Dopamine Generated from L-Dopa: Discrepancy Between Plasma Levels and Cardiac Effects[1] (37038)

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When L-dopa is administered to patients and experimental animals, cardiovascular and renal effects are produced, which are similar to those caused by dopamine (1). In a recent study from this laboratory, dopamine plasma levels were measured after oral administration of L-dopa to patients with Parkinson's disease and essential hypertension (2). Extremely high dopamine plasma levels were found, but there was no evidence of excessive cardiac stimulation or hypertension which should have resulted if these levels were attained with intravenously infused dopamine (1, 3).

In an attempt to resolve these paradoxical results, the present studies were designed to correlate dopamine plasma levels with changes produced in cardiac contractile force and renal blood flow in anesthetized dogs after intravenous administration of dopamine and L-dopa.

Methods. Mongrel dogs of either sex weighing 12 to 26 kg were anesthetized with intravenous sodium pentobarbital, 30 mg/kg. Supplemental pentobarbital was administered as needed to maintain light anesthesia. Body temperature was maintained at about 39° by means of a water-heated blanket. The cervical vagi were cut and the animal was respired by means of a Harvard respiratory pump through a cuffed endotracheal tube. The left femoral vein was cannulated for drug administration and the left femoral artery for measurement of arterial blood pressure by a Statham Pressure Transducer and blood sampling. Blood flow in the right renal artery was measured by means of a Statham Electromagnetic Flowmeter as previously described (4). Cardiac contractile force (C.F.) was measured from the right ventricle using a Walton-Brodie strain gauge arch (5). Cardiac contractile force, mean arterial blood pressure and renal blood flow were monitored simultaneously on a Beckman Dynograph recorder.

After cardiac contractile force, blood pressure and renal blood flow had stabilized, graded intravenous doses of norepinephrine (0.25 to 2 μg/kg) or isoproterenol (0.1 to 0.4 μg/kg) were administered intravenously to determine their maximum production of myocardial contractile force.

Determinations of the peak contractile force were repeated with the same amine at least once during each experiment. Serial blood samples were withdrawn before and at timed intervals after L-dopa administration or dopamine infusion for determining plasma dopamine and dopa concentration curves.

Heparin (1000 units/ml) and sodium metabisulfite (0.5 mg/2 ml) were added to the femoral arterial blood samples which were then centrifuged and the plasma frozen (−20°) until ready for assay. Dopa and dopamine plasma levels were measured by the method of Anton and Sayre (6).

We used the following drugs: L-dopa HCl (Hoffman-La Roche, Inc.), dopamine HCl (Sigma Chemical Company), L-norepinephrine bitartrate (Sigma Chemical Company), and isoproterenol HCl (Winthrop Laboratories). Doses of all compounds were based on the weight of the salt. L-dopa was dissolved in 0.9% saline containing 0.2 ml of 6 *N* HCl and administered in a volume of 50 ml at a pH of approximately 3 to 4. Norepinephrine,

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TABLE I. Dopamine Peak Plasma Levels and the Increments in Cardiac Contractile Force, Renal Blood Flow, and Mean Blood Pressure in Eight Dogs Following Administration of Dopamine and L-dopa.

Parameter measured	Treatment		
	Dopamine I.V. (6 μg/kg/min)	L-dopa I.V. (5 mg/kg)	Statistical significance
Cardiac contractile force	137 ± 17	110 ± 22	N.S.[b]
Renal blood flow	49 ± 11	33 ± 10	N.S.[b]
Mean blood pressure	1 ± 2	7 ± 14	
	(Maximum increment from control, %, Mean ± S.E.)[a]		

[a] Control values refer to the stabilized values before each drug administration.

[b] N.S. = Not significant ($p > 0.05$) for dopamine vs L-dopa group. The mean blood pressure increments in both treatment groups, unlike those of the contractile force and renal blood flow, are not significantly different from control.

isoproterenol and L-dopa were administered by intravenous injection. Dopamine was infused i.v. using a Harvard 900 Constant Infusion Pump. Student's *t* test for paired data was used when appropriate (7).

Results. Correlations of dopamine plasma levels with pharmacological activity were obtained in a total of 14 dogs. In a series of eight experiments, peak plasma concentrations of dopamine (39.2 ± 14.6 μg/100 ml, mean ± SE) following L-dopa administrations (5 mg/kg; i.v.) were consistently higher than the dopamine concentrations (1.5 ± 0.2 μg/100 ml) obtained after 15 min of intravenous dopamine infusions at a rate of 6 μg/kg/min. The average peak plasma dopamine levels were approximately 25 times higher after L-dopa injections than during dopamine infusions. The averaged data for the corresponding pharmacologic responses are summarized in Table I.

Cardiac contractile force and renal blood flow began to increase within five to ten minutes after the L-dopa injections and reached maximum values in approximately ten minutes. The average maximum increase in contractile force was 110 ± 22% ($p < 0.01$), and renal blood flow increased 33 ± 10% ($p < 0.05$). Arterial blood pressure did not change significantly from control, indicating that the increments in renal blood flow were not secondary to the rise in arterial blood pressure. The results in Table I considered in relation to the plasma concentrations of dopamine emphasized the marked discrepancy between the plasma dopamine levels and pharmacological effects.

In six additional experiments, correlations of dopamine plasma levels and pharmacological activity were determined during three infusion rates of dopamine (1.5, 3 and 6 μg/kg/min), and three injections of L-dopa (1.25, 2.5 and 5 mg/kg) using three dogs in each series. These data are shown in Fig. 1. As noted, dose-related increments in peak dopamine plasma concentrations, maximal renal blood flow and cardiac contractile force occurred with intravenous infusions of dopamine. Although much higher plasma concentrations of dopamine were recorded after the L-dopa injections, the cardiac contractile force and renal blood flow increments were not greater than during the dopamine infusions. Changes in arterial blood pressure were variable with both L-dopa and dopamine.

It was important to prove that the lower peak contractile force values obtained after L-dopa were not due to either beta-adrenergic blockade or nonspecific failure of the myocardium, or inability of response due to concomitant presence of L-dopa or dopamine metabolites. This was accomplished in two ways. First, in every experiment, either norepinephrine or isoproterenol was able to increase contractile force to a greater extent than L-dopa even during the time of the experiment when high concentrations of dopa and dopamine were present in the plasma. Second-

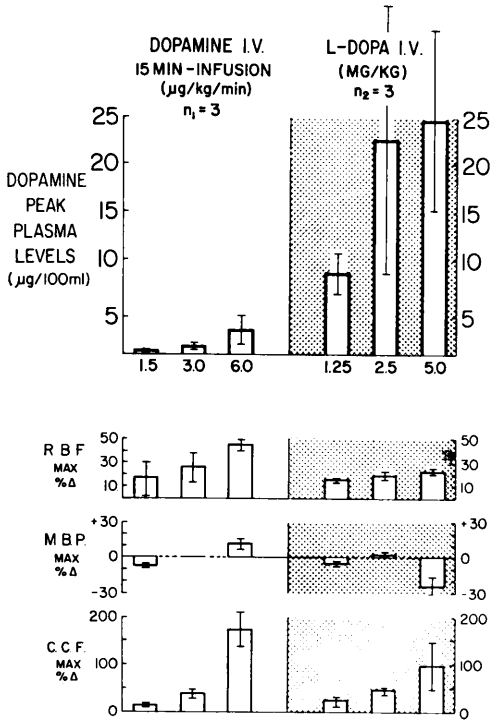

FIG. 1. Dopamine peak plasma concentrations and associated maximum responses of renal blood flow (RBF), mean blood pressure (MBP) and cardiac contractile force (CCF) after serial intravenous dopamine infusions and L-dopa injections in increasing doses. The bars represent the mean values ± S.E. in two series of dogs, one series receiving dopamine infusions ($n_1 = 3$, left panels) and the other following L-dopa injections ($n_2 = 3$, right panels).

ly, in five experiments of the first series, dopamine was infused at a rate of 6 μg/kg/min for 15 min during the maximum contractile force effect produced by a 2.5 mg/kg and 5 mg/kg dose of L-dopa. In each experiment, contractile force was increased further during the dopamine infusion. These data are summarized in Table II. Also shown in this table are plasma dopamine levels which were obtained during the administration of dopamine and L-dopa. Pronounced further increments in contractile force were produced by dopamine after the maximum C.F. effects of 2.5 and 5 mg/kg injections of L-dopa.

Figures 2 and 3 illustrate the effects of dopamine and L-dopa administration on cardiac contractile force and plasma dopamine levels in one of the above experiments. As shown in Fig. 2, i.v. infusion of 6 μg/kg/min of dopamine produced far greater increase in contractile force than 2.5 and 5 mg/kg of L-dopa. When the dopamine infusion was readministered during the period when L-dopa was exerting maximum contractile force effects, approximately the same effect on contractile force was attained as with the dopamine infusion alone. The marked discrepancy in dopamine levels is shown in Fig. 3.

In addition, the possibility was also considered that one of the metabolites from dopa or dopamine was producing an artefactual fluorescence that we were measuring as dopamine. Therefore, the following compounds were tested before and after extraction from plasma with Al_2O_3: VMA (vanillylmandelic acid), HVA (homovanillic acid), dihydroxyphenylacetic acid (dopac), dihydroxymandelic acid, 3-methoxydopamine, 3-methoxydopa and *N*-acetyldopamine. The compounds were used at a concentration at

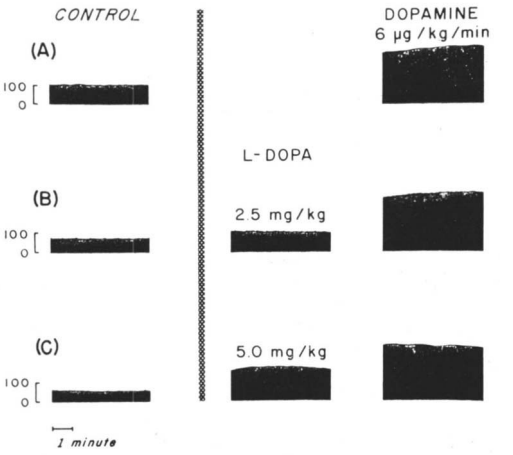

FIG. 2. Comparative contractile force responses in one representative experiment (Dog D-137) after dopamine infusion alone (A), L-dopa injections (middle panels) and following superimposed dopamine [third panels (B) and (C)]. The control contractile force response in (A) (the first horizontal thick band) corresponds to 100 g contractile force recorded from a Walton-Brodie strain-gauge arch sutured directly to the right ventricle. The corresponding dopamine plasma levels of this experiment are shown in Fig. 3.

TABLE II. Effects of Dopamine Infusion Alone and When Administered During Maximum Contractile Force Effects of L-dopa in Five Dogs.

	Maximum contractile force increment (% of control) mean ± SE	Dopamine peak plasma level (μg/100 ml) mean ± SE
A. Dopamine i.v. alone (6 μg/kg/min)	148 ± 22	1.3 ± 0.3
B. L-dopa 2.5 mg/kg i.v. alone	38 ± 4	17.4 ± 10.4
After superimposed dopamine (6 μg/kg/min)	186 ± 33[a]	[b]
C. L-dopa 5.0 mg/kg i.v. alone	121 ± 26	49.9 ± 22.6
After-superimposed dopamine (6 μg/kg/min)	278 ± 25[a]	[b]

[a] Indicates highly significant differences as compared to the preceding maximum contractile force increments achieved by L-dopa alone ($p < 0.001$).

[b] Dopamine plasma levels resulting from superimposed dopamine infusion can only be derived from the value in A, since the relatively high plasma dopamine values found following dopamine infusion in B and C were predominantly generated from L-dopa.

least 100 times that reported in animals and man after the ingestion of dopa (8, 9). Norepinephrine, epinephrine and their methylated derivates were not tested since only negligible amounts of these compounds are generated *in vivo* from exogenously administered dopa, and we previously had shown that some of these compounds might interfere only if present in excessive quantities (6). Under these conditions, 3-methoxydopa was the only compound producing significant fluorescence at a measurable concentration. However, based on the amount of this compound that might be generated from the dopa and since less than 0.01% was extracted by the Al_2O_3, it could be ruled out as a possible artefact. Extracts from several patients with high plasma levels of dopa and dopamine (2) were analyzed by paper chromatography, and dopa, dopamine and dopac were the only catechols detected. The concentrations of dopa and dopamine estimated by the qualitative paper chromatographic technique agreed within 50% of the values determined by the quantitative fluorometric method.

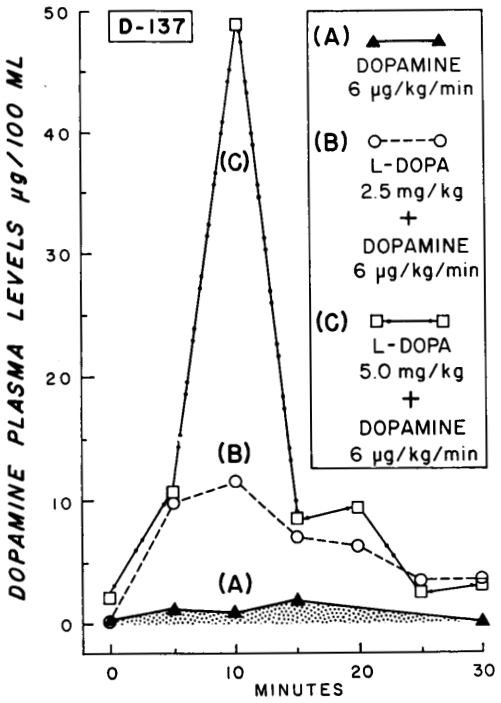

FIG. 3. Dopamine plasma concentration curves in Dog, D-137. The associated contractile force responses of this experiment are shown in Fig. 2.

Discussion. These experiments have demonstrated that there is a pronounced lack of correlation between dopamine plasma levels and cardiac contractility when L-dopa and dopamine are administered to the anesthetized dog. These data support our impression that a similar situation occurs in man (1–3).

The reason for this discrepancy in plasma

levels and pharmacological activity was not determined from these experiments. Clearly, however, it was not due to inability of the myocardium to respond either because of a specific or nonspecific block of dopamine.

A likely possibility is that the greater component of dopamine generated from L-dopa is in a pharmacologically inactive form, possibly as a conjugate. Indeed, strong acid hydrolysis of several plasma samples from L-dopa treated dogs has resulted in a two- to fivefold increment in plasma dopamine levels. Since the analysis of dopamine utilized an initial acid treatment to precipitate protein and subsequent acidification to elute the dopamine from Al_2O_3 (6), inadvertent partial hydrolysis of an acid labile conjugate of dopamine may account for the discrepancy between the chemical and physiological data.

Increased production of such a pharmacologically inert conjugate could explain the tolerance to the cardiac effects of L-dopa which occurs after prolonged administration of the drug (3).

Summary. Evidence has been presented in anesthetized dogs indicating that dopamine generated from L-dopa is predominantly in a pharmacologically inactive form whose identification is presently unknown, but there is some suggestion that it may be a labile conjugated derivative. The discrepancy between the high dopamine plasma levels after intravenous L-dopa administrations with the low cardiac contractile force responses were disclosed by comparison with the correlations obtained following dopamine infusions.

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