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DOPAMINE-INDUCED NEUROGENIC VASODILATATION IN THE INTACT HINDLEG OF THE DOG

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1 The dopamine-induced neurogenic vasodilatation, previously described in the isolated perfused hindleg of the dog, has been studied in anaesthetized dogs with intact circulation in the hindleg. Dopamine was administered intravenously and/or intra-aortically, either as a bolus injection of 4 or 16 μg/kg, or as a continuous infusion of 4, 8, 16 or 32 μg kg^{-1} min^{-1}.

2 Dopamine, given as a bolus injection or by infusion, reversibly inhibited synaptic transmission in the paravertebral lumbar ganglia, studied with preganglionic stimulation at 1 Hz. The inhibitory effect decreased gradually when the frequency of stimulation was increased to 16 Hz. The inhibition by dopamine was also present when spontaneous postganglionic activity was recorded. These effects were more pronounced on intra-aortic than on intravenous administration of dopamine.

3 In about half of the animals studied, injection or infusion of dopamine elicited a decrease of vascular resistance in the innervated femoral artery, whereas systemic blood pressure either did not change or decreased. In the denervated femoral artery, an increase in vascular resistance was always observed.

4 The decrease in femoral vascular resistance was considered to correspond with neurogenic vasodilatation caused by paravertebral ganglionic inhibition since (i) it only occurred in the innervated hindleg, (ii) blood pressure did not rise, (iii) this decrease was insensitive to atropine or propranolol and (iv) it was blocked by small doses of haloperidol. When hypovolemic shock was produced, the incidence of the neurogenic decrease of vascular resistance was smaller.

5 Dopamine also increased renal blood flow. This increase was not reduced by the occurrence of the neurogenic vasodilatation in the innervated femoral artery.

6 These results are consistent with the idea that the dopamine-induced neurogenic vasodilatation, originally described in the isolated perfused hindleg of the dog, also occurs when the circulation to the hindleg is intact. This suggests that, in the dog, the inhibitory effect of dopamine on sympathetic ganglia modulates its peripheral vasoconstrictor effects. In hypovolemic shock, where sympathetic nervous activity is high, the inhibitory effect of dopamine on sympathetic ganglia disappears and its direct vasoconstrictor effect on the vessels dominates.

Introduction

In 1963 McDonald & Goldberg reported that a neurogenic vasodilatation occurs in the isolated perfused hindleg of the dog on systemic administration of dopamine. It has been suggested that this phenomenon, which is due to inhibition of sympathetic ganglionic transmission (Bogaert & De Schaepdryver, 1967; Willems, 1973; Willems & Bogaert, 1975a,b) is not involved in the systemic hypotensive effect of dopamine (Eble, 1964; Goldberg, 1972). It is not even known whether this neurogenic vasodilatation after systemic administration of dopamine takes place in the intact hindleg, as the direct effect of dopamine on the femoral vascular bed is a vasoconstrictor one (McNay, McDonald & Goldberg, 1965).

We therefore decided to study in detail the effect of intravenous administration of dopamine, as a single injection and by infusion, on the vascular resistance in the intact hindleg and on the ganglionic transmission in the abdominal lateral sympathetic chain of the dog. Dopamine was also given by the intra-aortic route, as earlier experiments were performed in this way (Willems, 1973; Willems & Bogaert, 1975a).

Preliminary results of this work have been published (Bogaert, Willems & De Schaepdryver, 1975).

Methods

Ganglionic transmission

Nineteen mongrel dogs of either sex, with body weights ranging between 4 and 8 kg, were used. The

animals were anaesthetized with pentobarbitone sodium, in an intravenous dose of 30 mg/kg, further small doses being given as needed. The experimental preparation has been described in detail by Willems (1973). A bipolar platinum electrode was placed on the cut upper internodal segment of the fourth or fifth paravertebral ganglion and an electrical stimulus of 0.3 ms duration and supramaximal intensity was applied at a frequency of 1 Hz; in some experiments other frequencies were used, as indicated in the Results section. Postganglionic electrical activity was recorded by a second bipolar platinum electrode on the ramus communicans griseus of the ganglion. Permanent records were made on moving film with a Grass oscilloscope camera for simultaneous evaluation of the time course and the intensity of the effects of the substances studied. The results were measured as the maximal change in amplitude of the evoked spikes.

In 7 of the 19 experiments spontaneous electrical activity was followed on the oscilloscope. Recording from the undivided ramus gave reproducible electrical activity and allowed qualitative evaluation of the effect of dopamine.

Blood flow

Twenty-nine mongrel dogs of either sex, with body weights ranging between 12 and 38 kg, were used. They were anaesthetized as described above. Mean blood flow was measured with a Statham Multiflo M-400 electro-magnetic flowmeter. Blood flow in the right innervated femoral artery was monitored in all 29 dogs. In 17 of these dogs, blood flow in the denervated left femoral artery was also measured. The left hindleg was denervated by cutting the sciatic nerve and the lumbar paravertebral chain on that side. In 8 of the 29 dogs, blood flow in the left renal artery was measured. Blood pressure was measured from the brachial artery with a Statham pressure transducer. By dividing mean blood pressure by mean flow (Statham Cardiovascular Analyzer SP 1011), vascular resistance in the right femoral bed was continuously obtained. Heart rate was derived from the ECG by a cardiotachometer coupler. Blood flows, arterial blood pressure, vascular resistance and heart rate were registered on a Beckman Dynograph recorder R. Changes in flow and resistance after a drug are expressed as a percentage of the values found immediately before the drug was given.

In some experiments, hypovolemic shock was produced by bleeding the animal from the carotid artery into a reservoir. Bleeding was stopped either at the moment vascular resistance in the innervated femoral artery rose by 30%, or at the moment the decrease in blood pressure attained a steady state.

Further methodological aspects

Intravenous injections or infusions were given into the cephalic vein of the right foreleg. For intra-aortic injections or infusions, a catheter was introduced either via the left femoral artery (ganglionic transmission experiments), or via the left carotid artery (flow measurements) so that its tip was lying at the level of L4-L5.

Injections were always given in a volume of 0.2 ml, and 1 to 2 ml 0.9% w/v NaCl solution (saline) was used to flush the catheter. The agonists were injected in a single dose, the antagonists were injected slowly over 30 to 60 seconds. For control injections, saline was used, except for haloperidol, where the solvent of the latter was used. For the infusions, a volume of 0.5 ml/min, containing the appropriate concentration of the drug studied, was given during 5 to 10 minutes.

Values given in the text are means $\pm$ standard error of the mean. For statistical evaluation, Student's *t*-test was used.

Drugs

The following drugs, diluted in saline, were used: dopamine hydrochloride (Sigma), (–)-noradrenaline bitartrate (Sigma), (±)-isoprenaline hydrochloride (Winthrop), haloperidol (Janssen Pharmaceutica), acetylcholine chloride (Roche), atropine sulphate (Boehringer-Sohn), propranolol hydrochloride (ICI), tetraethylammonium iodide (Merck). The solubilization of haloperidol by the use of lactic acid was described previously (Willems, 1973). Doses of the drugs are expressed as the base.

Results

Ganglionic transmission

Preganglionic stimulation, 1 Hz, supramaximal intensity. In 7 dogs dopamine (16 μg/kg) was injected intravenously; it produced an inhibition of the ganglionic transmission of $57.20 \pm 6.29\%$. In 4 of these dogs the time course of the inhibition was followed: inhibition was maximal at 17.50 ± 1.04 s after injection. When the same dose of dopamine (16 μg/kg) was injected into the aorta, inhibition was more pronounced, $82.39 \pm 4.74\%$ ($n = 7$; $P < 0.05$) and occurred earlier, at 8.50 ± 0.55 s ($n = 4$; $P < 0.01$).

In the same series of dogs, dopamine was infused intravenously (8, 16 and 32 μg kg^{-1} min^{-1}) and intra-aortically (4, 8, and 16 μg kg^{-1} min^{-1}). For the duration of the infusion, a dose-dependent inhibition of the postsynaptic spike was observed; the results are given in Table 1A. As for single injections, the inhibitory effect on ganglionic transmission of infusions of dopamine is more pronounced for intra-aortic than for intravenous administration.

Preganglionic stimulation, 1 Hz, intensity giving 50% of maximal response. Stimulation was first

performed with supramaximal intensity, at 1 Hz, and the doses of dopamine which produced a clear-cut, but not complete ganglionic inhibition, were determined. Stimulation was continued at 1 Hz, but stimulation intensity was diminished until the postsynaptic spike obtained was 50% of the spike obtained with maximal stimulation intensity. The same doses of dopamine were then again injected or infused. In these conditions, dopamine (16 μg/kg), injected intravenously in 5 dogs, produced an inhibition of ganglionic transmission of 68.60 ± 6.86%. This inhibition was larger ($P < 0.05$) than that seen in the same dogs when stimulation intensity was maximal (48.80 ± 9.06%). The effect of lowering the intensity of stimulation, so that a 50% response was obtained, was also tested for infusions of dopamine; the results are summarized in Table 1B. In contrast to what happens with single injections, the effect of infusions of dopamine did not increase when a lower intensity of stimulation was used.

Preganglionic stimulation, supramaximal intensity, varying frequencies. In another series of 7 experiments, the intensity of stimulation was kept supramaximal but the frequency of stimulation was increased successively from 1 to 2, 4, 8 and 16 Hz, resulting in a decrease of the action potential amplitude of 14.21 ± 2.09% (2 Hz), 28.23 ± 4.74% (4 Hz), 34.92 ± 5.36% (8 Hz) and 50.57 ± 7.28% (16 Hz) respectively. At each frequency, once the amplitude was constant, dopamine was injected or infused in doses that produced near maximal inhibition at 1 Hz frequency of stimulation; this could only be obtained by giving dopamine intra-aortically. In 4 experiments, 8 μg/kg was injected. The ganglionic inhibition produced by this dose was of 71.81 ± 12.65% at 1 Hz, 69.84 ± 12.42% at 2 Hz, 65.08 ± 13.07% at 4 Hz, 43.69 ± 11.15% at 8 Hz and 12.25 ± 7.08% at 16 Hz: the inhibitory activity of dopamine decreases when the frequency of preganglionic stimulation is increased. Figure 1 shows a representative experiment.

In 3 experiments, 16 μg kg^{-1} min^{-1} was infused into the abdominal aorta. As for the single injections, the dopamine-induced ganglionic inhibition decreases with increasing frequency of stimulation: 86.67 ± 2.73% at 1 Hz, 60.67 ± 18.34% at 2 Hz, 55.33 ± 8.84% at 4 Hz, 26.00 ± 7.23% at 8 Hz and no inhibition at all at 16 Hz.

Spontaneous activity. Spontaneous electrical activity was recorded from the undivided postsynaptic nerve. Bursts of small potentials (10–20 μV) were observed at regular intervals (0.5–2 seconds). They completely disappeared upon injection of tetraethylammonium iodide (10 mg) into the abdominal aorta.

Table 1 Inhibitory effect of infusions of dopamine on ganglionic transmission in the dog

A. *Supramaximal stimulation, 1 Hz*

Infusion	*Dose (μg kg^{-1} min^{-1})*			
	4	*8*	*16*	*32*
i.v.		24.83 ± 2.85 *n*=6	35.90 ± 5.38 *n*=6	61.56 ± 7.40 *n*=5
ao.	36.00 ± 16.06 *n*=6	54.06 ± 10.48 *n*=7	75.38 ± 14.67 *n*=5	

B. *Stimulation giving 50% of maximal response, 1 Hz*

	Dose (μg kg^{-1} min^{-1})		
	8	*16*	*32*
i.v.	20.73 ± 1.53 *n*=4	39.54 ± 5.20 *n*=5	59.70 ± 8.92 *n*=4
ao.	41.80 63.60 *n*=2	66.70 60.00 *n*=2	

i.v. = intravenous; ao. = intra-aortic. The inhibition is expressed as percentage of control spike, mean ± s.e. mean; when $n = 2$, individual values are given.

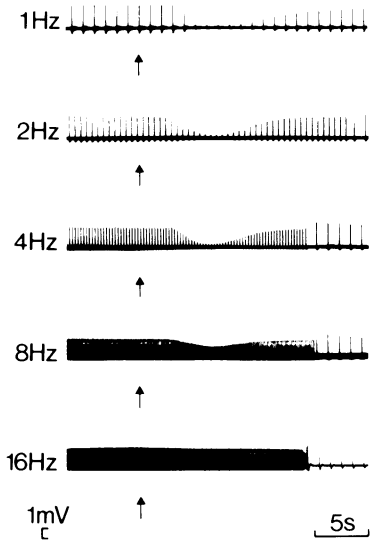

Figure 1 Lumbar paravertebral ganglion of the dog. Recording electrode on the ramus communicans griseus, stimulating electrode on the upper internodal segment. Inhibitory effect of dopamine (at arrows), 8 μg/kg intra-aortically, at different stimulation frequencies.

In 5 experiments, dopamine was injected as a single dose (16 μg/kg) intravenously or intra-aortically; in all cases a short-lasting inhibition of the spontaneous electrical activity occurred with a time course similar to that observed in the stimulated preparation. No change in systemic blood pressure was observed except in 2 dogs in which intravenous dopamine provoked a blood pressure rise.

In 4 experiments, dopamine (8 and 16 μg kg^{-1} min^{-1}) was infused intravenously, and in two of them also intra-aortically. Intravenous dopamine produced a decrease of the spike amplitude and spike frequency in 2 dogs; in one dog, blood pressure increased, whereas it decreased in the other. Intra-aortic dopamine decreased both spike amplitude and spike frequency; a blood pressure fall was seen in one dog.

Blood flow measurements

Denervated femoral artery. Dopamine (4 and 16 μg/kg) was given as a bolus injection intravenously (13 preparations) and intra-aortically (16 preparations) in a series of 17 dogs; all responded with a fall of femoral blood flow; blood pressure either increased, decreased or did not change. In all dogs femoral resistance increased. These results are shown in Table 2, classified according to the change in systemic blood pressure seen.

(−)-Noradrenaline (0.1 μg/kg), injected intravenously or intra-aortically in some of these dogs, always caused an increase in systemic blood pressure and a decrease in flow (i.v.: $+8.29 \pm 1.66$ mmHg; -25.11 ± 8.39%, respectively ($n=7$); ao.: $+5.00 \pm 1.00$ mmHg; -62.47 ± 2.53% respectively ($n=4$)).

Table 2 Effects of a bolus injection of dopamine on systemic blood pressure and on blood flow in the denervated femoral artery of the dog hindleg

	Intravenous injection			
	4 μg/kg (n=13)		*16 μg/kg (n=13)*	
n	8	5	2	11
BP	−16.00 ±3.63	+5.20 ±0.80	−23.00 −20.00	±11.45 ±1.87
F	−30.40 ±4.92	−40.68 ±4.77	−68.34 −57.70	−65.47 ±3.19
	Intra-aortic injection			
	4 μg/kg (n=10)		*16 μg/kg (n=6)*	
n	5	5	2	4
BP	−6.80 ±2.80	+4.00 ±0.63	−4.00 −12.00	+6.50 ±0.96
F	−42.68 ±6.11	−54.39 ±11.02	−93.33 −79.17	−86.10 ±6.06

BP = Changes in blood pressure, mean ± s.e. mean in mmHg; F = percentage change in blood flow, mean ± s.e. mean. The experiments in which an increase in systemic blood pressure occurred are contrasted with the others; n = number of animals showing the given combination of blood pressure change and blood flow change; for $n=2$, individual values are given.

In 13 of the 17 dogs, dopamine was infused intravenously or intra-aortically (4, 8 and 16 μg kg^{-1} min^{-1}); it always elicited a decrease of femoral flow (Table 3). As with bolus injections, blood pressure either increased or decreased, but femoral resistance increased in all dogs. Intravenous infusion of (–)-noradrenaline (0.05, 0.1 or 0.2 μg kg^{-1} min^{-1}) always increased systemic blood pressure and decreased femoral blood flow ($n=7$).

Innervated femoral artery. When dopamine (4 and 16 μg/kg) was injected intravenously (in 25 and 26 respectively out of 29 dogs), or intra-aortically (in 13 and 8 respectively out of the same 29 dogs), different patterns of flow and blood pressure responses were observed. In Table 4 the results are classified according to the direction of the changes of blood pressure and femoral resistance. An increase in femoral vascular resistance (accompanying either an increase or a decrease in systemic blood pressure) occurred in less than half of the preparations with intact innervation. In the other dogs, femoral vascular resistance decreased; some of them showed an increase, others a decrease of systemic blood pressure. The fall of femoral vascular resistance in the dogs in which 4 μg/kg caused a decrease of systemic blood pressure, was most pronounced when dopamine was injected intra-aortically. Figure 2 shows a representative experiment, depicting femoral blood flow and systemic blood pressure.

(–)-Noradrenaline (0.1 μg/kg), injected intravenously in 11 dogs, led to a decrease in femoral resistance in 9 dogs (–35.02 ± 8.21%). In all animals

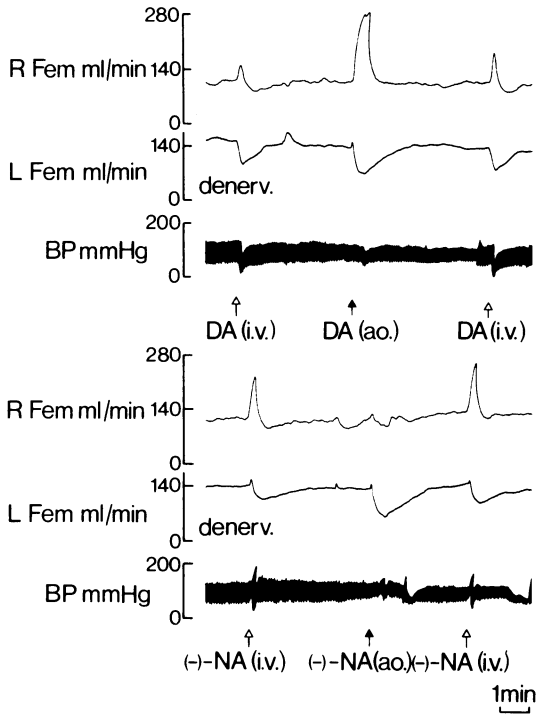

Figure 2 Right (R Fem.) and left (L Fem.) femoral blood flow in the dog; the left hindleg has been denervated (denerv.); BP = systemic blood pressure. Dopamine (DA, 4 μg/kg) and (–)-noradrenaline ((–)-NA, 0.1 μg/kg) were injected intravenously (i.v.) or intra-aortically (ao).

Table 3 Effects of a continuous infusion of dopamine on systemic blood pressure and on blood flow in the denervated femoral artery of the dog hindleg

	Intravenous infusion					
	4 μg kg^{-1} min^{-1} (n = 9)		*8 μg kg^{-1} min^{-1} (n = 13)*		*16 μg kg^{-1} min^{-1} (n = 7)*	
n	8	1	9	4	0	7
BP	–3.00 ± 1.46	+4.00	–3.33 ± 2.16	+12.00 ± 1.63		+14.29 ± 3.01
F	–21.55 ± 1.62	–44.40	–37.57 ± 4.98	–21.95 ± 4.01		–40.96 ± 7.09
	Intra-aortic infusion					
	4 μg kg^{-1} min^{-1} (n = 6)		*8 μg kg^{-1} min^{-1} (n = 3)*		*16 μg kg^{-1} min^{-1} (n = 2)*	
n	5	1	1	2	0	2
BP	–2.00 ± 0.89	+4.00	–16.00	+4.00 +4.00		+4.00 +8.00
F	–55.06 ± 7.43	–60.71	–81.82	–80.00 –66.67		–91.67 –82.61

BP = changes in blood pressure, mean ± s.e. mean in mmHg; F = percentage change in blood flow, mean ± s.e. mean. The experiments in which an increase in systemic blood pressure occurred are contrasted with the others; n = number of animals showing the given combination of blood pressure change and blood flow change; for $n = 1$ or 2, individual values are given.

showing a decrease in resistance, an increase in systemic blood pressure (+11.33 ± 1.49 mmHg; $n=9$) occurred. In two dogs both blood pressure and femoral resistance increased. In 5 dogs the same dose of noradrenaline was also injected into the abdominal aorta; femoral resistance rose (+84.29 ± 32.06%) as did systemic blood pressure (+8.00 ± 3.10 mmHg).

Propranolol, given in a dose (0.3 mg/kg, i.v.), which blocked the vasodilator effect of isoprenaline (0.1 μg/kg, i.v.), had no effect on the decrease of femoral resistance elicited by dopamine (i.v. or ao.); it did not influence (–)-noradrenaline-induced reflex vasodilatation ($n=3$).

Atropine (1 mg/kg, i.v.; $n=1$) blocked the vasodilator response to acetylcholine (10 μg/kg, i.v.) without any effect on the decrease in femoral resistance elicited by dopamine (i.v.).

Haloperidol (0.1 mg/kg, i.v. or 1 mg, ao.; $n=6$) blocked the fall in femoral resistance in the innervated femoral artery by intravenous or intra-aortic dopamine without influencing the (–)-noradrenaline-induced reflex vasodilatation (Figure 3).

Tables 5 and 6 show the response patterns when dopamine was infused (4, 8 and 16 μg kg^{-1} min^{-1}, i.v. and/or ao.). In these conditions, we observed a sustained decrease of femoral resistance in some dogs which showed a decrease of systemic blood pressure.

In 3 dogs, intravenous infusion of (–)-noradrenaline (0.05 μg kg^{-1} min^{-1}) also produced a decrease of femoral resistance (–5.13 ± 5.13%) but this decrease was accompanied by an increase in systemic blood pressure (+ 7.33 ± 4.37 mmHg). Higher doses (0.1 and 0.2 μg kg^{-1} min^{-1}) produced an increase in both femoral resistance and systemic blood pressure.

Table 4 Effects of a single injection of dopamine on systemic blood pressure and on blood flow in the innervated femoral artery of the dog hindleg

	Intravenous injection			
	4 μg/kg (n=25)		*16 μg/kg (n=26)*	
n	14	6	5	17
BP	−13.71 ± 1.76	+5.67 ± 0.80	−19.80 ± 2.11	+12.59 ± 1.28
R	−32.00 ± 5.40	−36.85 ± 11.01	−60.93 ± 11.21	−47.48 ± 7.06
n	3	2	0	4
BP	−12.67 ± 7.51	+2.00 +4.00		+13.00 ± 4.43
R	+26.30 ± 13.30	+13.60 +11.10		+63.39 ± 21.39
	Intra-aortic injection			
	4 μg/kg (n=13)		*16 μg/kg (n=8)*	
n	5	2	3	2
BP	−7.20 ± 2.65	+4.00 +2.00	−6.67 ± 4.81	+8.00 +4.00
R	−50.47 ± 13.14	−45.45 −16.67	−49.61 ± 10.87	−80.00 −50.00
n	1	5	1	2
BP	−2.00	+4.40 ± 0.40	−12.00	+6.00 +8.00
R	+83.83	+57.97 ± 18.96	+73.33	+211.11 +66.67

BP = changes in blood pressure, mean ± s.e. mean in mmHg; R = percentage change in vascular resistance, mean ± s.e. mean. The experiments are classified in four groups: no increase in blood pressure and femoral resistance, no increase in blood pressure with increase in femoral resistance, increase in blood pressure and femoral resistance, increase in blood pressure with no increase in femoral resistance; n = number of animals showing the given combination of blood pressure change and change in femoral resistance; for $n=1$ or 2, individual values are given.

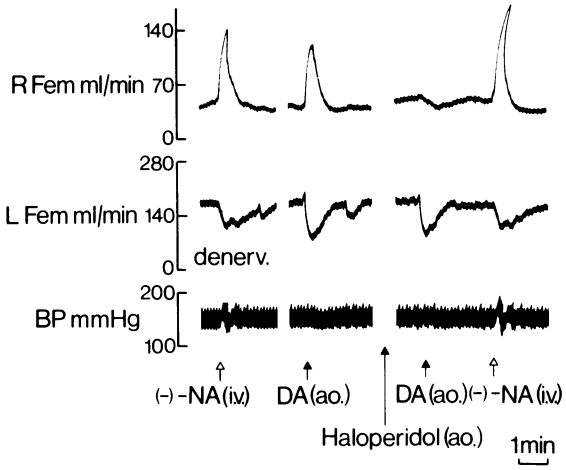

Figure 3 Right (R Fem.) and left (L Fem.) femoral blood flow in the dog; the left hindleg has been denervated (denerv.); BP = systemic blood pressure. Dopamine (DA, 2 μg/kg intra-aortically), (−)-noradrenaline ((−)-NA, 0.1 μg/kg intravenously), haloperidol (1 mg intra-aortically).

Renal artery and femoral artery blood flow. Dopamine (16 μg/kg, injected i.v.; $n=6$) increased both renal artery blood flow (+13.88 ± 3.28%) and blood pressure (+16.00 ± 2.31 mmHg).

Intravenous infusion of 4 μg kg^{-1} min^{-1} of dopamine ($n=7$) caused in 5 dogs a decrease of systemic blood pressure (−2.40 ± 1.60 mmHg) and an increase in renal flow (+19.30 ± 4.89%). In 2 dogs a decrease of both blood pressure and renal blood flow occurred. Intravenous infusion of 8 μg kg^{-1} min^{-1} of dopamine ($n=7$), elicited in 4 dogs a decrease in systemic blood pressure (−9.00 ± 3.42 mmHg) and an increase in renal flow (+27.75 ± 5.02%). In 2 dogs blood pressure and renal flow rose. In one dog no changes in blood pressure and renal flow were observed with this dose of dopamine. Intravenous infusion of 16 μg kg^{-1} min^{-1} of dopamine ($n=4$) produced an increase in blood pressure (+18.00 ± 1.15 mmHg) and an increase in renal flow (+16.40 ± 3.61%). In 5 of the dogs that showed an increase in renal blood flow, the infusion of dopamine caused a decrease in femoral resistance: this decrease started after the renal dilatation was already present. In none of the dogs was the occurrence of the femoral dilatation accompanied by a decrease in renal flow.

Femoral artery blood flow and severe blood loss. In 8 dogs, blood was withdrawn from the left femoral artery: in 5 dogs until vascular resistance in the intact right femoral bed increased by 30 to 50% and in 3 dogs bleeding was continued until systemic blood pressure stabilized at a lower level. When dopamine was then infused intravenously (8 μg kg^{-1} min^{-1}) only 1 out of the 8 dogs showed a decrease of both femoral resistance (−8.30%) and systemic blood pressure (−4.00 mmHg). In 2 other dogs a decrease in femoral resistance was accompanied by an increase in blood pressure. In 5 dogs both femoral resistance and systemic blood pressure increased.

Table 5 Effects of an intravenous infusion of dopamine on systemic blood pressure and on blood flow in the innervated femoral artery of the dog hindleg

	4 μg kg^{-1} min^{-1} (n=20)		*8 μg kg^{-1} min^{-1} (n=25)*		*16 μg kg^{-1} min^{-1} (n=14)*	
n	7	2	6	7	1	7
BP	−2.57 ± 1.29	+4.00 +4.00	−2.00 ± 1.37	+7.43 ± 1.84	−32.00	+18.86 ± 1.90
R	−27.88 ± 7.99	0 0	−28.77 ± 5.72	−29.02 ± 6.85	−38.46	−46.31 ± 8.47
n	7	4	10	2	1	5
BP	−5.43 ± 1.43	0	−6.20 ± 2.28	+12.00 +4.00	−4.00	+12.00 ± 2.83
R	+16.36 ± 4.81	0	+19.52 ± 8.08	+23.50 0	+29.17	+45.02 ± 34.45

BP = changes in blood pressure, mean ± s.e. mean in mmHg; R = percentage change in vascular resistance, mean ± s.e. mean. The experiments were classified in four groups: no increase in blood pressure and femoral resistance, no increase in blood pressure with increase in femoral resistance, increase in blood pressure and femoral resistance, increase in blood pressure with no increase in femoral resistance; n = number of animals showing the given combination of changes in blood pressure and in vascular resistance; for $n=1$ or 2, individual values are given.

Discussion

This study was performed in order to investigate in the intact hindleg of the dog the dopamine-induced neurogenic vasodilatation which had hitherto only been studied in the dog's isolated perfused hindleg (McDonald & Goldberg, 1963; Bogaert & De Schaepdryver, 1967; Willems & Bogaert, 1975a). The doses and the infusion rates of dopamine, used in the experiments presented here, were chosen because they show the experimentally and clinically interesting effects of dopamine: renal vasodilatation, increase in cardiac contractility, decrease in peripheral resistance, slight or no decline of systemic blood pressure and absence of chronotropic effect (McDonald & Goldberg, 1963; Goldberg, 1972; Ramdohr, Schüren, Biamino & Schröder, 1973; Setler, Pendleton & Finlay, 1975).

In many of the dogs, systemic administration of dopamine decreased femoral vascular resistance. However, only those experiments in which a fall in systemic blood pressure accompanies the decrease in femoral resistance, can be used to demonstrate a neurogenic mechanism because of the ganglionic inhibitory effect of dopamine (Willems, 1973). Indeed, if a decrease in femoral resistance occurs with increased systemic blood pressure, a neurogenic vasodilatation cannot be distinguished from reflex baroreceptor-induced changes in vascular resistance. Dopamine, injected intravenously, in some animals did produce a decrease of femoral resistance without concomitant increase in systemic blood pressure: this was observed in 14 out of 25 dogs receiving 4 μg/kg of dopamine and in 5 out of 26 dogs receiving 16 μg/kg.

The following observations suggest that the femoral dilatation, occurring without increase in blood pressure, corresponds to the neurogenic vasodilatation described in the isolated perfused hindleg.

A decrease in femoral vascular resistance after systemic administration of dopamine was only observed in the innervated hindleg; in the denervated hindleg an increase in vascular resistance always occurred. This vasoconstriction is due to a direct effect of dopamine on the femoral vasculature where it interacts with the α-adrenoceptor or with the 5-hydroxytryptamine receptor (Gilbert & Goldberg, 1975). Vasoconstriction also occurs when dopamine is injected directly into the innervated femoral artery (McDonald & Goldberg, 1963; McNay *et al.*, 1965). It is only after the administration of α-receptor antagonist drugs that the direct effect of dopamine on the femoral artery is a vasodilatation (McNay & Goldberg, 1966; Higgins, Millard, Braunwald & Vatner, 1973; Bell, Conway, Lang & Padanyi, 1975).

A fall in vascular resistance, requiring intact innervation of the hindleg, was also observed after the intravenous administration of (–)-noradrenaline, but in this case the fall in resistance was always accompanied by an increase in systemic blood pressure, suggesting that a classical baroreceptor-reflex is involved. Intra-aortic administration of (–)-noradrenaline always caused an increase in femoral resistance. We have shown previously that the doses of (–)-noradrenaline and dopamine needed for ganglionic inhibition are the same (Willems, 1973); this is also true for the neurogenic vasodilatation (Willems & Bogaert, 1975a). Such doses of (–)-noradrenaline are too high to be used in these experiments because they always give a pronounced increase in systemic pressure.

Our results confirm our previous reports (Willems, 1973; Willems & Bogaert, 1975a) that dopamine,

Table 6 Effects of an intra-aortic infusion of dopamine on systemic blood pressure and on blood flow in the innervated femoral artery of the dog hindleg.

	4 μg kg⁻¹ min⁻¹ (n=7)		*8 μg kg⁻¹ min⁻¹ (n=4)*		*16 μg kg⁻¹ min⁻¹ (n=4)*	
n	0	1	0	1	0	0
BP		+4.00		+4.00		
R		−41.38		−66.67		
n	5	1	2	1	1	3
BP	−2.40 +0.75	+4.00	−16.00 −2.00	+4.00	−4.00	+6.67 ±1.33
R	+29.77 ±8.06	+30.77	+21.43 0	+133.33	+52.38	+134.11 ±75.86

BP = changes in blood pressure, mean ± s.e. mean in mmHg; R = percentage change in vascular resistance, mean ± s.e. mean. The experiments were classified in four groups: no increase in blood pressure and femoral resistance, no increase in blood pressure with increase in femoral resistance, increase in blood pressure and femoral resistance, increase in blood pressure with no increase in femoral resistance; *n* = number of animals showing the given combination of blood pressure change and change in vascular resistance; for *n* = 1 or 2, individual values are given.

within the dose range used here, inhibits ganglionic transmission in the paravertebral ganglion when injected intra-aortically. Moreover they show that the same effect occurs after intravenous administration. The experiments using sub-maximal preganglionic stimulation, which is closer to the physiological situation than supramaximal stimulation, and the experiments with recording of spontaneous sympathetic activity demonstrate that the same phenomenon probably also occurs in the normally activated ganglion.

The fact that the ganglionic inhibition is less pronounced when a dose of dopamine is injected intravenously than intra-aortically parallels the observation by Bogaert & De Schaepdryver (1967) that for the same dose of dopamine, the neurogenic vasodilatation in the isolated perfused preparation is larger when it is injected intra-aortically. This is also suggested by the fact that in those experiments, in which 4 μg/kg of dopamine decreased both resistance in the innervated hindleg and systemic blood pressure, the effect on the femoral flow is larger when dopamine is injected intra-aortically than intravenously. That the same phenomenon does not occur with 16 μg/kg is probably due to the more pronounced direct vasoconstriction when that dose is given.

Propranolol and atropine, in doses antagonizing β-mimetic and muscarinic vasodilatation respectively, did not influence the vasodilatation elicited by intravenous dopamine. Haloperidol, which selectively inhibits dopamine-induced ganglionic inhibition (Willems, 1973) and dopamine-induced neurogenic vasodilatation in the isolated perfused hindleg (Willems & Bogaert, 1975a), blocked the dopamine-induced decrease in femoral resistance without any influence on the reflex dilatation produced by (−)-noradrenaline. The direct vasodilator effect of dopamine in the femoral vascular bed, which is observed after α-adrenoceptor blockade, has been attributed to β-adrenoceptor stimulation (McNay & Goldberg, 1966) but others have found this effect to be resistant to β-receptor blockade (Higgins *et al.*, 1973), and antagonized by ergometrine (Bell *et al.*, 1975). In our experiments, no α-receptor antagonist was given and intra-femoral dopamine elicited only a vasoconstriction. It is therefore unlikely that the fall of resistance which we observed in our experiments and which was found to be resistant to β-blockade but sensitive to haloperidol, can be explained by a direct effect on the femoral vasculature. In our infusion experiments, dopamine also inhibited ganglionic transmission for the duration of the infusion. Therefore in those experiments, in which vascular resistance decreased in the innervated hindleg during a continuous dopamine-infusion without increase in systemic blood pressure, we can assume that a neurogenic vasodilatation, caused by ganglionic inhibition, is present.

In our experiments, a small increase in renal blood flow occurred, which is in agreement with earlier observations (see Goldberg, 1972; Setler *et al.*, 1975). The neurogenic fall of femoral resistance, which we observed, did not influence the renal vasodilatation, the increase in femoral blood flow being probably too small to decrease renal blood flow.

Only 1 out of 8 dogs with reduced blood volume showed neurogenic vasodilatation with 8 μg kg^{-1} min^{-1} of dopamine, in contrast to 6 out of 25 normal animals. This is perhaps due to the decreasing ability of dopamine to inhibit ganglionic transmission in that situation; this is suggested by our observation that dopamine is in fact less potent as an inhibitor of transmission when stimulus frequency in the ganglionic preparation is increased, thus mimicking increased sympathetic activity in shock (Folkow, 1952). Very recently it has been suggested (Hall, Schwinghamer & Lalone, 1976) that after a rapid haemorrhage the increased vascular resistance in a dog limb is mainly due to circulating catecholamines and not to increased sympathetic tone. This could be an alternative explanation.

Finally we would conclude that, although the neurogenic vasodilatation induced by dopamine is not essential for its hypotensive effect (Eble, 1964; Goldberg, 1972), it is present in some animals and, as such, could contribute to the systemic effect.

Note added in proof: After completion of this paper, we observed that occasionally dogs respond to *local, intra-femoral injection* of dopamine in the innervated hindleg with a biphasic response: vasoconstriction followed by vasodilatation, a response similar to that described by Higgins *et al.* (1973). This phenomenon is clearly different from the response *to intravenous or intra-aortic administration* of dopamine described in our paper, i.e. vasodilatation preceding and dominating an occasional vasoconstriction (Figure 2).

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References

BELL, C., CONWAY, E.L., LANG, W.J. & PADANYI, R. (1975). Vascular dopamine receptors in the canine hindlimb. *Br. J. Pharmac.*, **55**, 167–172.

BOGAERT, M.G. & DE SCHAEPDRYVER, A.F. (1967). Dopamine-induced neurogenic vasodilatation in the hindleg of the dog. *Arch int. Pharmacodyn. Ther.*, **166**, 203–207.

BOGAERT, M., WILLEMS, J. & DE SCHAEPDRYVER, A. (1975). Dopamine-induced neurogenic vasodilatation in the dog. *Abstract 1558, VIth Int. Congr. Pharmac., Helsinki.*

EBLE, J.N. (1964). A proposed mechanism for the depressor effect of dopamine in the anesthetized dog. *J. Pharmac. exp. Ther.*, **145**, 64–70.

FOLKOW, B. (1952). Impulse frequency in sympathetic vasomotor fibres correlated to the release and elimination of the transmitter. *Acta physiol. scand.*, **25**, 49–76.

GILBERT, J.Cl. & GOLDBERG, L.I. (1975). Characterization by cyproheptadine of the dopamine induced contraction in canine isolated arteries. *J. Pharmac. exp. Ther.*, **193**, 435–442.

GOLDBERG, L.I. (1972). Cardiovascular and renal actions of dopamine. Potential clinical applications. *Pharmac. Rev.*, **24**, 1–29.

HALL, J.E., SCHWINGHAMER, J.M. & LALONE, B. (1976). Mechanisms of blood vessel constriction during hemorrhage. *Am. J. Physiol.*, **230**, 569–578.

HIGGINS, C.B., MILLARD, R.W., BRAUNWALD, E. & VATNER, S.F. (1973). Effects and mechanisms of action of dopamine on regional hemodynamics in the conscious dog. *Am. J. Physiol.*, **225**, 432–437.

McDONALD, R.H. & GOLDBERG, L.I. (1963). Analysis of the cardiovascular effects of dopamine in the dog. *J. Pharmac. exp. Ther.*, **140**, 60–66.

McNAY, J.L. & GOLDBERG, L.I. (1966). Comparison of the effects of dopamine, isoproterenol, norepinephrine and bradykinin on canine renal and femoral blood flow. *J. Pharmac. exp. Ther.*, **151**, 23–31.

McNAY, J.L., McDONALD, R.H. & GOLDBERG, L.I. (1965). Direct renal vasodilatation produced by dopamine in the dog. *Circulation Res.*, **16**, 510–517.

RAMDOHR, B., SCHÜREN, K.P., BIAMINO, G. & SCHRÖDER, R. (1973). Der Einfluss von Dopamin auf Hämodynamik und Nierenfunktion bei der schweren Herzinsuffizienz des Menschen. *Klin. Wschr.*, **51**, 549–556.

SETLER, P.E., PENDLETON, R.G. & FINLAY, E. (1975). The cardiovascular actions of dopamine and the effects of central and peripheral catecholaminergic receptor blocking drugs. *J. Pharmac. exp. Ther.*, **192**, 702–712.

WILLEMS, J.L. (1973). Dopamine-induced inhibition of synaptic transmission in lumbar paravertebral ganglia of the dog. *Naunyn Schmiedebergs Arch. Pharmac.*, **279**, 115–126.

WILLEMS, J.L. & BOGAERT, M.G. (1975a). Dopamine-induced neurogenic vasodilatation in isolated perfused muscle preparations of the dog. *Naunyn Schmiedebergs Arch. Pharmac.*, **286**, 413–428.

WILLEMS, J.L. & BOGAERT, M.G. (1975b). The influence of Imipramine on dopamine-induced ganglionic inhibition and neurogenic vasodilatation in the dog. *Naunyn Schmiedebergs Arch. Pharmac.*, **286**, 429–436.

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