

Loss of Central Nervous System Component of Dopaminergic Inhibition of Prolactin Secretion in Patients with Prolactin-Secreting Pituitary Tumors

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ABSTRACT The administration of L-dopa suppresses prolactin (PRL) secretion in normal subjects and in patients with hyperprolactinemia, although it is not known whether this effect, which requires the conversion of dopa to dopamine, is mediated peripherally or through the central nervous system. To distinguish between these effects, 10 normal subjects (6 male, 4 female) and 8 patients with hyperprolactinemia associated with pituitary tumors were given L-dopa, 0.5 g alone, or 0.1 g after a 24-h pretreatment with carbidopa, 50 mg every 6 h, which produces peripheral dopa decarboxylase inhibition. Similar degrees of PRL suppression were observed in normal subjects (basal plasma PRL 13 ± 2 ng/ml) after L-dopa alone ($48 \pm 4\%$) and after L-dopa plus carbidopa ($58 \pm 6\%$). In patients with pituitary tumors and elevated plasma PRL (73 ± 14 ng/ml), L-dopa alone led to PRL suppression comparable with that in normal subjects ($47 \pm 6\%$). However, L-dopa plus carbidopa resulted in only minimal suppression of plasma PRL ($19 \pm 4\%$) which was significantly less than after L-dopa alone ($P < 0.001$). Urinary homovanillic acid excretion, which reflected peripheral dopa decarboxylation was similar in controls and tumor patients after L-dopa both alone and after carbidopa pretreatment. Comparable suppression of PRL levels in response to a dopamine infusion ($4 \mu\text{g}/\text{kg}$ per min for 3 h) was observed in controls and tumor patients. The results indicate that although peripheral conversion of exogenous dopa to dopamine can suppress PRL secretion, in normals, the central nervous system conversion of dopa to dopamine in the presence of peripheral dopa decarboxylase inhibition is sufficient to account for its PRL-suppressive effects. In contrast, patients

with tumors, while retaining peripheral dopaminergic inhibitory effects on PRL secretion, exhibit a marked reduction of central dopaminergic inhibition of PRL secretion.

INTRODUCTION

Although hypothalamic control of prolactin (PRL)¹ secretion is now recognized to involve both stimulatory (1–5) and inhibitory (3, 6–8) components, the predominant influence appears to be inhibitory. A considerable amount of experimental data, using both animal and human models, now exists which indicates that this hypothalamic inhibitory tone is controlled to a major extent by a dopaminergic mechanism. In addition to its central actions, dopamine has also been shown to have a direct effect on the pituitary to inhibit PRL secretion, both in vitro (9–12) and in vivo when infused systemically in rats (13) and humans (14) or into a portal-hypophyseal vein (15).

The administration of L-dopa, the immediate biosynthetic precursor of dopamine, is also followed by a decrease in PRL secretion and has been widely used to demonstrate PRL suppressibility (16, 17). However, there are multiple sites at which exogenously administered L-dopa can exert its effects on PRL secretion. Dopa is converted to dopamine by the enzyme aromatic L-amino acid decarboxylase (dopa decarboxylase, DD) in peripheral nerve terminals throughout the body and the dopamine thus formed can reach the pituitary by the systemic circulation. DD activity is also present in the anterior pituitary, and the conversion of dopa to dopamine can therefore occur directly in the lactotroph (18). In addition, dopa, unlike dopamine, does penetrate the blood-brain barrier and its conversion to

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¹Abbreviations used in this paper: CNS, central nervous system; DD, dopa decarboxylase; HVA, homovanillic acid; PRL, prolactin.

dopamine within the hypothalamus or elsewhere in the central nervous system (CNS) can result in the release of a PRL-inhibiting factor or of dopamine itself into the portal hypophyseal circulation which in turn inhibits PRL secretion.

A distinction between the central and peripheral effects of L-dopa can be accomplished by the concomitant administration of a DD inhibitor such as carbidopa (L- α -methyldopa hydrazide) which, in a limited dose range, is relatively impermeable to the CNS and, therefore, results in selective inhibition of peripheral DD (19, 20). Inhibition of the effects of L-dopa by such an agent would indicate that a peripheral mechanism was involved, whereas a lack of inhibition would favor a central mechanism. The suppressive effects of L-dopa on PRL secretion have been reported to persist after the concomitant administration of carbidopa plus L-dopa in rats (18) and normal humans (21), suggesting that central effects alone are adequate to explain the PRL-suppressive effect of L-dopa in normal subjects. Evidence that peripheral effects alone are also sufficient to suppress PRL secretion has been reported by Diefenbach et al. (22) using stalk-sec-

tioned monkeys in which a silastic barrier prevented revascularization of the portal system.

Considerable evidence has been presented during the past few years to suggest alterations in neuroendocrine regulation in patients with growth hormone- and ACTH-secreting tumors (23-26). These observations have led to the hypothesis that the pathogenesis of at least some growth hormone- and ACTH-secreting pituitary tumors may involve excessive stimulation by growth hormone and ACTH-releasing factors. Administration of L-dopa to patients with PRL-secreting tumors has not given evidence for altered neuroendocrine regulation in that, suppression of PRL secretion has generally been observed (16, 17). However, the site of L-dopa action was not documented in these patients, inasmuch as the suppressive effects of L-dopa could have occurred by a direct action on the pituitary as well as by CNS mediation. The present study was therefore performed to determine the principal site of action of L-dopa in patients with PRL-secreting pituitary tumors and to search for possible alterations in central dopaminergic control mechanisms.

TABLE I
Clinical Summary of Patients with PRL-Secreting Pituitary Tumors

Patient	Age	Duration of disease	Galactorrhoea	Amenorrhoea	Neurological findings	Basal PRL	Radiographic findings	Other pituitary functions	Previous treatment
	yr	yr				ng/ml			
1	52	2.5	-	PM	Bitemporal hemianopsia	37	Sellar destruction	\pm TSH \downarrow GH	None
2	26	10	-	+	—	96	Size WNL; minimal erosion of floor	WNL	None
3	32	15	+	+	—	144	Enlarged with erosion of floor and clinoids	WNL	None
4	30	4	+	+	Headaches	147	Size WNL; min. erosion	WNL	None
5	27	7	+	+	—	60	Size WNL; asymmetric erosion of floor	WNL	None
6	28	5	+	+	—	58	Enlarged with erosion of floor	WNL	None
7	65	8	-	PM	Severe headaches	41	Enlarged with erosion of floor	\pm TSH \downarrow GH	Irradiation 8 yr before study
8	53	14	+	+	Headaches and minimal left eye superior temporal quadrantanopsia	67	Enlarged with erosion of floor and clinoids	\pm TSH \downarrow GH \downarrow ACTH	Irradiation + surgery (TF) 10 yr before study

+, Present;
-, Absent;

\downarrow , Decreased to absent response;
 \pm , Borderline decreased response;

TF, Transfrontal craniotomy;
PM, Postmenopausal.

WNL, within normal limits;

METHODS

Six male and four female normal volunteers, age 23–49 yr, were studied together with eight female patients, age 26–64 yr, in whom the diagnosis of a pituitary tumor had been previously established (Table I). The eight patients all had hyperprolactinemia. Five presented with galactorrhea and amenorrhea and one patient presented with secondary amenorrhea unassociated with galactorrhea. The remaining two patients, who were postmenopausal, presented with neurologic complications of their pituitary tumors (severe headaches and visual loss). All eight patients had radiographic evidence of a pituitary tumor and in two, the presence of the tumor was confirmed at surgery. Six patients were studied before treatment and two were studied 8 and 10 yr, respectively, after treatment which consisted of surgical removal plus irradiation in one patient and only irradiation in the other. However, hyperprolactinemia was present in both at the time of study. The surgically treated patient had evidence of pituitary-adrenal insufficiency and was on replacement glucocorticoid therapy. None of the 10 control subjects were receiving medication during the studies.

The experiments were conducted in the Clinical Research Center after an overnight fast. Informed consent was obtained from all subjects. Blood samples were collected via an indwelling needle, inserted into an antecubital vein at least 30 min before drug administration and kept patent with heparinized saline. On the 1st study day, blood samples for PRL measurement were collected immediately before the oral administration of 500 mg L-dopa, and every 30 min for a 3-h period. Urine was collected during the 3-h period after L-dopa and immediately frozen for the subsequent measurement of the dopamine metabolite, homovanillic acid (HVA). Upon completion of the L-dopa study, carbidopa (L- α -methyl-dopa hydrazide) 50 mg was given orally every 6 h for four doses and the next day, the L-dopa study was repeated. For this second study, a 100-mg dose of L-dopa was administered with 35 mg of carbidopa. This smaller dose of L-dopa, when administered in combination with carbidopa, has been reported to produce comparable plasma dopa levels (21) and is clinically observed to have similar anti-Parkinsonian effects.

In a separate experiment, four normal men, age 25–35 yr, four normal women, age 19–39 yr, and three of the patients with pituitary tumors were given an intravenous infusion of dopamine hydrochloride at the rate of 4 μ g/kg per min for 180 min using an infusion pump. The dopamine solution was diluted in 5% dextrose in water immediately before use and protected from light during the period of infusion. Blood pressure and pulse rate were monitored every 10 min before and during the infusion.

All blood samples were collected in heparinized tubes, immediately placed on ice, and then centrifuged. The plasma was then separated and frozen until the radioimmunoassay measurement of plasma PRL by a modification of the homologous double-antibody technique (27) was performed. The upper limit of normal in our laboratory is 20 ng/ml. Urinary HVA was measured by the method of Sato (28). Data were analyzed using Student's *t* test and analysis of variance (29).

RESULTS

The mean basal PRL of the 10 normal subjects was 13 ± 2 ng/ml (Mean \pm SEM). Pretreatment with carbidopa did not significantly increase basal PRL (14 ± 2 ng/ml) in the control subjects. The eight patients

with pituitary tumors had basal PRL levels ranging from 37 to 147 ng/ml with a mean of 73 ± 14 ng/ml which was not significantly altered by carbidopa pretreatment (70 ± 10 ng/ml).

Effects of L-dopa and of carbidopa + L-dopa on prolactin secretion. There was significant suppression of plasma PRL levels in control subjects beginning at 90 min ($P < 0.05$) after the administration of L-dopa alone (Fig. 1), and this response was not altered by previous administration of carbidopa. The time-course and degree of suppression noted after carbidopa plus L-dopa were similar to that seen after L-dopa alone. Although there was a greater mean maximum percent suppression ($58 \pm 6\%$) in the control subjects after carbidopa plus L-dopa alone ($48 \pm 4\%$), this difference was not of statistical significance ($0.1 > P > 0.05$).

Administration of L-dopa also resulted in suppression of basal PRL in all of the patients with PRL-secreting pituitary tumors, although in only three did PRL levels decrease to within normal limits (Fig. 2). In contrast to control subjects, pretreatment of tumor patients with carbidopa almost entirely eliminated the suppressive effects of L-dopa. The mean maximal percent suppression in tumor patients after carbidopa plus L-dopa was only $19 \pm 4\%$ as opposed to $47 \pm 6\%$ after L-dopa alone ($P < 0.01$). Comparison of the maxi-

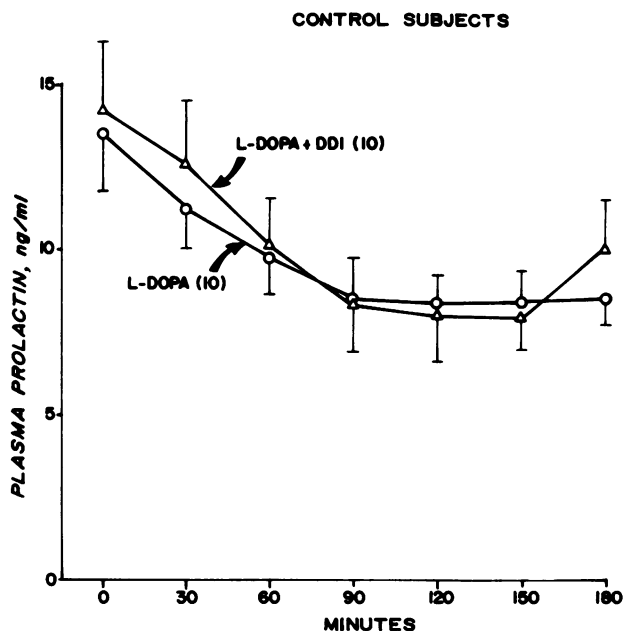


FIGURE 1 Plasma PRL levels in control subjects after L-dopa alone and after pretreatment with the dopa decarboxylase inhibitor (DDI), carbidopa. L-Dopa was administered at time 0 at a dose of 500 mg when given alone or 100 mg after 24 h of carbidopa pretreatment (50 mg orally, every 6 h). Shown are the Mean \pm SEM. Number of subjects are shown in parentheses.

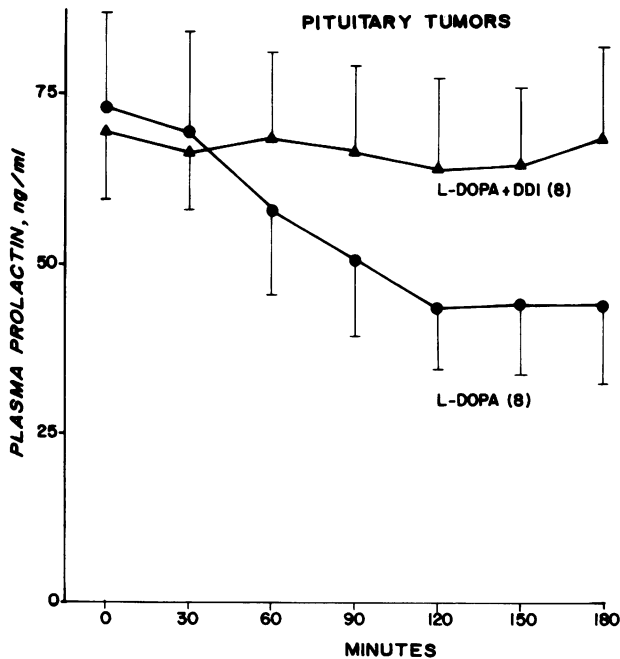


FIGURE 2 Plasma PRL levels in patients with pituitary tumors after L-dopa alone and after pretreatment with carbidopa. Details as given in the legend of Fig. 1.

mal percent suppression in the two groups of subjects (Fig. 3), revealed a highly significant difference in PRL suppression between control subjects and tumor patients after carbidopa plus L-dopa ($P < 0.001$). All of the tumor patients exhibited a reduction in the maximal degree of suppression by carbidopa pretreatment.

The administration of L-dopa alone caused moderate nausea in 3 of 10 controls and 3 of 8 tumor patients with vomiting occurring in 1. No nausea or vomiting occurred in response to L-dopa after previous administration of carbidopa.

HVA measurements. Urinary HVA excretion during the first 3 h after L-dopa administration was 25.9 ± 3.2 mg in the control subjects and 23.6 ± 3.1 mg in the patients with PRL-secreting tumors. After carbidopa pretreatment, the urinary HVA excretion in response to L-dopa was 2.9 ± 0.5 mg in controls and 2.5 ± 0.8 mg in tumor patients. After correction for the smaller dose of L-dopa used in the carbidopa plus L-dopa study, these results indicated a reduction in urinary HVA of 46 ± 7 and $42 \pm 6\%$ in the control and tumor groups, respectively.

Effects of dopamine infusion on PRL secretion. The intravenous infusion of dopamine resulted in comparable suppression of PRL levels in the eight normal controls and three tumor patients (Fig. 4) during the 180-min infusion period. At 60 min postinfusion, however, plasma PRL values rebounded to supranormal levels in the control subjects ($34 \pm 13\%$ above

base line) but not in the tumor patients ($9 \pm 6\%$ below base line). No significant cardiovascular effects were noted during the infusion of dopamine at the rate of $4 \mu\text{g/kg}$ per min and systolic blood pressure did not rise > 20 mm Hg in any subject.

DISCUSSION

The results of the present study are in agreement with the earlier report that the concomitant administration of carbidopa and L-dopa to normal subjects does not interfere with the inhibitory effects of L-dopa on PRL secretion (21). Our normal subjects exhibited a slightly greater suppression of PRL secretion after carbidopa plus L-dopa than after L-dopa alone, although the difference was not statistically significant. An enhancement of the inhibitory effect of L-dopa on thyrotropin-releasing hormone-induced PRL release by carbidopa has been recently reported (30). Our results are also consistent with the observation that previous administration of carbidopa does not impair the inhibitory effect of L-dopa on PRL secretion in rats (18). Our finding that pretreatment with carbidopa did not significantly increase basal PRL in the control subjects is at variance with the report by Brown et al. (31) in which plasma PRL was measured 6 and 7 days after continuous carbidopa treatment at a dose considerably greater than that used in the present study. The difference in dose and duration is important since it has been shown by direct measurement of DD

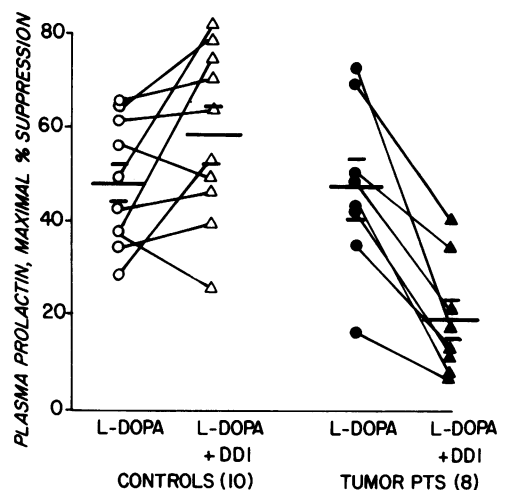


FIGURE 3 Maximal percent suppression of plasma PRL in control and tumor patients after L-dopa administration, either alone or after carbidopa pretreatment. Control subjects are represented by open symbols and tumor patients by closed symbols. The circles and triangles represent the maximal percent suppression after L-dopa alone, and after carbidopa plus L-dopa, respectively. The mean maximal percent suppression (\pm SEM) in the two groups are represented by the horizontal lines.

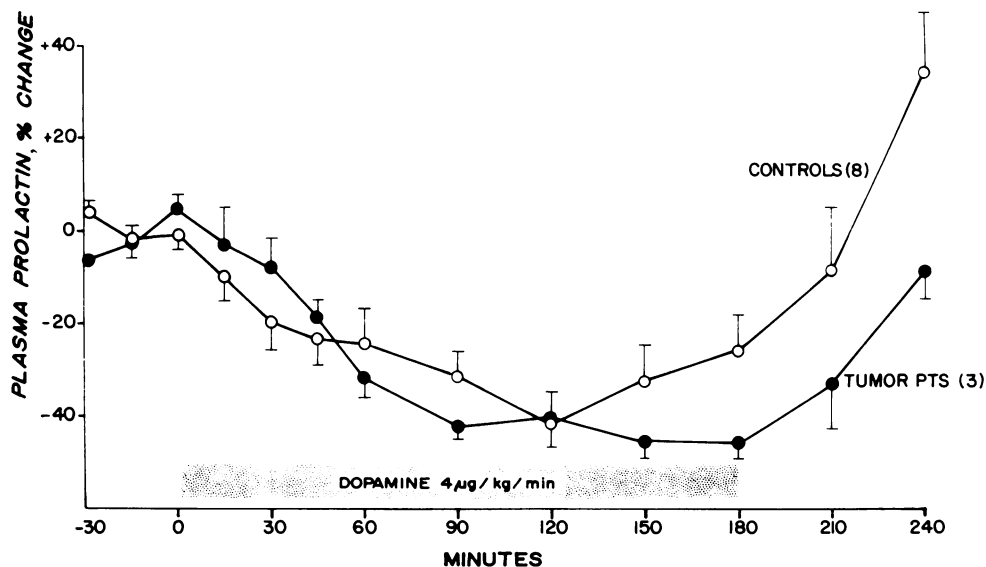


FIGURE 4 Percent change from basal PRL levels (\pm SEM) in control and tumor patients during and after dopamine infusion. Dopamine was infused (intravenously) for 180 min.

activity that an 80% inhibition of hypothalamic and cortical DD activity is produced by a single injection of carbidopa at a dose which does not increase plasma PRL levels in rats (18). It is therefore possible that the larger dose and longer duration used by Brown et al. (31) may have resulted in sufficient inhibition of CNS DD activity to interfere with the conversion of endogenous dopa to dopamine centrally, as well as in the periphery, thereby elevating basal PRL levels. The failure of carbidopa pretreatment to elevate basal PRL levels or to block the suppressive effects of L-dopa in the control subjects indicates that at the dose used in the present study, significant CNS DD activity persisted. The smaller dose of L-dopa which was used in combination with carbidopa has been previously reported to produce plasma dopa levels similar to those after the larger dose administered alone (21). It has also been shown that a five-fold greater dose of L-dopa is required to produce a similar elevation in mouse brain dopamine concentration as when L-dopa is administered in combination with a dopa decarboxylase inhibitor (20).

L-Dopa was capable of lowering plasma PRL in patients with pituitary tumors to levels comparable on a percentage basis to those in control subjects. This effect, however, was almost entirely blocked by pretreatment with carbidopa. Because of the possibility that peripheral DD inhibition might not be comparable in the two groups of subjects, the excretion of urinary HVA, the major dopamine metabolite, was measured during the 3-h period after L-dopa administration, as a reflection of the quantity of L-dopa converted to dopamine outside of the CNS in the absence and presence

of carbidopa. The comparability of urinary HVA levels in tumor patients and in the controls after L-dopa alone and in combination with carbidopa indicates that the difference in PRL suppression between normal and tumor patients was not due to differences in peripheral DD inhibition.

These results therefore indicate that after systemically administered L-dopa in normal subjects, both central and peripheral decarboxylation of dopa to dopamine are sufficient to account for the inhibition of PRL secretion. Pretreatment with carbidopa, as shown in Fig. 5, inhibits decarboxylation in a variety of sites including peripheral nerve terminals and the pituitary, thereby impairing dopamine formation. However, since the blood-brain barrier is relatively impermeable to carbidopa, the quantity of drug reaching the CNS at the dose employed in this study was insufficient to impair the central conversion of dopa to dopamine. The PRL-suppressive effects of dopamine occurred either as a consequence of its release into the portal blood or as the result of the release of a separate PRL-inhibiting factor. Thus, although the inhibitory effects of systemically administered L-dopa can occur as a result of peripheral conversion to dopamine, its central effects are sufficient to account for the observed PRL suppression.

It has been recognized that catecholamines which are excluded from most regions of the brain by the blood-brain barrier do accumulate in the median eminence after systemic administration (32). It is likely that carbidopa can also reach the area of the median eminence and therefore this site may need to be considered "peripheral" as used in the present discussion.

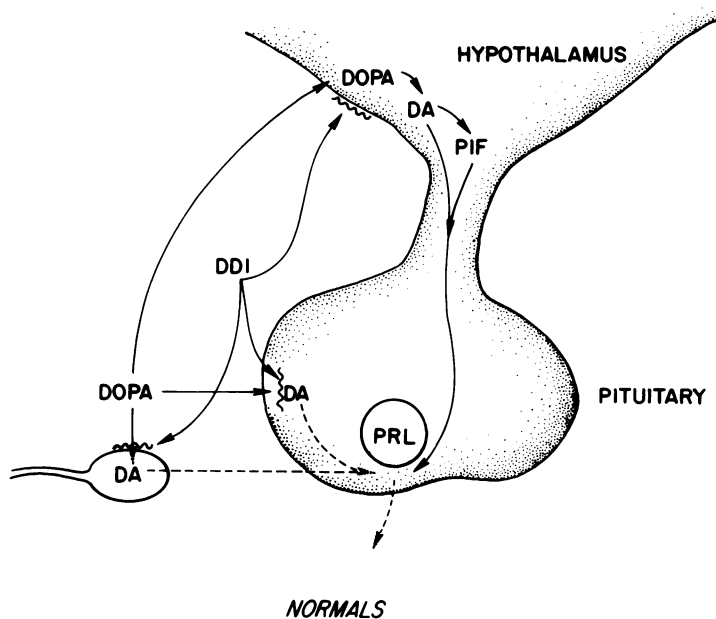


FIGURE 5 Proposed mechanism for the effect of pretreatment with carbidopa, a dopa decarboxylase inhibitor (DDI), on the PRL suppressive actions of L-dopa in normal subjects. Because the blood-brain barrier is relatively impermeable to the DDI, the peripheral conversion of dopa to dopamine in the pituitary and peripheral nerve terminals is selectively blocked whereas the central conversion of dopa to dopamine is unimpaired and the PRL-suppressive effects of dopamine, due either to its release into the portal system or by stimulating the release of a PRL-inhibiting factor, remain intact.

Whereas the present studies do not permit elucidation of the central site of dopa decarboxylation, it can be concluded that it is at a locus from which carbidopa is relatively excluded.

The nearly complete loss of the suppressive effects of L-dopa in patients with pituitary tumors after inhibition of the peripheral conversion of dopa to dopamine implies that the suppression observed after L-dopa alone occurred on the basis of peripheral conversion to dopamine. This interpretation is supported by the demonstration that these patients exhibited a normal PRL-inhibiting response to systemically infused dopamine, as has also been reported by Leblanc et al. (14), and explains why the use of L-dopa alone as a suppression test has not been of value in discriminating between normals and patients harboring PRL-secreting tumors.

The lack of PRL-suppression after carbidopa in the tumor patients can be explained by several hypotheses, as shown in Fig. 6. First (Fig. 6A), it is possible that patients with tumors have an impairment in dopa decarboxylation in the central dopaminergic tracts which regulate PRL secretion and the resultant loss of this central dopaminergic inhibitory tone could eventually lead to the development of a hypersecretory pituitary tumor.

Second, the loss of the central inhibitory effect

could be due to the lack of a separate prolactin-inhibiting factor or of an alteration in its central dopaminergic regulation. A clear distinction between these two alternatives is not possible from the present data, but both imply a potential role for altered neurotransmitter regulation in the pathogenesis of PRL-secreting tumors. A similar mechanism has been proposed by Krieger et al. (26) in relation to ACTH-secreting pituitary tumors. This possibility has assumed greater significance in light of the recent report that nonadenomatous pituitary lactotroph hyperplasia was found to be associated with hyperprolactinemia in five patients, one of whom also had a discrete pituitary adenoma (33). It is also possible that the hyperprolactinemia in some of the patients in the present study may have originated from normal lactotrophs whose vascular connections with the portal vascular system have been altered by a coexisting, non-PRL-secreting pituitary tumor. Histologic or biochemical confirmation of the presence of PRL in the tumor tissue would be required to exclude this possibility.

Third, (Fig. 6B), the results could be explained by an autonomous PRL-secreting pituitary tumor, which via a short loop feedback on the hypothalamus or elsewhere in the CNS, could result in increased secretion of prolactin-inhibiting factor to which the

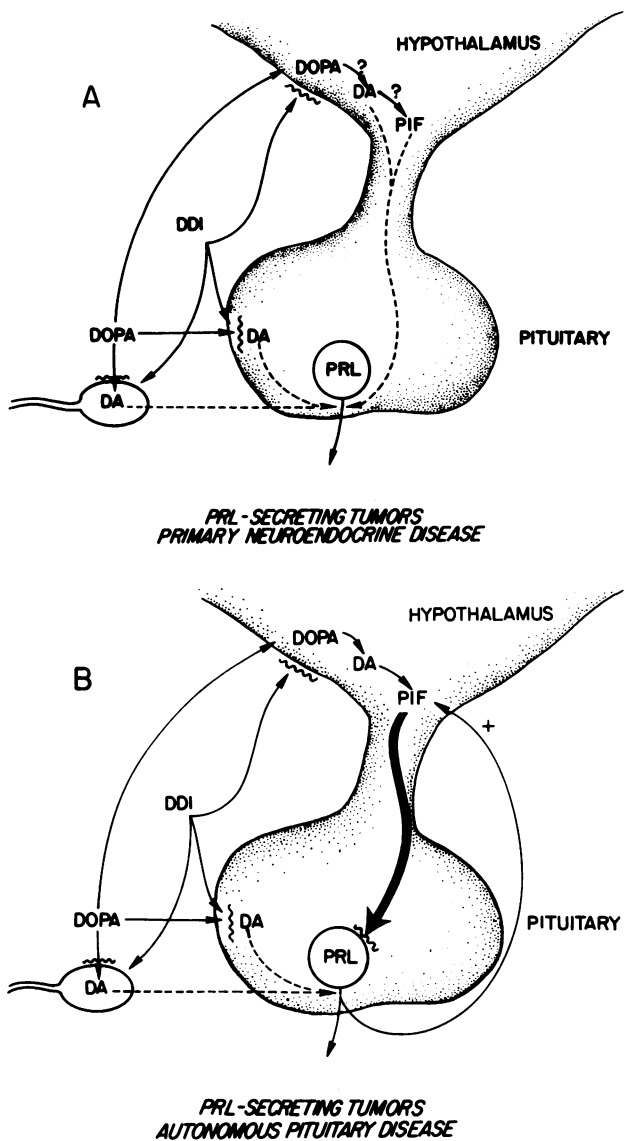


FIGURE 6 (A) Proposed mechanism for a primary neuroendocrine etiology of the loss of L-dopa suppression of PRL secretion after carbidopa pretreatment in patients with pituitary tumors. Peripheral conversion of dopa to dopamine is inhibited as in normal subjects (Fig. 5) and central-mediated suppression of the dopa effects are lacking due either to an impairment in the central conversion of dopa to dopamine or to a defect involving the release of a separate PRL-inhibiting factor. (B) Proposed mechanism for a primary pituitary defect resulting in the loss of L-dopa suppression of PRL secretion after carbidopa pretreatment in patients with pituitary tumors. The central dopaminergic inhibitory pathways remain intact. However, PRL, secreted by the autonomous pituitary tumor, via a short-loop feedback on the hypothalamus (or elsewhere in the CNS), increases the secretion of PRL-inhibiting factor to which the tumor is unresponsive. This hypothesis would require that the PRL-inhibiting factor be distinct from dopamine since tumor patients exhibited normal responsiveness to systemically infused dopamine.

tumor is unresponsive. This hypothesis would require that prolactin-inhibiting factor be distinct from dopamine since tumor patients exhibited normal responsiveness to exogenous dopamine.

It has been reported that after removal of PRL-secreting microadenomas, plasma PRL levels frequently return to normal, and in some patients cyclic menstruation returns (34-36). Although this might imply simply that an autonomous pituitary tumor had been removed with the reestablishment of "normal" neuroendocrine relationships, in none of the patients has postoperative evaluation of central dopaminergic function been performed using a protocol similar to that described in the present report. If such patients exhibit a normal PRL-suppressive effect of carbidopa plus L-dopa, the hypothesis of an autonomous pituitary tumor would be supported. However, the absence of normal PRL suppression by carbidopa plus L-dopa after removal of the adenoma would provide strong evidence for a primary central dopaminergic defect leading secondarily to a hypersecretory state and ultimately resulting in tumor formation. If this latter hypothesis is correct, some patients can be expected to show manifestations of recurrent disease during long-term follow-up and the postoperative evaluation of CNS dopaminergic tone may be useful in predicting the subsequent clinical course.

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