital, Montreal 112, Quebec, Canada*

**ABSTRACT** Stimulation and inhibition tests are proposed for evaluating prolactin secretion. Thyrotropin-releasing hormone (TRH) stimulates the release of prolactin from the pituitary. Chlorpromazine acts presumably at the hypothalamic level to increase prolactin secretion. L-Dopa (D,L- $\alpha$ -hydrazino- $\alpha$ -methyl- $\beta$ -[3,4-dihydroxyphenyl]) has the opposite effect; it inhibits prolactin secretion and may be effective in suppressing galactorrhea.

## INTRODUCTION

With the availability of a specific radioimmunoassay for human prolactin (1) we have sought to find drugs which would reliably stimulate or inhibit the secretion of prolactin. Such agents would be most helpful in the laboratory assessment of disorders of pituitary prolactin secretion. Our studies indicate that the secretion of prolactin is stimulated by phenothiazines and thyrotropin-releasing hormone (TRH)<sup>1</sup> and inhibited by L-Dopa. The latter also has proved useful in the therapy of galactorrhea.

## METHODS

*Administration of phenothiazines (chlorpromazine).* 11 normal female volunteers (ages 18–21 yr.) were given 25

Dr. Hwang is a Fellow of the Medical Research Council of Canada.

Dr. Guyda's current address is Montreal Children's Hospital, 2300 Tupper St., Montreal, Canada; Dr. Tyson's current address is Department of Gynecology and Obstetrics, Johns Hopkins Medical School, Baltimore, Md.; and Dr. Barbeau's current address is The Clinical Research Institute, University of Montreal, Montreal, Canada.

*Received for publication 27 October 1971 and in revised form 13 December 1971.*

<sup>1</sup> *Abbreviations used in this paper:* HGH, human growth hormone; PIF, prolactin-inhibiting factor; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

mg chlorpromazine either orally or intramuscularly, and blood samples were taken after 0, 15, 30, 60, and 90 min. Serum prolactin concentrations were measured by radioimmunoassay (1).

*TRH intravenously.* Serum prolactin and TSH concentrations were measured at 0, 15, and 30 min after the administration of 800  $\mu$ g TRH intravenously as a single bolus. Synthetic TRH was used (2). The response in 12 normal individuals (6 males and 6 females) was compared with that in 2 female subjects who were on phenothiazines and who had elevated basal prolactin levels. TSH was measured by Dr. C. Y. Bowers (3).

*Administration of L-Dopa.* Serum prolactin and HGH were determined in 12 patients with Parkinson's disease who were receiving their first dose of L-Dopa. 500 mg of L-Dopa were given orally and blood samples were taken at — 30 min, 0, 1, 2, 3, 6, and 24 hr. In addition six patients, five of whom had elevated prolactin levels and four of whom had galactorrhea, were studied after receiving 500 mg of L-Dopa. A summary of their clinical findings is outlined in Table I.

## RESULTS

*Effect of chlorpromazine on serum prolactin levels.* Table II shows that after the oral administration of chlorpromazine no consistent change in serum prolactin occurred until 90 min, whereas intramuscularly the drug caused a more rapid increase in serum prolactin. The maximum concentration occurred at 60 or 90 min and in all patients there was at least a two-fold increase in serum prolactin. Some subjects who received the parenteral dose of chlorpromazine experienced hypotension of sufficient severity to require bed rest for a 3 hr period.

*Effect of TRH on serum prolactin.* As shown in Table III, TRH caused a significant increase in both TSH and prolactin concentrations. The mean increase in both hormones was greater in female subjects, but large individual variation in response was evident. In two patients who were on phenothiazines and who had chronically elevated basal serum prolactin concentrations, the administration of TRH caused a greater ab-

TABLE I  
*Patients with Pituitary Dysfunction Receiving L-Dopa*

Patient	Age	Sex	Diagnosis	Therapy	Galactorrhea	Menses	Pituitary status			
							HGH	ACTH	TSH	HPr
D. D.	18	F	Chromophobe adenoma	Surgery and irradiation	9 months	Primary amenorrhea	O	A	A	225
N. C.	42	M	Pituitary tumor	Irradiation in 1965	None	—	A	A	A	200
T. M.	4	F	Pituitary tumor	None	None	None	‡	N	N	350
E. L.	27	F	Idiopathic	None	5 yr	Absent 5 yr	O	N	N	150
M. H.	31	F	Chromophobe adenoma	Surgery and irradiation in 1969	3 yr	Hysterectomy	A	A	A	40
C. L.	13	F	Idiopathic	None	2 months	Primary amenorrhea	N	N	N	25

N, Normal; A, Deficient; O, Unknown.

\* Serum prolactin (HPr) ng/ml; normal value is <30 ng/ml.

‡ Serum HGH  $\geq$  500 ng/ml.

solute increase in serum prolactin than was observed in normal adult females.

*Effect of L-Dopa on serum prolactin and on galactorrhea.* After the administration of L-Dopa there was a consistent decline in serum prolactin with the lowest values occurring between 2 and 3 hr. A concomitant but much less reproducible increase in serum HGH was observed. Fig. 1 shows the temporal response of four representative patients. Without exception at 2 or 3 hr in a total of 12 patients serum prolactin was less than 4 ng/ml during this period.

Fig. 2 shows the effect of L-Dopa on six patients with disorders of prolactin secretion. In four patients (No. 1-4, Table I) with markedly elevated prolactin levels (> 50 ng/ml) there was a prompt decrease in serum prolactin concentrations. In two patients with normal or near normal prolactin levels (M. H. and C. L.) the fall in serum prolactin was minimal, yet in both of these patients there was a marked reduction of the galactorrhea within the first 2 days.

Patient M. H. had a reduction of her galactorrhea within 48 hr of receiving L-Dopa 250 mg three times a day, and complete disappearance after 1 wk of therapy. Unfortunately, her galactorrhea returned after 6 wk of therapy and was unresponsive to an increased dosage of 500 mg three times a day. Patient C. L. had cessation of her galactorrhea within 24 hr of her test dose of L-Dopa and it has not recurred during 5 months follow-up.

## DISCUSSION

With the availability of a specific radioimmunoassay for human prolactin it is now possible to examine the factors regulating prolactin secretion in health and disease in man. TRH, which was thought to be the specific hypothalamic factor regulating TSH secretion (4), causes a rapid discharge of prolactin in man. In more than 20 subjects studied so far the mean increase after TRH in males and females was 20 ng/ml and 40 ng/ml, respectively (5). Chlorpromazine in our

TABLE II  
*Effect of Chlorpromazine on Serum Prolactin*

No. of patients	Route of administration	Serum prolactin					
		Time, min	0	15	30	60	90
		ng/ml					
6	Oral		9.4 ±4.1*	5.5 ±3.9	9.0 ±6.3	7.5 ±5.4	20.8 ±6.8‡
5	Intramuscular		7.8 ±3.0	12.5 ±5.5	19.7 ±4.7‡	29.7 ±9.5‡	22.8 ±8.6‡

\*  $\pm$ SD

‡ Difference in prolactin concentration vs. "0" time sample  $P < 0.01$ .

TABLE III  
Serum TSH and Prolactin Concentrations after TRH (800 µg)

No. of patients	Sex	TSH				Prolactin		
		Min	0	15	30	0	15	30
				$\mu U/ml$			$ng/ml$	
6	M	3 $\pm$ 1.6*	14 $\pm$ 6.6	17 $\pm$ 7.8	9 $\pm$ 4.6	33 $\pm$ 17	29 $\pm$ 12	
6	F	4 $\pm$ 0.7	47 $\pm$ 29	49 $\pm$ 32	13 $\pm$ 5.7	80 $\pm$ 32	59 $\pm$ 30	
2‡	F	2§	25	32	72	196	167	

\* ±SD.

† Both patients were taking phenothiazines.

§ Mean.

A twofold increase beyond the basal TSH and prolactin concentration occurred in each subject after TRH. The difference between the mean 0 and 15 or 30 min TSH and prolactin concentration is highly significant  $P < 0.005$ .

experience also causes an increase and in this regard our results are similar to those reported by Kleinberg, Wharton, and Frantz (6).

The mechanism by which TRH and chlorpromazine increase serum prolactin is different. The former acts directly on the pituitary cell as shown by Tashjian, Barowsky, and Jensen (7) whereas the latter acts via

the hypothalamus depleting catecholamines which results in a decrease in the secretion of prolactin-inhibiting factor (PIF) which in turn leads to an increase in serum prolactin (8). L-Dopa has the opposite effect. It increases catecholamine levels in the hypothalamus increasing PIF and thus decreasing prolactin secretion. Therefore, we suggest that the application of each of these tests in patients with hypothalamic pituitary disorders will be helpful. A response to TRH indicates the presence of functional pituitary tissue. The lack of a response to chlorpromazine suggests a hypothalamic disorder if the TRH response is normal. A failure to respond to L-Dopa would indicate that the pituitary is functioning autonomously and is no longer under hypothalamic control. If there is a response to L-Dopa along with elevated levels of serum prolactin it suggests that the "set point" for prolactin secretion has been adjusted upwards.

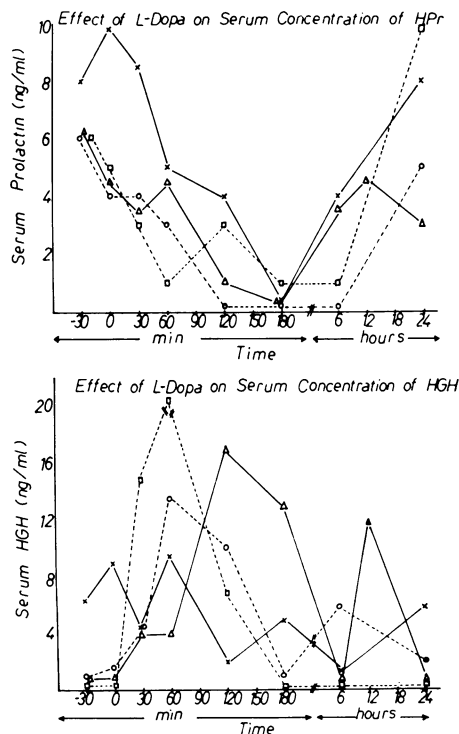


FIGURE 1 Effect of 500 mg L-Dopa orally on serum concentration of prolactin (HPr) and GHG in four male subjects with Parkinson's disease. The drug was given at 0 time.

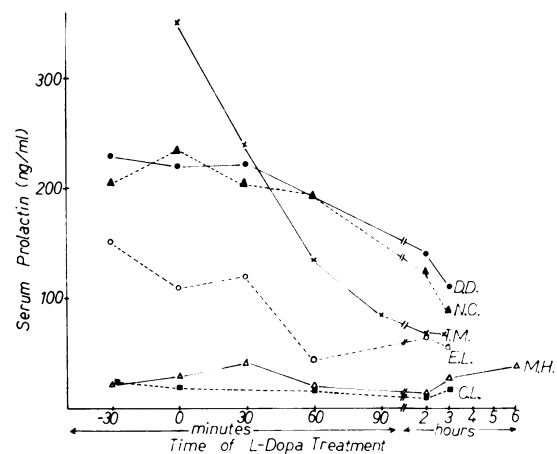


FIGURE 2 Effect of 500 mg L-Dopa orally on serum prolactin concentrations in patients with pituitary dysfunction. The drug was given at 0 time.

A more detailed analysis of the clinical response to L-Dopa and the changes in serum prolactin is warranted. Patients with and without pituitary tumors, regardless of the presence or absence of galactorrhea, respond to the administration of L-Dopa with a lowering of serum prolactin. Two patients (T. M. and N. C.) had pituitary tumors and elevated prolactin levels but did not have galactorrhea. In addition to the elevated prolactin, T. M. also had an elevated GHG value and gigantism but no breast enlargement and no breast secretion, demonstrating that the combination of an increase of prolactin and GHG levels in themselves will not lead to galactorrhea. Moreover, sustained elevations of prolactin alone are not enough to produce gynecomastia as patient N. C. was studied 3 yr after irradiation of his tumor and presumably he had elevated prolactin levels throughout this period.

The most fascinating response was observed in patient M. H. who had persistent profuse galactorrhea despite irradiation and attempted surgical removal of a pituitary chromophobe adenoma 2 yr before the present investigation. Her serum prolactin was elevated only slightly (40 ng/ml) and failed to decrease significantly with L-Dopa. Despite this lack of change in serum prolactin there was a dramatic reduction in her galactorrhea 48 hr after she was started on L-Dopa 250 mg three times a day and by 1 wk the galactorrhea had virtually disappeared. Unfortunately it recurred 6 wk later while on L-Dopa therapy. These findings suggest that L-Dopa or a metabolite of L-Dopa may temporarily, at least, block the effect of prolactin on the breast tissue directly, or more likely that it suppresses the secretion of other factors which may be involved in milk secretion. The responsiveness of the prolactin-secreting pituitary tumors to pharmacological agents which increase or decrease prolactin secretion in normal individuals supports Sherman and Kolodny's contention that pituitary tumors in many instances are not primary but arise secondarily as a result of a hypothalamic disorder (9). Malarkey, Jacob, and Daughaday (10) have recently provided additional data on the effects of L-Dopa on nonpuerperal galactorrhea. One patient in their study who was on L-Dopa therapy for a prolonged period did not have decreased lactation or lowered basal prolactin levels, but all patients had an acute decrease in serum prolactin after ingestion of 0.5 g of L-Dopa. L-Dopa, therefore, deserves additional evaluation as a drug in other clinical circumstances where a decrease in prolactin secretion is desirable. For example, it may provide a useful medical alternative to hypophysectomy in patients with metastatic breast carcinoma, since there is considerable evidence

to suggest that prolactin is the important pituitary hormone which facilitates mammary tumor growth in other species (11).

## ACKNOWLEDGMENTS

The authors thank the following for their part in this study: Doctors R. Volpe, P. Higgins, G. Leboeuf, L. Kovacs, and A. Slowe who provided samples on their patients after L-Dopa. The studies with TRH could not have been performed without the help of Dr. C. Y. Bowers of New Orleans. We gratefully acknowledge the technical assistance of Mrs. Jean Parodo and Mrs. Patricia Champagne and the secretarial help of Miss Francine Dupuis. This work was supported by the Medical Research Council of Canada, Grant MA 2525, and U. S. Public Health Service Child Health and Human Development Grant HD 01727-07.

## REFERENCES

1. Hwang, P., H. Guyda, and H. Friesen. 1971. A Radioimmunoassay for human prolactin. *Proc. Nat. Acad. Sci. U. S. A.* **68**: 1902.
2. Chang, J. K., H. Sievertsson, C. Bogentoft, B. L. Currie, K. Folkers, G. D. Daves. 1971. Synthesis of pyroglutamylhistidylprolinamide and unusual fragmentation. *J. Med. Chem.* **14**: 481.
3. Bowers, C. Y., A. V. Schally, A. Kastin, A. Arimura, D. S. Schalch, C. Gual, E. Castimeda, and K. Folkers. 1971. Synthetic thyrotropin-releasing hormone. Activity in men and women, specificity of action, inhibition by triiodothyronine, and activity orally. *J. Med. Chem.* **14**: 477.
4. Bowers, C. Y., A. V. Schally, D. S. Schalch, C. Gual, A. J. Kastin, D. Folkers. 1970. Activity and specificity of synthetic thyrotropin-releasing hormone in man. *Biochem. Biophys. Res. Commun.* **39**: 352.
5. Bowers, C. Y., H. Friesen, P. Hwang, H. Guyda, and K. Folkers. 1971. Prolactin and thyrotropin release in man by synthetic pyroglutamylhistidylprolinamide. *Biochem. Biophys. Res. Commun.* **45**: 1033.
6. Kleinberg, D. L., R. N. Wharton, and A. G. Frantz. 1971. Rapid Release of Prolactin in Normal Adults following Chlorpromazine Stimulation. 53rd Program of Endocrine Society Meetings, San Francisco. 126.
7. Tashjian, A. H., J. Barowsky, and D. J. Jensen. 1971. Thyrotropin-releasing hormone: direct evidence for stimulation of prolactin production by pituitary cells in culture. *Biochem. Biophys. Res. Commun.* **43**: 516.
8. Kamberi, I. A., R. S. Mical, and J. C. Porter. 1971. Hypophysial portal vessel infusion, in vivo demonstration of LRF, TRF and PIF in pituitary stalk plasma. *Endocrinology.* **89**: 1042.
9. Sherman, L., and H. D. Kolodny. 1971. The hypothalamus, brain-catecholamine, and drug therapy for gigantism and acromegaly. *Lancet.* **1**: 682.
10. Malarkey, W. B., L. S. Jacobs, and W. H. Daughaday. 1971. Levodopa suppression of prolactin in nonpuerperal galactorrhea. *N. Engl. J. Med.* **285**: 1160.
11. Pearson, O. H., O. Llerena, L. Llerena, A. Molina, and T. Butler. 1969. Prolactin dependent rat mammary cancer: a model for man? *Trans. Ass. Amer. Physicians. Philadelphia.* **82**: 225.