Modification of the Cardiovascular Effects of L-Dopa in Anesthetized Dogs by Inhibitors of Enzymes Involved in Catecholamine Metabolism

By Ronald D. Robson

ABSTRACT

The influence of various enzyme inhibitors on the cardiovascular effects of L-dopa (methyl ester) has been studied to determine the sites of action of the drug or a responsible metabolite. L-Dopa, 10 mg/kg, iv, had minor early effects on heart rate and blood pressure in normal dogs, but in animals with inhibition of monoamine oxidase (MAO), it caused tachycardia and severe hypotension of gradual onset. When MAO was inhibited, earlier doses of a dopamine β-oxidase inhibitor (FLA 63) did not significantly modify the effects of L-dopa; prior administration of a decarboxylase inhibitor, NSD 1055 or Ro 4-4602, prevented all but the initial effects; selective extracerebral decarboxylase inhibition with MK 486 (L-α-hydrazino-α-methyldopa) prevented the tachycardia but not the hypotension. DL-threo-Dihydroxyphenylserine caused an initial rise in blood pressure in dogs with MAO inhibition, had less pressor activity when peripheral decarboxylase was also inhibited, and in both cases did not cause the hypotension characteristic of L-dopa. L-Dopa enhanced pressor responses and especially associated bradycardic responses to norepinephrine in dogs with MAO inhibition. This action was prevented by all decarboxylase inhibitors but not FLA 63. Responses to angiotensin were similarly augmented. Thus, MAO inhibition enabled L-dopa to induce severe hypotension, which appeared to rely on a central conversion to dopamine; the other effects were probably mediated by peripherally formed dopamine.

KEY WORDS: heart rate, angiotensin, dopamine β-oxidase inhibition, blood pressure, DL-threo-dihydroxyphenylserine, norepinephrine, MAO inhibition, decarboxylase inhibition.

Interest in the cardiovascular actions of L-dopa has been renewed with the discovery that hypotension attributable to the drug has frequently attended its use in the treatment of Parkinsonism (1, 2). The hypotensive action may be due to L-dopa or a metabolite, since dopamine lowers blood pressure in guinea pigs (3) and in cats (4). Burn and Rand (4) suggested that the action might be due to competition of dopamine and norepinephrine at vascular receptor sites, resulting in a loss of tone because the weaker vasoconstrictor, dopamine, reduced their occupation by norepinephrine. More recently, other investigators (5, 6) have demonstrated that L-dopa causes impairment of peripheral sympathetic nerve function. An alternative hypothesis that hypotension induced by L-dopa may rely on a central action has received support from experiments by Henning and Rubenson (7) in which L-dopa lowered blood pressure in rats, provided an opposing peripherally mediated vasoconstriction was suppressed. Osborne and Moe (8) concluded that L-dopa caused venous pooling in dogs by a central neural action because the effect was prevented by inhibition of cerebral and extracerebral dopa decarboxylase but persisted after selective...
inhibition of peripherally located enzyme. In patients with neurologic or psychiatric disorders, Watanabe et al. (9) found that reductions in blood pressure caused by L-dopa were potentiated by the addition of an extracerebral dopa decarboxylase inhibitor and suggested that the hypotension was caused by an action on the central nervous system.

Prominent in the recent investigations has been the use of dopa decarboxylase inhibitors, which, by their differing effectiveness in inhibiting centrally or peripherally located enzyme, have variously modified the effect of L-dopa and thereby enabled deductions to be made concerning the site of action. Interference with enzymes involved in the metabolism of L-dopa has been used in the present experiments in an attempt to explain the manner in which L-dopa causes cardiovascular changes in dogs.

Methods

Mongrel dogs (10 to 15 kg) of either sex were anesthetized with barbitral sodium (200 mg/kg, iv) and pentobarbital sodium (approximately 20 mg/kg, iv). A cuffed endotracheal tube was inserted routinely in all animals and artificial respiration with a positive pressure respirator applied when necessary. Arterial blood pressure was measured from a femoral artery via a cannula connected to a Statham P23AA transducer. Heart rate was measured with a Beckman 9853B cardiocotachometer triggered by the lead II electrocardiogram. Records of heart rate, blood pressure, and electrically integrated mean blood pressure were displayed on a Beckman type RM Dynograph.

Drugs were injected intravenously (unless specified otherwise) via a cannulated femoral vein and doses expressed in terms of the base. L-Dopamine hydrochloride and L-Dopa-dihydroxyphenylserine were injected in aqueous solution over a period of 1 minute. Angiotensin and L-Dopa-dihydroxyphenylserine were injected in a logarithmic range of doses starting with 0.0625 or 0.125 μg/kg; the doses were given approximately 5 minutes apart, beginning 10 minutes after L-dopa. When selected enzyme inhibitors were given 30 minutes before L-dopa, dose-response relationships of the pressor agents were usually obtained during this interval. In studies of the influence of drug treatment on heart rate changes produced by the pressor agents in these nonvasoconstricted dogs, the predominant change of the frequently biphasic response before treatment was used.

The following enzyme inhibitors were used: FLA 63 (bis [(hexahydro-4-methyl-1H, 1, 4-diazepin-1-yl) thiocarbonyl] disulphide), an inhibitor of dopamine γ-oxidase (10). NSD 1055 (4-bromo-3-hydroxybenzyloxyamine), an inhibitor of dopa decarboxylase (11) and dopa-amine γ-oxidase (12); the decarboxylase inhibitors, Ro 4-4602 (L-serine, 2-[2, 3, 4-trihydroxybenzyl] hydrazine hydrochloride) (13) and MK 486 (L-c-carboxy-dopamine) (14). All inhibitors were injected in saline solution, except MK 486, which was injected intraperitoneally as an aqueous suspension. Phenetazine, 20 mg/kg, ip, was injected approximately 18 hours prior to study iv to inhibit monoamine oxidase (MAO) (15).

\[\text{FIGURE 1}\]

\text{Mean values (±SE) of heart rate (HR, beats/min) and mean blood pressure (BP, mm Hg) of groups of anesthetized dogs at various times after L-dopa, 10 mg/kg, iv. Initial values were measured shortly before injection of L-dopa at 0 minutes. a: Effects of L-dopa in four normal dogs. b: Seven dogs received phenetazine, 30 mg/kg, iv, 18 hours earlier. c: Four dogs pretreated with phenetazine were given L-dopa 30 minutes after FLA 63, 15 mg/kg, iv.}\]
RESULTS

EFFECT OF L-DOPA ON HEART RATE AND BLOOD PRESSURE

Figure 1 shows heart rate and blood pressure at intervals after L-dopa, 10 mg/kg, for normal dogs and dogs pretreated with phenelzine or phenelzine plus FLA 63. Blood pressures and corresponding heart rates were measured at the times of optimum change in individual dogs. In the group of normal dogs, L-dopa caused an initial rise in blood pressure accompanied by a transient bradycardia. The pressor response was followed by a brief hypotensive phase before blood pressure and heart rate returned to normal levels, approximately 6 minutes after L-dopa. Thereafter, blood pressure and heart rate remained normal up to 50 minutes after dosage (Fig. 1a). In the second group of dogs, L-dopa was injected approximately 18 hours after phenelzine, 20 mg/kg, ip. In the presence of MAO inhibition, L-dopa also caused a persistent tachycardia and a later, severe fall in blood pressure. An intermediate recovery of blood pressure toward normal was reliably obtained, reached a peak at a group mean time of 10 minutes, and was followed by a gradual fall in pressure to a minimum value at 50 minutes after L-dopa (Table 1). The onset of this rise in blood pressure coincided approximately with the onset of a prolonged tachycardia. Two hours after L-dopa, blood pressure and heart rate had returned to control levels (Fig. 1b). In addition to pretreatment with phenelzine, the third group of four dogs were injected with the dopamine β-oxidase inhibitor, FLA 63, 15 mg/kg, 30 minutes before L-dopa (Fig. 1c). Blood pressure and heart rate were temporarily lowered by FLA 63, but had returned to normal before L-dopa was administered. The nature and time course of the polyphasic response to L-dopa was essentially the same, but the early fall in blood pressure was greater after pretreatment with FLA 63.

The influence of prior doses of MK 486, 10 mg/kg, ip (Fig. 2a), or NSD 1055, 100 mg/kg (Fig. 2b), was studied on the cardiovascular effects of L-dopa, 10 mg/kg, in two groups of dogs pretreated with phenelzine. The initial pressor response and bradycardia were obtained in both groups, but subsequent effects were different from those obtained with L-dopa in dogs with inhibition of MAO only. Thus, after treatment with the extracerebral decarboxylase inhibitor (MK 486), L-dopa did not cause an intervening rise in blood pressure after the initial pressor response, and pressure uniformly declined to a minimum value after a group mean time of 98 minutes. Two hours after treatment, although some recovery was apparent, blood pressure remained below the control level. Heart rate did not differ from the initial value 30 minutes after L-dopa and became gradually slower over the course of the experiment (Fig. 2a). After cerebral and extracerebral decarboxylase inhibition with NSD 1055, apart from the early pressor response and accompanying bradycardia, blood pressure and heart rate

<table>
<thead>
<tr>
<th>30-minute pretreatment</th>
<th>No. dogs</th>
<th>Mean blood pressure (immediately before L-dopa, minimum after L-dopa, 2 hours after L-dopa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>7</td>
<td>120 ± 10.7 72 ± 6.4 110 ± 9.7</td>
</tr>
<tr>
<td>MK 486, 10 mg/kg, ip</td>
<td>5</td>
<td>120 ± 11.7 50 ± 7.7 107 ± 8.8</td>
</tr>
<tr>
<td>MK 486, 25 mg/kg, ip</td>
<td>4</td>
<td>128 ± 4.3  73 ± 17 78 ± 16</td>
</tr>
<tr>
<td>Ro 4-4602, 25 mg/kg, iv</td>
<td>4</td>
<td>127 ± 8.5  113 ± 14 109 ± 13</td>
</tr>
<tr>
<td>NSD 1055, 100 mg/kg, iv</td>
<td>5</td>
<td>104 ± 15.4 105 ± 15 100 ± 10</td>
</tr>
<tr>
<td>FLA 63, 15 mg/kg, iv</td>
<td>4</td>
<td>134 ± 8.3  71 ± 9.2 143 ± 24</td>
</tr>
</tbody>
</table>

All dogs received phenelzine (20 mg/kg, ip) 18 hours earlier.
CARDIOVASCULAR EFFECTS OF L-DOPA

B (10 mg/kg + L-Dopa)

(JPhenslent * NSD 1055 + L-Dopa)

Time (min) after L-Dopa

FIGURE 2

Same notation as in Figure 1. Both groups of five dogs had received phenelzine, 30 mg/kg, ip, 18 hours earlier. L-Dopa, 10 mg/kg, iv, was injected, 30 minutes after MK 486, 10 mg/kg, ip (a) or after NSD 1055, 100 mg/kg, iv (b).

were not altered significantly by L-dopa (Fig. 2b).

Representative records illustrating the modification by MK 486, 10 mg/kg, ip, of the effects of L-dopa in dogs pretreated with phenelzine are shown in Figure 3. The peripheral dopa decarboxylase inhibitor prevented the secondary rise in blood pressure, and heart rate was slowed rather than increased by L-dopa; hypotension was more severe and the time course extended.

Other dogs with MAO inhibition were given L-dopa 30 minutes after MK 486, 25 or 40 mg/kg, ip, or Ro 4-4602, 25 mg/kg. Either dose of MK 486 prevented the tachycardia and secondary rise in blood pressure after L-dopa, but the hypotensive phase persisted. The result was very similar to that shown in Figure 2a. Prior treatment with Ro 4-4602 prevented all but the initial effects of L-dopa in the same way as NSD 1055 (Fig. 2b).

Table 1 shows mean values of blood pressure immediately before L-dopa, at the time of maximum hypotension, and 2 hours after L-dopa. All groups of dogs were pretreated with phenelzine and five groups received additional enzyme inhibitors as indicated. The fall in blood pressure after L-dopa was greater following MK 486, 10 mg/kg, ip, treatment, although the difference in hypotensive levels of this group compared to the L-dopa control was of borderline statistical significance ($P = 0.053$). The larger dose of MK 486 did not alter the severity of the hypotension induced by L-dopa. Both doses of MK 486, however, delayed recovery of blood pressure, as shown by a comparison of the 2-hour measurements. Prior doses of the cerebral and extracerebral decarboxylase inhibitors (Ro 4-4602 or NSD 1055) prevented the hypotensive action of L-dopa, but the response was essentially normal in the presence of dopamine β-oxidase inhibition with FLA 63.

EFFECT OF L-DOPA ON PRESSOR AND CHRONOTROPIC RESPONSES TO NOREpinePHRINE AND ANGIOTENSIN IN DOGS GIVEN MAO

Mean responses of groups of dogs pretreated with phenelzine to norepinephrine or angiotensin before and after various treatments are shown in Figures 4 and 5. The columns show resting levels (flat end), magnitude and direction of change in heart rate, and systolic blood pressure after increasing doses of pressor agents. Figure 4 (left) shows the effects of norepinephrine before (white columns) and after L-dopa (black columns). Treatment with L-dopa, 10 mg/kg, caused tachycardia and hypotension. Although pressor responses were potentiated, it appeared that this effect was not entirely responsible for the marked increase in associated bradycardias. For example, initial pressor
Systolic blood pressure (BP, mm Hg), and responses to indicated doses of norepinephrine (left, five dogs), and angiotensin (right, four dogs). All dogs were pretreated with phenelzine, 20 mg/kg, ip. Columns show levels immediately before each dose of a pressor agent and the direction and magnitude of responses before (white columns) and after (black columns) L-dopa, 10 mg/kg. A significant increase in responses to particular doses was obtained where indicated (*P < 0.05; **P < 0.01).

Responses to 0.5 and 1.0 μg/kg norepinephrine were greater than the response after L-dopa to 0.25 μg/kg, yet the latter dose was associated with a greater bradycardia. Statistical analysis of these results showed that pressor responses to 0.25 and 0.5 μg/kg norepinephrine were not significantly altered by L-dopa, although the associated bradycardias were significantly enhanced (P < 0.05, P < 0.01, respectively). A comparison of the average effect of all doses of norepinephrine showed that negative chronotropic activity was enhanced (P < 0.05) at a time when blood pressure changes were not significantly altered by L-dopa. Responses to angiotensin were modified in a similar manner by L-dopa, although this case it was not possible to show a statistical dissociation between enhanced pressor and bradycardic responses (Fig. 4, right).

Appropriate sections of Figure 5 show the effects of L-dopa given 30 minutes after FLA 63 or MK 486. Prior administration of FLA 63 did not prevent the potentiation by L-dopa of the bradycardic responses to various doses of norepinephrine, and L-dopa continued to cause hypotension and tachycardia (Fig. 5, left). The low dose of MK 486 did not prevent the enhancement by L-dopa of bradycardias associated with norepinephrine pressor activity (middle). Generally, a significant enhancement (P < 0.05) of negative chronotropism was associated with an insignificant change in pressor responsiveness. The mean chronotropic responses to increasing doses of norepinephrine were initially negligible (white columns) in this group because predominantly positive chronotropic responses of two dogs largely compensated for the negative responses of the other three dogs. After L-dopa, all dogs exhibited bradycardias in response to norepinephrine (black columns). As shown by

![Figure 4](image-url)  ![Figure 5](image-url)

FIGURE 4
Mean heart rate (HR, beats/min), systolic blood pressure (BP, mm Hg), and responses to indicated doses of norepinephrine (left, five dogs), and angiotensin (right, four dogs). All dogs were pretreated with phenelzine, 20 mg/kg, ip. Columns show levels immediately before each dose of a pressor agent and the direction and magnitude of responses before (white columns) and after (black columns) L-dopa, 10 mg/kg. A significant increase in responses to particular doses was obtained where indicated (*P < 0.05; **P < 0.01).

FIGURE 5
Same notation as in Figure 4. All dogs were pretreated with phenelzine, 20 mg/kg, ip. Responses to norepinephrine were obtained beginning approximately 10 minutes after L-dopa, 10 mg/kg (black columns). L-Dopa was injected 30 minutes after FLA 63, 15 mg/kg (four dogs), or MK 486, 10 mg/kg, ip (four dogs, middle) or MK 486, 25 mg/kg, ip (four dogs, right). Control responses to norepinephrine (white columns) obtained during this interval.
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Records of heart rate (HR, beats/min), blood pressure (BP, mm Hg), and responses to indicated doses (µg/kg) of norepinephrine of dogs pretreated with phenelzine. a: NSD 1055, 100 mg/kg, followed in 30 minutes by L-dopa (DME), 10 mg/kg, was given as indicated between the first and second series of norepinephrine doses. b: Same as section a except that MK 486, 10 mg/kg, ip, was substituted for NSD 1055. c: FLA 63, 15 mg/kg, was followed in 30 minutes by DME. These doses were repeated and the dog vagotomized. d: Same as section c except that carotid sinus denervation was substituted for vagotomy. A third dose of DME was given. (Arrows indicate injections.)

Doses of NSD 1055, 100 mg/kg, and 30 minutes later of L-dopa, 10 mg/kg, did not appreciably alter responses to norepinephrine (Fig. 6a). When the same dose schedule was used in a second dog with MK 486, 10 mg/kg, substituted for NSD 1055, the pressor responses to norepinephrine became larger and somewhat more prolonged, and were associated with marked negative chronotropic activity (Fig. 6b). This augmentation of bradycardic responses was similar to that produced by L-dopa alone in animals with MAO inhibition (Fig. 4a).

Administration of FLA 63, 15 mg/kg, followed by L-dopa (Fig. 6c) caused pressor responses to become slightly larger and less transient. However, changes in blood pressure were accompanied by severe bradycardias after treatment with FLA 63 plus L-dopa, and even small pressor responses to 0.0625 and 0.125 µg/kg norepinephrine induced marked cardiac slowing in contrast to the earlier negligible rate changes associated with much larger increases in blood pressure. These effects persisted for approximately 2 hour and were reproducible with subsequent doses of L-dopa. The responses to norepinephrine (Fig. 6c) were obtained when bilateral vagotomy had been performed shortly after repeat doses of FLA 63 and L-dopa. Norepinephrine now caused dose-related tachycardias. There was a distinct enhancement of pressor activity which was probably in large part a consequence of vagotomy. The final experiment shown in Figure 6d was similar in design to that shown in Figure 6c except that bilateral carotid sinus denervation was performed instead of vagotomy. Carotid sinus denervation converted bradycardias induced by norepinephrine to positive chronotropic responses in the same manner as vagotomy. In this experiment, a third dose of L-dopa, 10 mg/kg, was given, after which heart rate changes associated with slightly increased pressor responses reverted to bradycardias, although of smaller magnitude than those obtained prior to carotid sinus denervation.

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In two dogs pretreated with phenelzine, \( \text{DL}-\text{threo-dihydroxyphenylserine}, 10 \text{ mg/kg}, \) caused tachycardia followed by bradycardia and a precipitous rise in mean blood pressure \((122 \pm 22 \text{ mm Hg})\). After returning to normal levels in approximately 3 minutes, there was no subsequent alteration of heart rate or blood pressure characteristic obtained with L-dopa under these conditions. There were similarly no late changes when \( \text{DL}-\text{threo-dihydroxyphenylserine}, 20 \text{ mg/kg}, \) was injected 30 minutes after MK 486, 25 mg/kg, ip, in three other dogs in which MAO was inhibited, but the initial pressor effect was less \((76 \pm 35 \text{ mm Hg})\) despite the larger dose.

**Discussion**

A comparison of the cardiovascular effects of L-dopa, 10 \text{ mg/kg, iv}, in normal dogs and in dogs with MAO inhibition shows that, apart from initial effects common to both groups, in the latter group there were a persistent tachycardia and a minor secondary rise in blood pressure followed by profound hypotension. L-Dopa and the metabolites formed by transamination are resistant, but dopamine formed by decarboxylation of L-dopa is susceptible to oxidative deamination (16). Consequently, the latter effects of L-dopa were probably due to the formation of dopamine (or norepinephrine by the action of dopamine \( \beta\)-oxidase) which, under the protection afforded by MAO inhibition, attained effective concentrations.

Prevention of these effects by prior treatment with the decarboxylase inhibitors NSD 1055 (11) and Ro 4-4602 (13) supports this contention. The additional dopamine \( \beta\)-oxidase inhibitory activity of NSD 1055 (12) could have contributed to the overall effect if the production of norepinephrine was ultimately responsible for the major effects of L-dopa. However, prior treatment with FLA 63 (10) in a dose of 15 mg/kg, iv, to cause specific dopamine \( \beta\)-oxidase inhibition in the dog (H. Corrodi, personal communication), did not influence the tachycardia or reduce the severity of the late hypotensive action of L-dopa. Nevertheless, the immediate hypotensive effect was larger after FLA 63. This could be a consequence of a presumably greater elevation of tissue dopamine levels when L-dopa was administered during inhibition of MAO and dopamine \( \beta\)-oxidase. Ayitey-Smith and Varma (17) found that inhibition of dopamine \( \beta\)-oxidase did not antagonize the hypotensive action of \( \alpha\)-methyl dopa in immunosympathectomized rats. In contrast, Hemming and Rubenson (7) found that FLA 63 prevented hypotension after L-dopa in the presence of peripheral decarboxylase inhibition, and reported preliminary experiments which showed that inhibition of dopamine \( \beta\)-oxidase prevented the hypotensive action of \( \alpha\)-methyl dopa in rats. A further indication that the hypotensive action of L-dopa in dogs relied on the formation of dopamine rather than norepinephrine was obtained with the administration of suitable doses of \( \text{DL}-\text{threo-dihydroxyphenylserine}, \) which had early pressor activity but failed to cause the subsequent hypotension characteristic of L-dopa in dogs with inhibition of MAO alone, or of MAO and peripheral decarboxylase. \( \text{DL}-\text{threo-dihydroxyphenylserine} \) is decarboxylated in the brain and periphery to norepinephrine without an intermediate formation of dopamine (18).

Modification of the effects of L-dopa by prior administration of a selective inhibitor of peripheral decarboxylase should indicate the relative importance of central and peripheral decarboxylation in the production of the cardiovascular actions of L-dopa. \( \text{NL}-\text{alpha-hydrizino-alpha-methyl dopa} \) inhibits extracerebral decarboxylase but has little effect on centrally located enzyme (14); inhibitory activity is restricted to the L-isomer, MK 486 (19). Only the hypotensive action of L-dopa persisted after a range of doses of MK 486 and this, in conjunction with the prevention by cerebral and extracerebral decarboxylase inhibition with Ro 4-4602 (20), suggests that the fall in blood pressure was dependent on a central conversion of L-dopa to dopamine. As a result of the modifications produced by intravenous Ro 4-4602, 25 mg/kg, and MK 486, 20 mg/kg, Osborne and Moe (8) concluded that L-dopa caused venous pooling in dogs by a central
neural action. A similar mechanism for the hypotensive action of L-dopa in dogs was proposed by Minsker et al. (21), who used Ro 4-4602, 100 mg/kg, and MK 486, 15 mg/kg and 15 mg/kg respectively. The failure of L-dopa after either decarboxylase inhibitor to cause the tachycardia or protracted secondary rise in blood pressure normally seen in dogs pretreated with phenelzine, suggests that these responses were due to the peripheral formation of dopamine or possibly dopamine-induced release of norepinephrine (22).

Decarboxylation of an intravenous dose of L-dopa will cause the appearance of dopamine in the circulation, and elevated levels will also be obtained within adrenergic nerves because of intraneuronal decarboxylase. It has been suggested that receptor competition may occur between dopamine and norepinephrine (4). Evidence of impairment of sympathetic nerve function has been obtained (5, 6), and Thoenen et al. (23) have shown that electrical stimulation released dopamine from sympathetic nerves of cats pretreated with disulfiram. Pretreatment with DL-α-hydrazino-α-methyldopa was shown to enhance the increase in brain dopa and dopamine following intraperitoneal injection of dopa in rats (19), and the effect of peripheral decarboxylase inhibition on the hypotensive action of L-dopa may depend, therefore, on the relative modification of central and peripheral contributions. An augmentation of the central action may be counteracted by a complete loss of a peripheral hypotensive component when enzyme inhibition is sufficiently severe. A lesser degree of inhibition may still enhance brain levels of L-dopa and its metabolites but be insufficient to prevent a significant peripheral formation of dopamine with a possible capacity to lower blood pressure. Such considerations may explain why the hypotensive action of L-dopa was not diminished after large doses of MK 486 but was apparently greater after the 10 mg/kg dose in dogs or after the acenim compound in man (9). Although MK 486, 10 mg/kg, was sufficient to prevent the tachycardia after L-dopa, there was apparently some formation of dopamine, because changes induced by L-dopa in response to injected norepinephrine persisted after this dose, but not after 55 mg/kg, ip.

In animals with MAO inhibition increases in pressor responses to the higher doses of norepinephrine were sometimes statistically significant, although average values for the range of doses were never significantly greater after L-dopa. After MK 486, 25 mg/kg, when L-dopa caused hypotension there was no enhancement of pressor responses at any dose level, so that lowered blood pressure would not seem to be responsible. Possibly, interference with norepinephrine uptake by metabolites of L-dopa normally may cause the augmentation and also explain the slightly more prolonged responses. Pressor responses to all doses of angiotensin were significantly greater after L-dopa in animals pretreated with phenelzine, and in this case lower blood pressure may have been an important cause of the greater pressor activity. Bradycardia produced by the pressor agents was significantly enhanced by L-dopa, although the greater rate changes with angiotensin could have arisen solely in response to the larger pressure responses. Bilateral vagotomy or carotid sinus denervation by interference with reflex negative chronotropic influences allowed dose-related tachycardias to be produced after norepinephrine, however, predominantly bradycardic responses could be restored by L-dopa after carotid sinus denervation, presumably because of an action on the functional baroreceptor of the aortic arch. The indications that baroreceptor sensitivity was increased may not be unexpected. Dopamine stimulates chemoreceptors of the dog (24), and stimulation of the sympathetic innervation of the carotid sinus increases the sensitivity of the baroreceptors to a given change in pulse pressure (25). The significant metabolite of L-dopa involved in the potentiation of responses to norepinephrine appeared to be extracerebral dopamine, since the effects persisted after FLA 63 but not after NSD 1055, Ro 4-4602, or the larger doses of MK 486.
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References
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