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Species Specificity in the TSH Response to the Administration of L-Dopa (37807)

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When the titer of circulating thyroid hormone is elevated by hyperthyroidism (1,2) or by exogenous thyroid hormone (3), the secretion of TSH from the anterior pituitary is selectively inhibited. On the other hand, an episodic or persistent decrease of circulating thyroid hormone produced by antithyroid drug (3) or by primary hypothyroidism (4) results in an increased secretion of TSH. These findings constitute the basis of the so-called pituitary–thyroid feedback theory, and this theory is applicable to man and experimental animals. Recent studies have shown that L-dopa can lower plasma TSH in patients with primary hypothyroidism (5) but is without effect in normal subjects (6,7). Although this finding may suggest that a substance other than thyroid hormone controls TSH secretion in man, the exact mechanism of action of L-dopa in lowering TSH is not known at present. If L-dopa specifically inhibits pituitary release of TSH, it is theoretically possible that L-dopa also inhibits TSH release in experimental animals as well as in man with a high level of circulating TSH. In order to test this hypothesis, the experiments were performed in patients with primary hypothyroidism, in rats receiving methimazole, and in mice injected with TRH. The results suggest that there is species specificity in the TSH response to the administration of L-dopa.

Materials and Methods. Four hospitalized patients were diagnosed as having primary hypothyroidism by a number of physical findings and laboratory data such as thyroidal ^{131}I uptake, plasma protein bound iodine, plasma T_4 and plasma TSH. The patients received no medication before the experiment. Breakfast was withheld on the morning of each test. In one patient, 500 mg of L-dopa were given orally, and, just before and 15, 30, 45, and 60 min after L-dopa administration, the blood samples were obtained. In the other three patients, 500 μg of TRH were injected intramuscularly, and, just before and 15, 30, 45, 60, and 90 min after TRH administration, the blood samples were obtained. Five days later, the second measurement of TSH was performed as follows: the patients received 500 mg L-dopa orally and, 2.5 hr later, the patients received 250 mg L-dopa orally. With the second dose of L-dopa, 500 μg TRH was injected intramuscularly and, just before and 15, 30, 45, 60, and 90 min after TRH administration, the blood samples were obtained. After centrifugation, the plasma was stored at —20° until use. Plasma TSH was measured by radioimmunossay.[1]

In the experiments using rats, two experiments were performed. In the first part of this experiment, 24 male Wistar rats, weighing approximately 120 g, were used. The animals were fed a low iodine diet with or without methimazole (0.05%) L-dopa (7 mg/10 g diet) or both for 14 days. In the second part of this experiments, 36 male Wistar rats, weighing approximately 160 g, were used. The animals were fed a low iodine diet with or without methimazole (0.05%) and injected

[1] Radioimmunoassay kit for TSH was obtained from Daiichi Pharmaceutical Co., Tokyo. It is reported that TSH standard and TSH antibody were imported from USA, Calbiochem Inc.

with saline (0.5 ml) or graded doses of L-dopa (5, 10, 30, and 50 mg) twice daily for 14 days. Twelve hours after the last dose of L-dopa, autopsy was performed. The weight of the thyroid and pituitary was expressed as mg per 100 g body wt.

In the experiment on mice, 30 male DDY mice, weighing 30 g, were used. The animals were divided into five equal groups. At first, the animals received saline (0.5 ml) or a similar volume of L-dopa subcutaneously, and then received TRH (0.5 μg) or saline subcutaneously 30 min thereafter. Thirty minutes after TRH or saline, the animals were killed, and the thyroids were removed. Intrathyroidal colloid droplets were measured as previously reported (8).

Results. Effect of L-dopa administration on plasma concentration of TSH in patients with primary hypothyroidism. In patient 1 (Fig. 1A), the basal concentration of plasma TSH was apparently high. After ingestion of 500 mg L-dopa, plasma TSH decreased markedly with time. In patients 2, 3, and 4 (Fig. 1B, C, and D), the basal level of plasma TSH varied greatly from patient to patient. After TRH injection, plasma TSH increased markedly regardless of their basal values. The maximal increase of plasma TSH was found 45 min after TRH administration. In the second measurement, the patients received L-dopa twice, and TRH was injected with the second dose of L-dopa. As shown in Fig. 1B, C, and D, the basal level of plasma TSH was depressed by L-dopa administration in all patients. Also, it was shown that an increase of plasma TSH in response to TRH administration was markedly depressed by L-dopa administration.

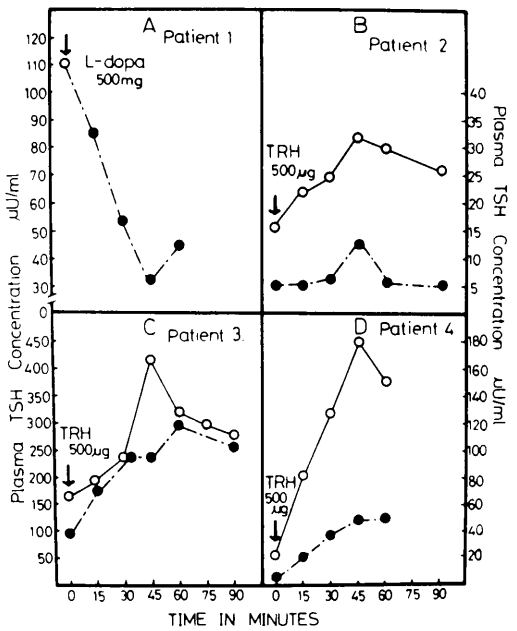

FIG. 1. Effects of L-dopa administration singly or in combination with TRH on plasma TSH concentration in primary hypothyroidism. In Patient 1, 500 mg L-dopa was given orally at 0 time. In Patients 2, 3, and 4, TSH was measured twice with intervals of 5 days. In the first measurement (open circle), TRH (500 μg) was injected intramuscularly at 0 time. In the second measurement (solid circle), the patients received 500 mg L-dopa orally and, 2.5 hr later, received second dose of L-dopa (250 mg). With the second dose of L-dopa, TRH (500 μg) was injected intramuscularly (0 time). Circle indicates the mean value of duplicate determinations.

Effect of L-dopa administration on the development of goiter in rats fed methimazole. In the first part of this experiment (group 1 of Table 1), the animals were fed methimazole, L-dopa, or both. L-dopa did not affect thyroid and pituitary weights. Methimazole administration produced goiter without affecting pituitary weight. The combined use of L-dopa and methimazole produced goiter very similar to that produced by methimazole alone.

In the second part of this experiment (group II of Table 1), the animals fed methimazole were subcutaneously injected with graded doses of L-dopa daily. Methimazole again produced goiter but this goiter development was not affected by simultaneous administration of graded doses of L-dopa (10–100 mg). Pituitary weight was not affected by large doses of L-dopa.

Effect of L-dopa administration on pituitary–thyroid response induced by TRH in mice. In the control animals with saline, only a small number of intrathyroidal colloid droplets were found (Table II). Administration of L-dopa did not significantly increase the intrathyroidal colloid droplets. In contrast, TRH significantly increased intrathyroidal colloid droplets. This TRH effect was not influenced by pretreatment with L-dopa.

TABLE I. Effect of L-Dopa Administration on the Development of Goiter in Rats Fed Methimazole.

	Group	No. of animals	Body weight (g)	Thyroid weight (mg)	Pituitary weight (mg)
I.	Control	6	122.7 ± 2.1*	8.9 ± 0.3	3.4 ± 0.2
	M	6	117.5 ± 2.1	27.2 ± 0.8[a]	3.6 ± 0.3
	L-Dopa	6	119.2 ± 4.7	8.2 ± 0.3	3.5 ± 0.2
	M + L-dopa	6	127.5 ± 5.6	27.5 ± 0.9[a]	3.6 ± 0.2
II.	Control	6	171.4 ± 7.6	7.5 ± 0.5	3.2 ± 0.2
	M	6	159.3 ± 7.0	20.1 ± 1.4[a]	3.0 ± 0.3
	M + L-dopa (10 mg)	6	170.8 ± 4.5	20.6 ± 1.2[a]	2.9 ± 0.2
	M + L-dopa (30 mg)	6	161.4 ± 4.0	19.1 ± 0.8[a]	3.3 ± 0.3
	M + L-dopa (60 mg)	6	145.0 ± 7.9	18.6 ± 2.5[a]	3.1 ± 0.2
	M + L-dopa (100 mg)	6	148.8 ± 10.9	19.3 ± 2.7[a]	3.0 ± 0.4

Group I: M = animals were fed a low iodine diet with methimazole (0.05%) for 14 days. L-dopa = animals were fed a low iodine diet with L-dopa (7 mg/10 g diet) for 14 days. M + L-dopa = animals were fed methimazole and L-dopa.

Group II: M = animals were fed a low iodine diet with methimazole (0.05%) for 14 days. M + L-dopa = animals were fed methimazole and injected with L-dopa indicated. Thyroid and pituitary weights were expressed as mg/100 g body wt. * = mean ± SE, [a] = significantly different from the control ($p < 0.05$).

Discussion. In agreement with the previous report (5), our present study indicated that acute administration of L-dopa depressed the plasma concentration of TSH in patients with primary hypothyroidism. If L-dopa specifically lowers plasma TSH as was found after thyroxine administration, two sites of action may be considered to account for our finding. First, L-dopa acts on the hypothalamus to inhibit the release of TRH. Second, L-dopa acts on the pituitary thyrotropic cells to block the action of TRH. Unfortunately, however, no attempt has since been made to clarify which one of these two possibilities is actually operating. To shed some light on this problem, an increase of plasma TSH in response to TRH was studied while the patients were taking L-dopa. Two doses of L-dopa apparently depressed the plasma TSH concentration and markedly depressed an increase of TSH in response to TRH. A possible explanation would be that L-dopa acts on the pituitary thyrotropic cells to block the action of TRH. To make this theory concrete, a number of experimental studies are required to exclude the other possibilities. Thus, L-dopa was administered orally to rats fed methimazole to see if L-dopa prevents goiter development by chronically lowering plasma TSH. In spite of feeding more than 7 mg of L-dopa (3.4 g/60 kg/day), goiter was not prevented at all. Subsequent study further indicated that even 100 mg of L-dopa (35.4 g/60 kg/day) failed to depress the goiter development produced

TABLE II. Effect of L-Dopa Administration on Pituitary–Thyroid Response Induced by TRH in Mice.

Group	Treatment		No. of animals	Intrathyroidal colloid droplets per 25 follicles
	1st injection	2nd injection		
1	saline	+ Saline	6	16 ± 6*
2	L-dopa (5 mg)	+ Saline	6	22 ± 11
3	Saline	+ TRH (0.5 μg)	6	417 ± 51[a]
4	L-dopa (0.5 mg)	+ TRH (0.5 μg)	6	471 ± 70[a]
5	L-dopa (5 mg)	+ TRH (0.5 μg)	6	508 ± 83[a]

First injection was made intraperitoneally, and, 30 min later, second injection was made similarly. Autopsy was made 30 min after second injection* = mean ± SE.[a] = significantly different from the control ($p < 0.05$).

by methimazole. Since TSH was the only factor responsible for the development of goiter under our experimental conditions, the data clearly indicated that huge doses of L-dopa failed to depress chronically the high concentration of circulating TSH in rats, and that huge doses of L-dopa did not interfere with thyroidal response to TSH.

It is still possible, however, that acute administration of L-dopa can depress plasma TSH concentration but chronic administration of L-dopa is without effect due to some unknown reasons. To test this possibility, the effect of a single injection of L-dopa on TRH action was studied in mice. As reported previously (9), a single injection of TRH produced an increase of intrathyroidal colloid droplets by augmenting TSH secretion from the anterior pituitary. A small dose (0.96 g/60 kg) or large dose (9.6 g/60 kg) failed to depress an increase of intrathyroidal colloid droplets which was produced by an increased secretion of TSH. This clearly indicated that an acute administration of L-dopa also failed to depress an increased secretion of TSH in response to TRH in mice.

From the data thus accumulated, it is established that an acute administration of L-dopa lowers plasma TSH and prevents an increase of TSH in response to TRH in patients with primary hypothyroidism but fails to do so in rats and mice. Although it is not known why TSH response to the administration of L-dopa is different between man and experimental animals, this species specificity in TSH response to L-dopa provides a basis for further investigations on hypothalamo–pituitary–thyroid interplay.

Summary. Acute administration of L-dopa (500–750 mg) lowered plasma TSH concentration and depressed an increase of plasma TSH in response to TRH in patients with primary hypothyroidism. In contrast, chronic administration of small or large doses of L-dopa failed to depress the development of goiter in rats treated with methimazole, indicating that plasma TSH concentration was not lowered by L-dopa in methimazole fed animals. Acute administration of L-dopa also failed to prevent an increase of intrathyroidal colloid droplets produced by an increase of TSH secretion in response to TRH. It is suggested that there is species specificity in the TSH response to the administration of L-dopa.

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ERRATUM

Vol. 144, No. 2 (1973), in the article, "Influences of Splanchnic Blood Flow on Epinephrine-Induced Hyperkalemia," by S. D. Guthrie and Q. R. Murphy, pp. 581-586:

1. p. 582, line 23 (left col.): Fig. 1 should read Fig. 3. Then the legend of Fig. 3 should then read "in 6 dogs anesthetized with Na pentobarbital.

2. Page 582, line 1 (right col.): Fig. 1 should read Fig. 3.

3. Page 583, line 1 (right col.): Fig. 3 should read Fig. 1. Then the legend for Fig. 1 should read in "6 dogs anesthetized with cyclopropane."