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AN ANALYSIS OF THE PERIPHERAL EFFECTS OF L-DOPA ON AUTONOMIC NERVE FUNCTION

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1 The ability of intravenous L-DOPA to block sympathetic and parsympathetic nerves has been studied in cats and dogs pretreated with a monoamine oxidase inhibitor.

2 L-DOPA inhibited positive chronotropic and pressor responses to dimethylphenylpiperazinium (DMPP) and McN-A-343 in dogs, and contractions of the nictitating membrane produced by these ganglion stimulants in cats.

3 Responses of the cat nictitating membrane to preganglionic stimulation were inhibited by L-DOPA to a greater extent than those to postganglionic stimulation of the cervical sympathetic chain.

4 In dogs, L-DOPA had no vagolytic action, but depressed vasoconstrictor responses elicited in the perfused hind-limb by electrical stimulation of the lumbar sympathetic chain.

5 The degree of lumbar sympathetic chain inhibition correlated with the pressor response following L-DOPA, and both effects were prevented by prior decarboxylase inhibition.

6 These results suggest that the decarboxylation products of L-DOPA do not impair parasympathetic nerve activity but depress sympathetic nerve function predominantly by inhibiting both muscarinic and nicotinic sites of sympathetic ganglia.

Introduction

Hypotension following L-DOPA has been described in a variety of experimental procedures, and a number of mechanisms have been advanced to explain the action. From the results of the influence of central and peripheral decarboxylase inhibitors, hypotension was considered to be centrally-mediated in rats (Henning & Rubenson, 1970) and dogs (Minsker, Scriabine, Stokes, Stone & Torchiana, 1971; Robson, 1971; Watanabe, Parks & Kopin, 1971). Other investigators found that L-DOPA also caused impairment of sympathetic nerve function (Farmer, 1965; Whitsett, Halushka & Goldberg, 1970; Whitnack, Leff, Mohammed & Gaffney, 1971; Dhasmana & Spilker, 1973). In dogs pretreated with a monoamine oxidase inhibitor, Antonaccio, Robson & Burrell (1974) concluded that hypotension after L-DOPA was predominantly reliant on a central mechanism, although they also obtained evidence for impairment of peripheral sympathetic nerve function. While L-DOPA has the capacity to cause adrenergic neurone blockade, sympathetic nerve function may also be impaired by an action at ganglia since Bogaert & de Schaepdryver (1967) and Willems, Hoszowska-Owczarek & Bogaert (1972) have shown that dopamine depresses transmission through sympathetic ganglia.

By reference to the effects of classical autonomic blocking drugs, the present study attempts to determine the importance of ganglion blockade relative to adrenergic neurone blockade as the cause of impairment of sympathetic nerve function after L-DOPA.

Methods

Mongrel dogs selected at random for size and sex were anaesthetized with either Dial-urethane solution (0.6 ml/kg i.v.) or sodium pentobarbitone plus sodium barbitone (25 and 250 mg/kg i.v., respectively).

Autonomic drug interactions

The right femoral artery and left femoral vein were cannulated for the measurement of blood pressure and injection of drugs, respectively. For vagal nerve stimulation, the right vagus was cut, bathed in mineral oil and stimulated peripherally at 8 Hz, with pulses of 10V and 5 ms duration through

platinum electrodes for 30 seconds. Heart rate was measured with a Beckman calibrating cardiotachometer triggered from the blood pressure pulse.

Perfused hind limb

The left jugular vein was cannulated for the intravenous administration of drugs. The right carotid artery was cannulated for blood pressure measurements. Heart rate was monitored as above. The left external iliac artery was cannulated and blood passed through a Sigma-motor pump back into the left femoral artery at a constant flow. The perfusion pressure was adjusted so that it approximated mean arterial blood pressure. The left lumbar sympathetic chain was isolated at approximately the L-3 level, crushed and bathed with mineral oil. Fifteen minutes after the administration of atropine sulphate (1 mg/kg i.v.) platinum electrodes were placed around the lumbar sympathetic chain peripheral to the crushed area and the nerves stimulated intermittently at 0.2, 0.3, 0.6, 1.2, 3.6 and 11.0 Hz, with square-wave impulses of supramaximal voltage and 5 ms duration.

Nictitating membrane preparation

Cats of either sex weighing from 2.2 to 4.5 kg were anaesthetized with Dial-urethane solution (0.7 ml/kg i.p.). The cats were then bilaterally vagotomized and spinalized according to the method of Burn (1952). Contraction of the nictitating membrane was recorded isometrically with a Grass Model FT10 force-displacement transducer. The initial membrane tension on all membranes was 8 grams.

The sectioned preganglionic and the intact postganglionic cervical sympathetic nerves were placed on bipolar platinum electrodes and bathed in mineral oil. The stimuli were square-wave pulses of 2 ms duration, 15V at a frequency of 5Hz for 10 seconds.

Drugs were injected into the nictitating membrane by clamping the internal carotid artery above the origin of the lingual artery as described by Trendelenburg (1954). Drugs were injected into the superior cervical ganglion by clamping the common carotid and external carotid arteries distal to the injection into the lingual artery. Intravenous injections were made into the femoral vein and blood pressure was measured from the femoral artery. Heart rate was measured with a Beckman cardiotachometer triggered from the blood pressure pulse.

Drugs

For the inhibition of monoamine oxidase (MAO), dogs and cats were pretreated with one dose of Su-11739 (*N*-methyl-*N*-2-propyl-l-indanamine) 3 mg/kg subcutaneously either 1 h or 24 h before the experiment as noted (Huebner, Donoghue, Plummer & Furness, 1966; Robson, Antonaccio, & Rinehart, 1972).

Other drugs used were: atropine sulphate, chlorisondamine hydrochloride, L-3,4-dihydroxyphenylalanine methylester (L-DOPA), dimethylphenylpiperazinium iodide (DMPP), adrenaline

Table 1 Effects of drugs on blood pressure [BP, mmHg] and heart rate [HR, beats/min] in dogs*.

Drug	n	*Initial Level*		*Time after drug*			
				10 min		*120-180 min*	
(i.v.)		*BP*	*HR*	*BP*	*HR*	*BP*	*HR*
L-DOPA	4	140.6	138.6	221.4	241.4	105.3	161.1
(10 mg/kg)		±9.2	±4.2	±13.9	±8.8	±9.0	±19.6
				P<0.02	*P*<0.001	*P*<0.01	
Guanethidine	3	107.3	182.0	110.3	158.0	99.3	142.0
(1 mg/kg)		±9.7	±13.0	±11.3	±13.9	±9.3	±19.2
							P<0.05
Chlorisondamine	3	119.3	147.0	87.0	127.0	85.0	108.0
(1 mg/kg)		±4.5	±6.0	±8.7	±4.4	±6.9	±3.0
					P<0.02	*P*<0.05	*P*<0.001
Methylphenidate	4	130.5	157.5	131.0	181.5	124.8	159.8
(10 mg/kg)		±7.5	±5.5	±6.3	±9.9	±9.2	±14.6

*Dogs given L-DOPA were pretreated 24 h earlier with the monoamine oxidase inhibitor Su-11739 (3 mg/kg s.c.). Dial-urethane anaesthesia.

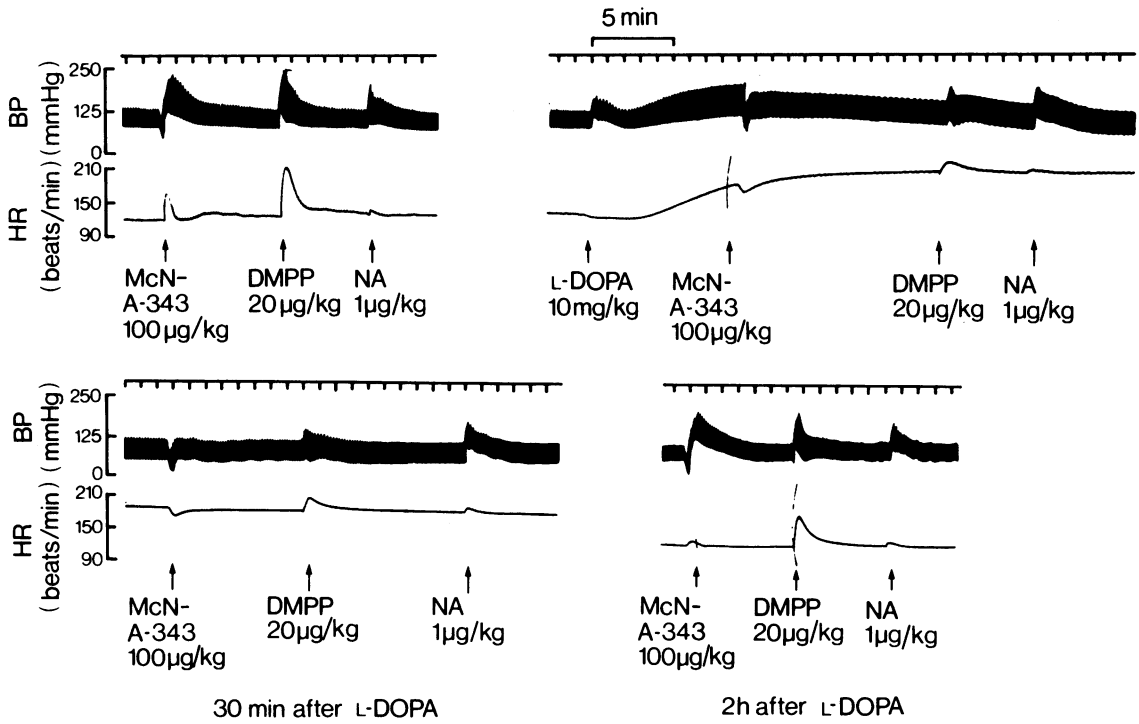

Fig. 1 The effects of L-DOPA (10 mg/kg i.v.) on blood pressure (BP; mmHg), heart rate (HR; beats/min) and responses to McN-A-343, dimethylphenylpiperozinium (DMPP) and noradrenaline (NA) in a bilaterally-vagotomized dog pretreated with the monoamine oxidase inhibitor. Sodium pentobarbitone + barbitone anaesthesia.

hydrochloride, guanethidine monosulphate, hexamethonium hydrochloride, McN-A-343 (4-*m*-chlorophenylcarbamoyloxy-2-butynyl trimethylammonium chloride), methylphenidate hydrochloride, MK-486 (L-α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)propionic acid), (−)-noradrenaline monohydrate bitartrate, and (−)-oxprenolol hydrochloride.

All doses refer to the salt.

Results

Drug interactions in dogs

Blood pressure and heart rate of dogs pretreated with the MAO inhibitor were elevated 10 min after L-DOPA (10 mg/kg i.v.); subsequently, hypotension developed with minimal pressure values occurring 2-3 h after treatment (Table 1). In other groups of dogs not treated with the MAO inhibitor, guanethidine (1 mg/kg i.v.) and methylphenidate (10 mg/kg i.v.) had no important effects, whereas chlorisondamine (1 mg/kg i.v.) caused persistent hypotension and bradycardia (Table 1).

During the early hypertensive phase after L-DOPA, the pressor responses to DMPP and McN-A-343 were markedly inhibited, although the initial depressor action of McN-A-343 persisted (Figure 1). The antagonism of the pressor responses was not a consequence of L-DOPA-induced hypertension since the response to noradrenaline was unaffected and the antagonism of the ganglion stimulant persisted after blood pressure had returned to normal (Fig. 1, 30 min after L-DOPA). Pressor responses to DMPP and McN-A-343 had recovered 2 h after L-DOPA. However, it was not possible to dissociate an apparent antagonism by L-DOPA of the positive chronotropic actions of the agents from the marked and persistent tachycardia which followed L-DOPA (Figure 1).

Depressor responses and bradycardia induced by vagal stimulation were enhanced 30 min after L-DOPA in dogs pretreated with the MAO inhibitor (Figure 2a). The action was probably a consequence of the elevated pre-stimulation levels since there was no enhancement when blood

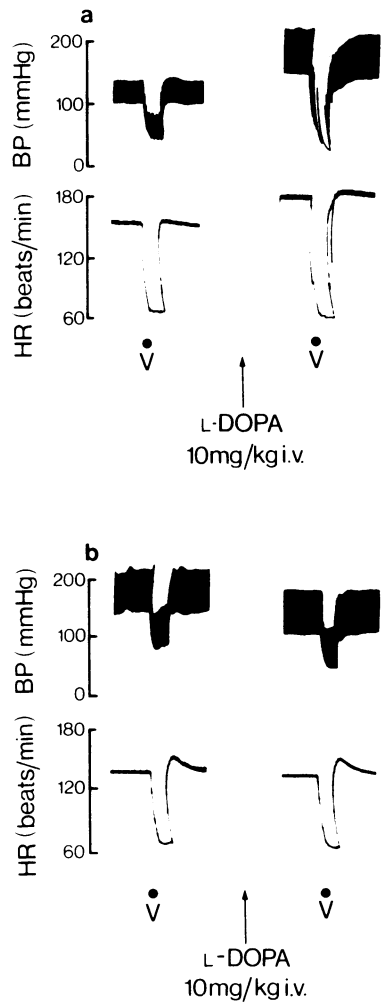

Fig. 2 Effect of vagus nerve stimulation (V) at 8 Hz for 30 s (15-20V) on blood pressure (BP) and heart rate (HR) of dogs pretreated with the monoamine oxidase inhibitor before and 30 min after L-DOPA (10 mg/kg i.v.). Sodium pentobarbitone + barbitone anaesthesia. (a) No β-adrenoceptor blockade; (b) pretreated with (−)-oxprenolol (0.5 mg/kg i.v.).

pressure was not elevated, and when prior β-adrenoceptor blockade prevented a tachycardia after L-DOPA (Figure 2b).

The effects of L-DOPA (10 mg/kg i.v.) on responses to DMPP, McN-A-343 and noradrenaline in dogs pretreated with the MAO inhibitor and on responses to vagal stimulation in dogs that had been treated with an antagonist of β-adrenoceptors are summarized in Table 2. In other groups of vagotomized dogs without prior β-adrenoceptor blockade or MAO-inhibition, guanethidine (1 mg/kg i.v.) had no effect on responses to vagal stimulation, inhibited responses to McN-A-343, and enhanced pressor responses to DMPP and noradrenaline. Chlorisondamine (1 mg/kg i.v.) antagonized the actions of DMPP and vagal stimulation, and enhanced the actions of McN-A-343 and noradrenaline. Methylphenidate (10 mg/kg i.v.) had no effect on responses to DMPP, antagonized McN-A-343 and vagal stimulation, but potentiated responses to noradrenaline (Table 2).

Effect of drugs of vasoconstrictor responses to lumbar sympathetic chain stimulation in the dog

L-DOPA (10 mg/kg i.v.) had no effect on hind-limb vasoconstrictor responses to lumbar sympathetic chain stimulation in atropine-treated dogs, although the frequency-response curve was significantly depressed by L-DOPA in dogs pretreated with the MAO inhibitor (Figure 3a). Impairment of sympathetic nerve function, which was largely dissipated 120 min after L-DOPA, was prevented by inhibition of extracerebral dopa decarboxylase with MK-486 25 mg/kg (not shown). Sixty minutes after guanethidine (1 mg/kg i.v.) or chlorisondamine (2 mg/kg i.v.) responses to sympathetic chain stimulation were severely depressed (Figure 3b). Changes in blood pressure, hind-limb perfusion pressure and heart rate produced by the various drugs are shown in Table 3. As previously described, L-DOPA (10 mg/kg i.v.) caused hypertension followed by severe hypotension and persistent tachycardia in dogs pretreated with the MAO inhibitor. Perfusion pressure was not significantly altered. Ten minutes after the administration of the peripheral dopa decarboxylase inhibitor MK-486 (25 mg/kg i.v.), the initial pressor effects and tachycardia induced by L-DOPA were prevented and the drug now caused significant hypotension after 30 minutes. Chlorisondamine (2 mg/kg i.v.) significantly lowered all measured functions, whereas guanethidine (1 mg/kg i.v.) decreased only systemic blood pressure and heart rate after 60 minutes.

The maximum MAO-inhibitory effect of Su-11739 occurs several hours after a single dose and, therefore, variable degrees of enzyme inhibition would be expected to occur shortly after dosage because of differences in the onset of action in individual dogs. Starting 1 h after Su-11739 (3 mg/kg s.c.), femoral vasoconstrictor responses to 0.6 Hz stimulation of the lumbar sympathetic chain were determined before and 60 min after L-DOPA (10 mg/kg i.v.). The degree of inhibition of responses to nerve stimulation showed a highly significant correlation with the

peak hypertensive response to L-DOPA which occurred 5-10 min after administration of the drug (Figure 4).

Effect of L-DOPA on responses of cat nictitating membrane

These experiments were performed in spinalized cats that had been pretreated with the MAO inhibitor. As expected, close arterial injection of McN-A-343 (5 μg/kg) or DMPP (3 μg/kg) to the superior cervical ganglion caused much greater contractions of the nictitating membrane than did the same doses when given close arterial injection to the membrane. Control responses were also obtained to adrenaline (1 μg/kg) by the latter route, and to pre- and postganglionic stimulation of the cervical sympathetic chain (Table 4). Fifteen minutes after L-DOPA (3 mg/kg) was administered by close arterial injection to the superior cervical ganglion, responses to the ganglion stimulants by the same route were markedly inhibited. The response to adrenaline was unaffected, and the response to preganglionic electrical stimulation was antagonized more effectively than that to postganglionic sympathetic chain stimulation (Table 4). Mean blood pressure (45.6 ± 3.5 mmHg) and heart rate (123.8 ± 9.1 beats/min) were not affected by L-DOPA. A representative experiment is shown in Figure 5.

Discussion

The comparative effects of L-DOPA (in the presence of MAO-inhibition), guanethidine, chlorisondamine and methylphenidate on responses to activation of autonomic nerve activity by electrical stimulation or injection of agonists are summarized in Table 5. The profiles of

Table 2 Change in blood pressure (Δ BP, mmHg) and heart rate (Δ HR, beats/min) in response to reference agents before and at intervals after L-DOPA, guanethidine, chlorisondamine and methylphenidate given intravenously in vagotomized dogs.

Drug		*Control responses*		*Responses after Drug*			
				10 min		*120-180 min*	
		Δ BP	Δ HR	Δ BP	Δ HR	Δ BP	Δ HR
+	(1)	106 ± 9	100 ± 12	64 ± 18*	62 + 9*	107 ± 17	75 ± 7
L-DOPA +	(2)	70 ± 9	51 ± 11	0 ****	0 ****	63 ± 11	30 ± 9
(10 mg/kg)	(3)	46 ± 5	32 ± 13	45 ± 4	9 ± 1	41 ± 3	12 ± 3
	++ (4)	−46 ± 8+	−47 ± 10	−52 ± 19	−49 ± 13	−58 ± 15	−69 ± 4
	(1)	86 ± 31	62 ± 25	104 ± 23	71 ± 21	96 ± 32	54 ± 18
Guanethidine	(2)	67 ± 13	50 ± 14	11 ± 5**	14 ± 13	17 ± 6**	13 ± 8*
(1 mg/kg)	(3)	35 ± 7	26 ± 10	53 ± 9***	18 ± 11	43 ± 8	15 ± 9
	(4)	−31 ± 12	−87 ± 16	−44 ± 10	−75 ± 11	−48 ± 8	−83 ± 5
	(1)	114 ± 10	94 ± 16	24 ± 1****	4 ± 1**	31 ± 5**	40 ± 28
Chlorisondamine	(2)	87 ± 20	52 ± 9	159 ± 9**	111 ± 3***	159 ± 6*	87 ± 34
(1 mg/kg)	(3)	42 ± 3	23 ± 8	74 ± 3	38 ± 9*	77 ± 4***	31 ± 9**
	(4)	−54 ± 3	−112 ± 13	−14 ± 5****	23 ± 37*	−0.3 ± 10***	11 ± 29*
	(1)	138 ± 19	63 ± 20	152 ± 8	78 ± 14	145 ± 17	103 ± 18
Methylphenidate	(2)	77 ± 16	47 ± 10	12 ± 4**	65 ± 13	49 ± 15	63 ± 12
(10 mg/kg)	(3)	73 ± 7	18 ± 14	105 ± 10***	44 ± 13*	95 ± 8	72 ± 10
	(4)	−63 ± 13	−105 ± 19	−32 ± 5	−53 ± 8*	−48 ± 16	93 ± 12

* $P<0.05$
** $P<0.02$
*** $P<0.01$
**** $P<0.001$

References Agents: (1) DMPP (20 μg/kg); (2) McN-A-343 (100 μg/kg); (3) Noradrenaline (1 μg/kg); (4) Vagus nerve stimulation.

+24 h after Su-11739 (3 mg/kg s.c.).
++10 min after (−)-oxprenolol (0.5 mg/kg i.v.).

(Sodium pentobarbitone + barbitone anaesthesia).

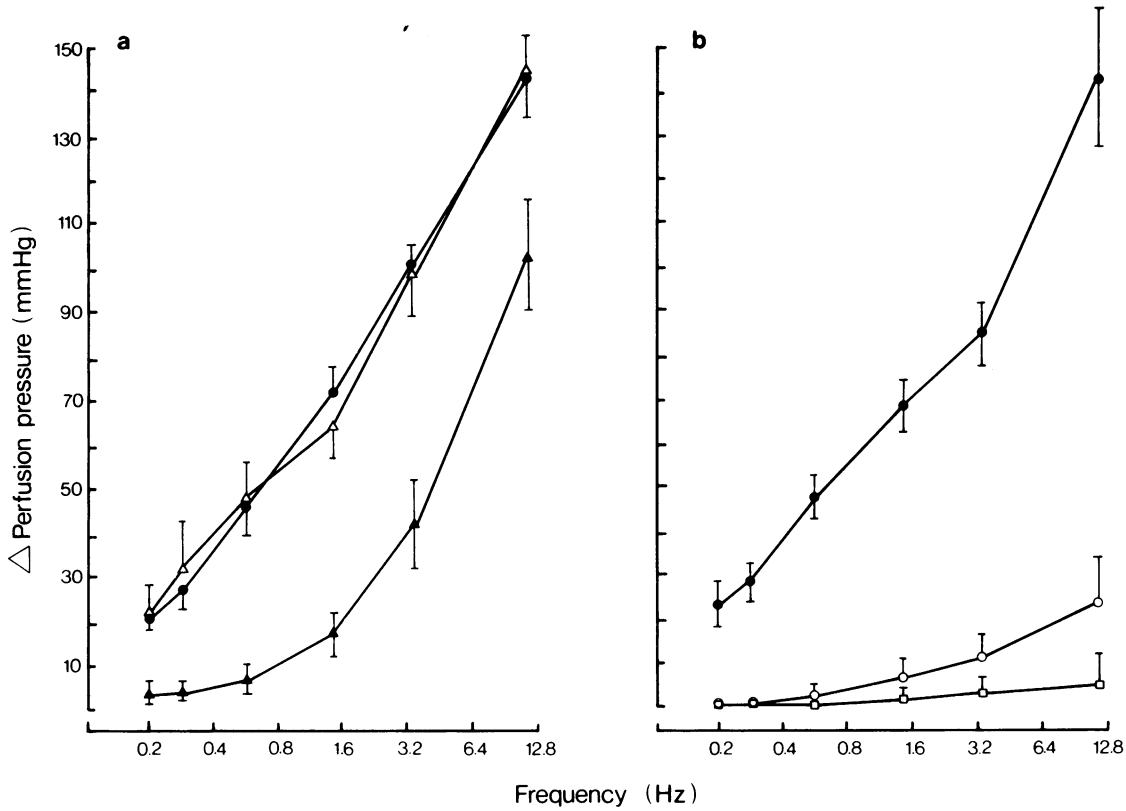

Fig. 3 The effects of sympathetic blocking agents on pressor responses to lumbar sympathetic chain stimulation in the perfused hind limb of dogs. Dial-urethane anaesthesia.
(a) A comparison of control responses (●) and responses 60 min after L-DOPA (10 mg/kg i.v.) in dogs not inhibited with the monoamine oxidase inhibitor (△) and in dogs receiving a monoamine oxidase inhibitor (SU-11739, 3 mg/kg s.c.) 24 h prior to the experiment (▲).
(b) A comparison of control responses (●) and responses 60 min after either guanethidine (1 mg/kg i.v.) (○) or chlorisondamine (2 mg/kg i.v; □).

L-DOPA and guanethidine were similar to the extent that both drugs had no effect on responses to vagal stimulation and depressed responses to lumbar sympathetic chain stimulation. However, L-DOPA antagonized responses to DMPP (a nicotinic ganglion stimulant) and to McN-A-343 (a muscarinic stimulant of sympathetic ganglia), whereas adrenergic neurone blockade, as previously described by Roskowski (1961), caused depression of responses to McN-A-343 but had no effect or enhanced responses to DMPP. Guanethidine antagonizes responses due to activation by DMPP of sympathetic ganglia in adrenalectomized animals, but responses in intact animals may be unaltered or enhanced since guanethidine, which potentiates responses to injected noradrenaline or adrenaline, does not prevent adrenal catecholamine discharge induced by DMPP (Boura & Green, 1965). Thus, although L-DOPA has been found to impair sympathetic nerve function in this and earlier studies (Farmer, 1965; Whitnack *et al.*, 1971; Antonaccio *et al.*, 1974; Dhasmana & Spilker, 1973), the overall profile is dissimilar from that of classical adrenergic neurone blocking agents.

Inhibition of transmission across sympathetic ganglia has been previously demonstrated after dopamine (Libet & Tosaka, 1970; Willems *et al.*, 1972; Sakanashi, 1972), and other catecholamines (Marazzi, 1939; Lundberg, 1952; Eccles & Libet, 1961; Willems *et al.*, 1971; Sakanashi, 1972). Since the vasoconstrictor response to lumbar sympathetic chain stimulation in dogs was markedly depressed by chlorisondamine, it was possible that the actions of L-DOPA were due to sympathetic ganglion blockade as a result of the formation of dopamine, which was protected from oxidative deamination by inhibition of monoamine oxidase. To determine the significance

of ganglion blockade relative to adrenergic neurone blockade as the cause of impaired sympathetic nerve function, recourse was made to local application of L-DOPA to the cervical sympathetic ganglia of cats pretreated with the MAO inhibitor. In these studies, L-DOPA preferentially inhibited responses of the nictitating membrane to pre- rather than post-ganglionic stimulation of the cervical sympathetic chain and markedly inhibited responses to DMPP and McN-A-343. It appears, therefore, that L-DOPA can exert appreciable sympathetic ganglion blocking activity. Nevertheless, L-DOPA, while resembling chlorisondamine in some respects, did not impair transmission across vagal ganglia and depressed rather than enhanced responses to McN-A-343.

Inhibition of responses to McN-A-343 without an effect on parasympathetic ganglia was a feature of L-DOPA and methylphenidate, although the drugs had dissimilar effects on responses to DMPP (Table 5). In their analysis of the actions of McN-A-343 and DMPP, Levy & Ahlquist (1962) found that the former, muscarinic ganglion stimulant, was antagonized by agents which release (e.g., amphetamine, guanethidine) or potentiate the actions of catecholamines (methylphenidate, pheniprazine), whereas such agents did not depress and sometimes enhanced effects due to sympathetic nerve stimulation by DMPP. Potentiation of the pressor response to DMPP by methylphenidate could be achieved, in the absence of an antagonistic effect at nicotinic ganglion sites, by prevention of adrenergic neuronal uptake of catecholamines released by activation of adrenergic neurones or the adrenal medulla. An association between sympathomimetic activity and antagonism of

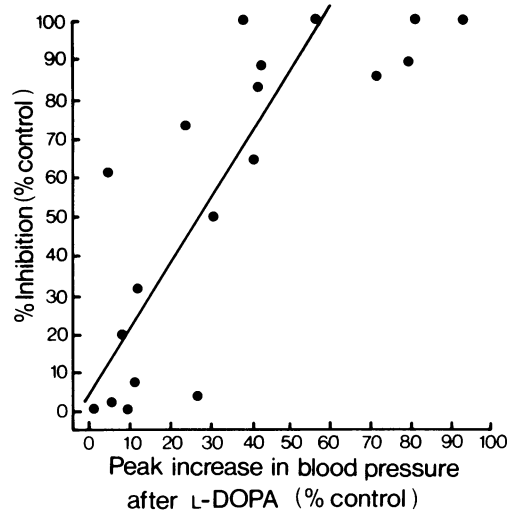

Fig. 4 Correlation of the inhibition of the perfused hind-limb vasoconstrictor response to stimulation of the lumbar sympathetic chain (0.6 Hz) with the maximum pressor response to L-DOPA (10 mg/kg i.v.) in individual dogs which had received Su-11739 (3 mg/kg s.c.) 60 min earlier. $r = 0.797$; $P < 0.001$.

Table 3 Effects of various drugs on blood pressure (BP, mmHg), heart rate (HR, beats/min), and perfusion pressure (PP, mmHg) of dogs prepared for hind limb perfusion.

Drug	*Control*			*30 min after drug*			*60 min after drug*		
	BP	*HR*	*PP*	*BP*	*HR*	*PP*	*BP*	*HR*	*PP*
L-DOPA (10 mg/kg i.v.)	155.0 ±9.8	142.0 ±12.5	132.5 ±8.5	180.8 ±13.9 *P*<0.02	209.0 ±11.5 *P*<0.01	142.5 ±14.9	107.5 ±13.0 *P*<0.02	210.8 ±19.6 *P*<0.02	118.8 ±8.3
L-DOPA (10 mg/kg i.v.) +MK 486 (25 mg/kg i.v.)	128.3 ±4.4	138.3 ±13.4	132.3 ±3.7	69.3 ±10.7 *P*<0.01	126.3 ±2.0	113.0 ±15.3	62.0 ±14.6 *P*<0.02	126.7 ±10.8	96.7 ±16.9
Chlorisondamine (2 mg/kg i.v.)	145.0 ±6.8	186.0 ±13.2	115.0 ±8.7	– –	– –	– –	48.3 ±8.3 *P*<0.01	138.0 ±6.2 *P*<0.02	88.3 ±10.9 *P*<0.05
Guanethidine (1 mg/kg i.v.)	130.8 ±3.5	154.6 ±15.8	112.8 ±7.0	– –	– –	– –	104.8 ±6.7 *P*<0.05	128.6 ±14.1 *P*<0.05	126.8 ±12.4

Dial-urethane anaesthesia.

All dogs were pretreated with atropine (1 mg/kg i.v.). In addition, dogs receiving L-DOPA were pretreated with Su-11739 (3 mg/kg s.c.) for 24 hours.

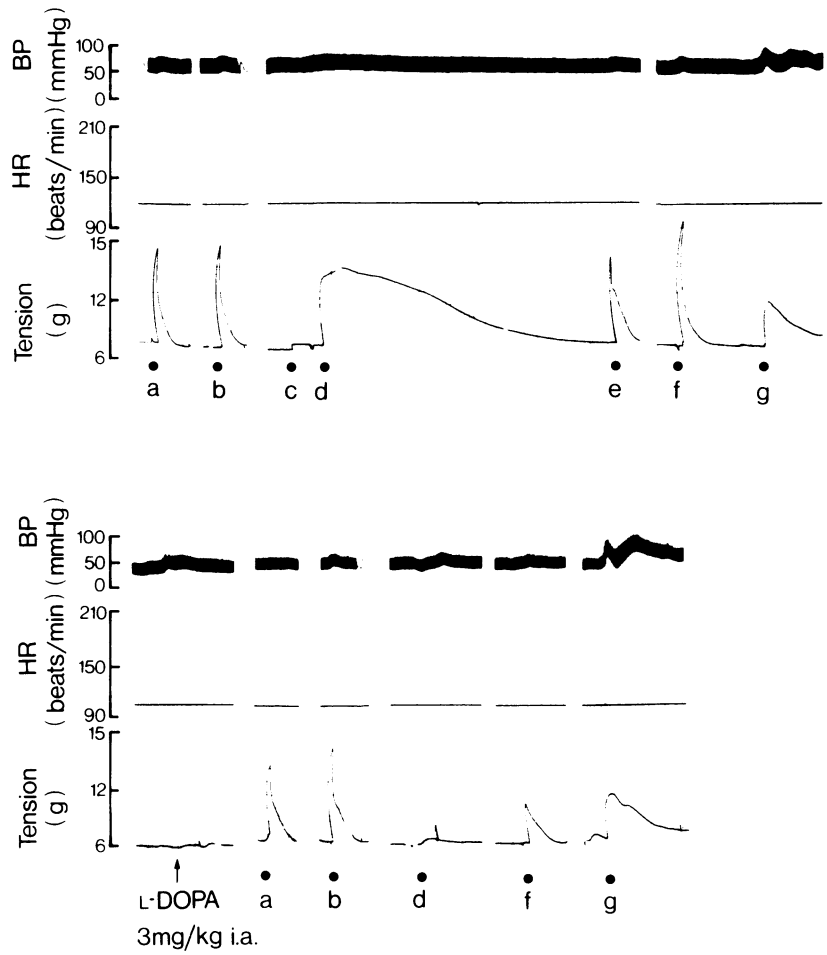

Fig. 5 The effect of L-DOPA (3 mg/kg i.a.) on responses of the cat nictitating membrane to various stimuli. (a) Pre-ganglionic stimulation (5 Hz, 2 ms for 5 sq, 5V); (b) post-ganglionic stimulation (5 Hz 2 ms for 5 s, 5V); (c) McN-A-343 (5 μg/kg; to the membrane); (d) McN-A-343 (5 μg/kg; to the ganglion); (e) Dimethylphenylpiperazinium (DMPP; 3 μg/kg; to the membrane); (f) DMPP (3 μg/kg; to the ganglion); (g) Adrenaline (1 μg/kg; to the membrane). Cat was spinalized vagotomized bilaterally and treated with the monoamine oxidase inhibitor Su-11739 (3 mg/kg). Dial urethane anaesthesia.

McN-A-343, which was apparent for the drugs studied by Levy & Ahlquist (1962), may be applicable to clonidine (Constantine & McShane, 1968; Antonaccio & Robson, 1973) and be extended to L-DOPA. The severity of impairment of lumbar sympathetic chain function, which was probably due to antagonism of nicotinic ganglion sites, was significantly correlated with the magnitude of the early pressor response to L-DOPA.

In animals pretreated with the MAO inhibitor, L-DOPA while having features in common with guanethidine, chlorisondamine and methylphenidate, overall exhibits a quite dissimilar profile from any one of the reference drugs. The unique profile may arise because L-DOPA after decarboxylation, can antagonize nicotinic and muscarinic sites of sympathetic ganglia, yet has no effect on parasympathetic ganglia. Although L-DOPA can cause adrenergic neurone blockade, as previously shown by Farmer (1965) and Whitnack *et al.*, (1971), responses to preganglionic sympathetic nerve stimulation may be further reduced by impairment of ganglionic transmission.

Table 4 Responses of nictitating membrane in spinalized, bilaterally vagotomized cats before and after L-DOPA (3 mg/kg).

Stimulus	*Control*	*15 min after L-DOPA*
McN-A-343 5 μg/kg (to membrane)	0.03 ± 0.9	–
McN-A-343 5 μg/kg (to ganglion)	8.7 ± 1.6	−0.5 ± 0.4 $P<0.01$
DMPP 3 μg/kg (to membrane)	5.1 ± 1.5	–
DMPP 3 μg/kg (to ganglion)	11.4 ± 1.3	4.2 ± 2.2 $P<0.05$
Adrenaline 1 μg/kg (to membrane)	4.8 ± 0.5	5.0 ± 1.4
Preganglionic stimulation	9.1 ± 0.5	5.4 ± 1.7 $P<0.05$
Postganglionic stimulation	12.5 ± 1.7	9.9 ± 1.9 $P<0.05$

The cats had been pretreated 24 h earlier with Su-11739 (3 mg/kg s.c.). Values expressed in gm of tension ± the standard error of the mean. [n=5] Dial-urethane anaesthesia.

Table 5 Summary of the comparison between the effects of L-DOPA and those of classical autonomic blocking agents on electrical or chemical activation of the autonomic nervous system.

Drug	*Pre-ganglionic sympathetic nerve stimulation*	*Post-ganglionic sympathetic nerve stimulation*	*DMPP*	*McN-A-343*	*Vagus nerve stimulation*	*Adrenaline or noradrenaline*
L-DOPA	↓ ↓	↓	↓ ↓	↓ ↓ ↓	——	——
Nicotinic ganglion blocker (C6; Chlorisondamine)	↓ ↓ ↓	——	↓ ↓ ↓	↑ ↑	↓ ↓ ↓	↑
Muscarinic ganglion blocker (Methylphenidate)	———	↑ ——	↑ ↑	↓ ↓ ↓	—— ↓	↑ ↑
Adrenergic neurone blocker (Guanethidine)	↓ ↓ ↓	↓ ↓ ↓	—— ↑	↓ ↓	——	↑

The number of arrows indicates the degree of effect. ↑— or —↓ indicates little or no effect in the direction indicated.

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