Effect of L-Dopa on Anterior Pituitary Hormone Release in Man

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Synopsis

The response of GH, TSH, FSH and LH secretion to L-dopa administration was investigated in 14 normal subjects and 9 patients with Parkinson's disease in order to evaluate this catecholamine precursor as a pituitary function test. The oral administration of 0.5 or 1.0 g L-dopa stimulated GH release in 6 out of 10 normal individuals and 4 out of 6 patients. The peak levels of plasma GH were observed between the periods of 30-90 min after L-dopa, and the peak values of plasma GH were 8.9 ± 1.9ng/ml in normal subjects and 8.1 ± 2.3 in the patients, but the peak GH levels were less than those observed in the cases of arginine load or insulin-induced hypoglycemia. The remaining 6 subjects and 5 cases (2 normals and 3 patients) who received a single intravenous administration of 50 mg L-dopa showed minimal response to L-dopa. Blood glucose, plasma TSH, FSH, LH and insulin levels did not change significantly after the L-dopa administration in all cases, including the subjects in whom plasma GH levels were elevated by L-dopa. Three normal females with normal menstrual cycle were examined in their follicular and luteal phases, but showed no response in plasma FSH and LH secretion to L-dopa in either phase.

These results indicate that L-dopa has a relatively great potential as a provocative agent for stimulating GH release but only a limiting merit as a pituitary function test because of less reliability than arginine or insulin-induced hypoglycemia. The L-dopa has no significant effect on TSH, FSH and LH secretion in man.

It is well known that the secretion of anterior pituitary hormone is regulated by hypothalamic hypophysiotropic hormone. On the other hand, informations about possible relation between catecholamine and anterior pituitary hormone release has been accumulated from the several lines of investigations. Histochemical studies (Fuxe, 1963; Fuxe and Hökfelt, 1966) indicate that dopamine is the primary amine in the median eminence and that granules containing dopamine are located in close relation to the capillaries of the hypothalamo-hypophyseal portal system. These observations have led to speculation that dopamine may play an important role in the regulation of anterior pituitary hormone release. Indeed, recent studies with animal experiment incriminated a dopamine role in the releases of ACTH (King and Thomas, 1968; King 1969), GH (Müller et al., 1968), FSH (Schneider and McCann 1969); Kamberi and McCann 1969) and LH (Kamberi et al., 1970; Schneider and McCann, 1970).

Since catecholamines do not cross the blood-brain barrier, but L-dopa does, the administration of large doses of L-dopa could increase the content of dopamine and other catecholamine in the hypothalamus. Therefore, it can be considered that the administration of L-dopa to man offers a unique opportunity to evaluate the effects of this
catecholamine precursor on anterior pituitary hormone release.

It has been recently demonstrated that L-dopa stimulated GH release in normal subjects (Saito et al., 1971) as well as in patients with Parkinson’s disease (Boyd et al., 1970, 1971). If L-dopa could show the effects on anterior pituitary hormone secretion other than GH, it could be used as a more useful test for pituitary function, because this might be used to test the release of several hormones at one time. Therefore, the effects of L-dopa on plasma levels of TSH, FSH and LH as well as GH were examined in man.

Materials and Methods

Fourteen normal adults (11 males and 3 females) and 9 patients with Parkinson’s disease (8 males and 1 female) were studied at bed rest after the overnight fasting. The subjects ranged in age from 22 to 81 years as shown in Table 1. The patients had no noteworthy endocrine abnormalities, and 4 were untreated and 5 withheld from anticholinergic medication for 2 days prior to the tests.

At 9 AM, blood was drawn for control levels of blood glucose, plasma immunoreactive GH, TSH, FSH, LH and insulin. A single oral dose of 0.5 or 1.0 g L-dopa was given and blood samples were drawn at 30, 60, 90, 120, 180 min, except in some cases in whom blood samples were obtained at 6 and 24 h. The plasma was separated and kept frozen until measurement.

Instead of the oral administration, a dose of 50 mg L-dopa was given intravenously in 2 normals and 3 patients with Parkinson’s disease.

In 3 women with normal menstrual cycle, L-dopa test was performed in both follicular and luteal phases in order to clarify if any difference was observed in gonadotropin secretion.

Plasma GH, TSH, FSH, LH and insulin were determined by the double antibody radioimmunoassay technique. The kits for radioimmunoassay of human TSH, FSH, and LH were kindly supplied by the National Institute of Health, U.S.A., Human Thyrotropin Research Standard A used as a standard in TSH assay were obtained from the National Institute of Medical Research, England. Human Pituitary Extract Reference Preparation LER 907 (1 mg = 20 IU FSH and 48 IU LH of 2nd IRP preparation), provided by NIH, was used as a standard in FSH and LH assay. The kits for radioimmunoassay of GH and insulin were purchased from the Dainabot Radioisotope Laboratory, Tokyo. The labeling of these hormones was performed with $^{125}$I, and the labeled hormones were repurified by gel filtration before use. Blood glucose was measured by Somogyi method.

The L-dopa was furnished by Kyowa Hakko Co., Tokyo and L-dopa solution used for the intravenous administration by Sankyo Co., Tokyo.

Results

Plasma growth hormone:

Prior to L-dopa administration, plasma GH levels of normal individuals were less than 0.4 - 2.5 ng/ml. After a single oral dose of L-dopa, there was observed a rise in plasma GH of 5 ng/ml or more above the control values in 6 out of 10 normal subjects (Fig. 1). The peak responses occurred between 30-90 min after the administration and the maximum values were 7.1 - 17.2 ng/ml. Plasma GH subsequently declined towards base line levels. The GH response to L-dopa was minimal in remaining 4 subjects. The plasma GH values at 24 hr were not significantly different from the control values in all cases. There was no rise in plasma GH in 2 normal subjects who had received a single intravenous injection of 50 mg L-dopa.

Four patients with Parkinson’s disease showed a response of plasma GH (more than 5 ng/ml above the control levels) to L-dopa, but the increment of plasma GH was less than 5 ng/ml in the other two patients (Fig. 2). The intravenous injection of 50 mg L-dopa had no effect on plasma GH in 3 patients.

The peak values of plasma GH after oral administration of L-dopa was obtained at 60 and 90 min, and its mean ±SE (8.1 ± 2.3 ng/ml) was slightly less than in normal subjects (8.9 ± 1.9 ng/ml).

Comparison of the effect of L-dopa on plasma GH levels with that of arginine load and insulin-induced hypoglycemia:

Plasma GH levels in response to L-dopa was compared with those to L-arginine (infusion of 0.5 g/kg for 30 min) and insulin
L-DOPA AND PITUITARY HORMONE RELEASE

Fig. 1. Effect of L-dopa on plasma GH levels in ten normal subjects. Solid lines: a single oral dose of 0.5 g L-dopa, dotted lines: a single oral dose of 1.0 g L-dopa.

Fig. 2. Effect of a single oral dose of 0.5-1.0 g L-dopa on plasma GH levels in six patients with Parkinson's disease.

hypoglycemia (intravenous injection of 0.1 U/kg) in each of 7 normal subjects. The shaded areas of Figure 3 indicate the range of plasma GH response to L-dopa. As shown in Figure 3, the plasma GH levels were markedly increased in response to arginine load or insulin-induced hypoglycemia in all cases. The peak values of plasma GH in these tests were 22.9 ± 2.2 ng/ml and 27.9 ± 4.0 ng/ml, respectively. These values were apparently higher than those obtained by the L-dopa administration, in which the peak values were 8.9 ± 1.9 ng/ml.

Plasma thyrotropin:
Plasma TSH levels remained constant or
Fig. 3. Plasma GH levels in response to L-dopa, L-arginine and insulin in seven normal subjects. The shaded areas indicate the range of GH response to L-dopa in ten normal subjects.

Table 1. Effect of L-dopa on plasma TSH in normal subjects and patients with Parkinson's disease

<table>
<thead>
<tr>
<th>Case</th>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Dose of L-dopa</th>
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<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>6</th>
<th>24</th>
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<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
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<td>3.5</td>
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</tr>
<tr>
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<td>K.K.</td>
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<td>M</td>
<td>**</td>
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<td>0.5</td>
<td>0.5</td>
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<td>0.5</td>
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<td>2.5</td>
<td>1.5</td>
<td>2.0</td>
<td>1.5</td>
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<td>0.5 g p.o.</td>
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<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
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<td>M</td>
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<td>3.0</td>
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<td>1.7</td>
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<tr>
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<td>3.9</td>
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* Parkinson’s disease

TSH in microunits per milliliter
L-DOPA AND PITUITARY HORMONE RELEASE

Fig. 4. Plasma FSH and LH levels in response to a single oral dose of 0.5 or 1.0 g L-dopa in ten normal subjects and six patients with Parkinson's disease. The bars represent mean ± S.E.

slightly variable within normal range throughout the sampling hour in normals and patients with Parkinson's disease (Table 1).

Plasma follicle stimulating hormone:
The plasma FSH levels did not change significantly after the oral (Fig. 4) and intravenous administration of L-dopa in each group. The base-line levels of plasma FSH were somewhat higher in patients with Parkinson's disease than in normal adults, probably due to the age differences between two groups (Fig. 4).

Plasma luteinizing hormone:
The control value of plasma LH was slightly higher in patients with Parkinson's disease than in normals as observed in case of plasma FSH. The response of plasma LH to L-dopa was not significantly changed in either group as shown in Figure 4.

Effect of L-dopa on plasma FSH and LH in females with normal menstrual cycle:
A dose of 1.0 g L-dopa was given to 3 females with normal menstrual cycle in their follicular and luteal phase. The control values of plasma FSH and LH were not so different in either phase. The administration of L-dopa did not show any significant effect on plasma FSH and LH levels in either phase (Table 2).

Blood glucose and plasma insulin:
The levels of blood glucose and plasma insulin were not altered significantly in both normals and patients with Parkinson's disease throughout the study (Fig. 5).

Side effect:
In no subjects, there was any significant toxic effect. Only 3 normal individuals (case 3, 12 and 13) and 1 patient (case 18) noticed slight nausea, but it lasted in short time.

Discussion
There have been many reports suggesting possible relations between catecholamines and anterior pituitary hormone release, and the various loci at which catecholamines could participate in controlling anterior pituitary hormone release are considered (Wurtman, 1970). In animal studies, dopamine was known to stimulate the releases of ACTH (King and Thomas, 1968; King, 1969), GH (Müller et al., 1968), FSH (Schneider and
Table 2. Effect of L-dopa on plasma FSH and LH levels in three females with normal menstrual cycle

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Hormone</th>
<th>Follicular phase</th>
<th>Luteal phase</th>
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<td></td>
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<td>H.N.</td>
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<td>FSH*</td>
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<td></td>
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<td>FSH</td>
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<tr>
<td></td>
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<td>LH</td>
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<tr>
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<td>FSH</td>
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<tr>
<td></td>
<td></td>
<td>LH</td>
<td>1.7</td>
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</table>

* FSH and LH in milli units per milliliter.
A dose of 1.0 g L-gopa was given orally to three normal females during their follicular and luteal phase.

McCann, 1969; Kamberi and McCann, 1969) and LH (Kamberi et al., 1970; Schneider and McCann, 1970) in vivo and in vitro, although the mechanism by which dopamine causes anterior pituitary hormone secretion is at present only speculative. Since L-dopa, an amino acid precursor of dopamine and epinephrine, crosses the blood-brain barrier unlike dopamine, the administration of large doses could increase the content of these catecholamines. Indeed, L-dopa stimulates GH secretion in normal subjects (Saito et al., 1971; Eddy et al., 1971; Kansal et al., 1972) and in patients with Parkinson’s disease (Boyd et al., 1970, 1971).

If L-dopa could influence on human anterior pituitary hormone secretion other than GH as seen in animal experiments, the administration of L-dopa to individuals in normal and diseased state might offer a unique opportunity to evaluate the reserves of anterior pituitary hormones. This might be a very convenient test, because the reserve of the pituitary hormones could be examined at one time.

We demonstrated that oral doses (0.5 or
1.0 g) of L-dopa caused a significant rise in plasma GH in the majority of normal subjects and patients with Parkinson's disease. This rise could not be accounted for the change of blood glucose levels or stress-like factors, because the test was performed under basal condition and blood glucose levels did not change throughout the study. Boyd et al. (1970) also demonstrated that L-dopa-induced increase in plasma GH level could not be blocked by either oral or intravenous glucose administration.

However, the elevation of plasma GH was not consistently observed in all cases tested, the peak of plasma GH levels ranged during the period of 30 to 90 min, and the peak values of plasma GH were varied from 1.9 to 17.2 ng/ml. Such a variability might be due to the individual difference in speed or quantity of intestinal absorption of L-dopa. In addition, GH response to L-dopa was shown to be somewhat lower than that observed in arginine load or insulin-induced hypoglycemia as demonstrated in the present paper. Therefore, the oral administration of L-dopa is considered to have a limited merit as a stimulation test for GH.

The intravenous injection (present study) or infusion over 60 min (Matsuoka et al., 1972) of 50 mg L-dopa did not show any rise in plasma GH, although the intravenous infusion of 100 mg over 60 min (Imura et al., 1971; Matsuoka et al., 1972; Nakai et al., 1972) have been reported to enhance GH release. These data suggest that the dose and route of L-dopa administration may concern to the stimulation of GH release.

L-dopa has been known for some time to induce hyperglycemia in animals (Holtz and Credner, 1944) and dopamine is the agent responsible for this hyperglycemic effect (Hakanson et al., 1967). In human beings, the intravenous administration of dopamine elevates blood glucose (Horwitz et al., 1962; Mueller and Horwitz, 1962) and plasma free fatty acid (Pilkington et al., 1966) but to much lesser degree than does epinephrine. However, the present study demonstrated no effect of L-dopa on blood glucose and plasma insulin levels. This is in agreement with Eddy et al. (1971), Van Woert and Mueller (1971) and Boyd et al. (1971). These data do not indicate that the L-dopa and the subsequent GH release directly stimulate insulin secretion.

As to the relations between dopamine and gonadotropin secretion, several papers have been published. Schneider and McCann (1969) have demonstrated a dopamine role in the discharge of LH-releasing factor from the median eminence, and Kamberi et al. (1971) reported that the infusion of dopamine into the ventricle of the rat caused the increase of gonadotropin concentration in hypophyseal portal vein. In humans, the injection of L-dopa was reported to evoke a rise in plasma FSH level (Dickey et al., 1971). These facts seem to indicate that dopamine or its precursor, L-dopa, may be involved in gonadotropin secretion. On the contrary, we could not find any rise of plasma FSH and LH in all subjects even in cases in whom plasma GH levels apparently increased in response to L-dopa. The same results were recently obtained by Matsuoka et al. (1972).

There are, at least, two possibilities to explain the discrepancy of the data. One is that L-dopa acts on gonadotropin release as like as GH through dopaminergic mechanism, but enough dopamine to stimulate gonadotropin release is not synthesized in the hypothalamus because of the short supply of L-dopa. However, the short supply of L-dopa is unlikely, because the oral administration of 0.5 g L-dopa have also an effect on prolactin secretion, probably due to working on prolactin-release inhibiting factor (Kleinberg et al., 1971; Turkington, 1972). The other possibility is that the stimulation of GH secretion is not mediated by dopaminergic mechanism but through non-specific factors. Fuxe and Hökfelt (1967) found little histochemical change in dopamine levels in the median eminence after a series of stimuli known to influence GH secretion, and concluded that
the dopamine neurons have no effect on GH secretion. If this is the case, gonadotropin secretion should not be affected by L-dopa. The lack of TSH response to L-dopa may support the latter possibility. True mechanism by which L-dopa acts on hypophyseal hormone release remains to be solved, but L-dopa could not be applied to test the pituitary reserves of TSH, FSH, and LH, at least in the way described in the present study.

Acknowledgments

We are grateful to Dr. Naokata Shimizu for his advise and to Miss Sumiko Miyata for technical assistance.

We wish to acknowledge the National Pituitary Agency, Endocrinology Study Section, and National Institute of Arthritis and Metabolic Diseases, U.S.A. for the generous supplies of the radioimmunoassay kits for human TSH, FSH and LH. Human Thyrotropin Research Standard A was kindly provided by the National Institute for Medical Research, England.

References