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Actions of dopamine and apomorphine on the vasoconstrictor responses of perfused mesenteric arteries of mouse, rat and rabbit

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Dopamine (10^{-7}–10^{-6} M) and apomorphine (5×10^{-7} – 5×10^{-6} M) inhibited the vasoconstrictor responses of the perfused mesenteric artery preparations of rat, rabbit and mouse to adrenergic nerve stimulation but did not affect responses to added noradrenaline. The inhibitory effects of both dopamine and apomorphine were prevented by haloperidol (3×10^{-7} M) but not by yohimbine (3×10^{-8} M) in rat and rabbit mesenteric artery preparations. In contrast, yohimbine (3×10^{-8} M), but not haloperidol, antagonized the inhibitory effect of dopamine and apomorphine in mouse mesenteric artery preparations. In higher concentrations, dopamine (10^{-6}–10^{-4} M) produced a direct vascoconstrictor effect, which involved post-junctional α-adrenoceptors in all three species. However, in preparations contracted with 10^{-7} M 5-hydroxytryptamine and in the presence of phentolamine (3×10^{-7} M) and propranolol (10^{-6} M), dopamine (10^{-6}–10^{-4} M) produced a direct relaxant effect in rabbit mesenteric artery preparations but not in those of rat and mouse. It is suggested that inhibition of neurogenic vasoconstrictor responses, by dopamine and apomorphine, may be mediated through a specific prejunctional inhibitory dopamine receptor in the mesenteric artery of rat and rabbit whereas in the mouse they involve activation of α-adrenoceptors.

Specific dopamine receptors which mediate vasodilatation have been identified in renal, mesenteric (Goldberg 1972), coronary (Schuelke et al 1971) and cerebral (von Essen 1972) vascular beds. Such vascular dopamine receptors are in a post-junctional location (Goldberg et al 1978). It has been postulated that postganglionic sympathetic nerves also contain dopamine receptors, stimulation of which inhibits the release of noradrenaline following nerve stimulation (Langer 1974). Inhibition of stimulation-induced noradrenaline overflow by dopamine has been reported for rabbit ear artery (Hope et al 1978), cat spleen and nictitating membrane (Enero & Langer 1975) and mouse vas deferens (Hurst et al 1979). Such inhibition by dopamine may be due to an action on specific prejunctional dopamine receptors (Hope et al 1978) or through a prejunctional α-adrenoceptor (Hurst et al 1979). Species variations exist. For example, an inhibitory prejunctional dopamine receptor is present in rat vas deferens (Tayo 1977), but not in that of guinea-pig (Stjarne 1975) and mouse (Hurst et al 1979). We have investigated the effects of dopamine and apomorphine on constrictor responses in mesenteric artery preparations of rat, rabbit and mouse. The aim is to determine whether dopamine acts on pre- or post-junctional receptors and to obtain evidence, if any, of species differences in the distribution of such receptors.

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METHODS

Adult albino rabbits (2–2·5 kg), Sprague-Dawley rats (250–300 g) and mice (20–25 g) were anaesthetized with pentobarbitone sodium (40 mg kg^{-1} i.v. for rabbits, 40 mg kg^{-1} i.p. for rats) and 25% urethane (1·5 g kg^{-1} i.p. for mice).

In rat and mouse, the superior mesenteric artery was cannulated and the preparation excised as described by McGregor (1965). In rabbit, a branch of the mesenteric artery was cannulated and excised along with the corresponding piece of mesentery, which was about the same size as the rat preparation. The artery was perfused with Krebs solution maintained at 37 °C and bubbled with 5% CO_2 in oxygen, at a constant flow rate of 5 ml min^{-1} for rat and rabbit and 1 ml min^{-1} for mouse. Vasoconstriction was monitored as changes in perfusion pressure via a pressure transducer connected to a Devices M2 recorder.

Stimulation of perivascular adrenergic nerves was carried out with a pair of platinum electrodes, one of which was positioned around the proximal end of the artery and the other on the supporting plate. A Grass S44 stimulator was used to deliver 1 ms square wave pulses at 20 Hz and 10 V for 30 s and repeated every 5 min. The constrictor responses obtained were due to activation of intramural nerves and not to activation of smooth muscle cells as they were abolished by 10^{-6} M tetrodotoxin.

Vascoconstrictor responses to noradrenaline were obtained by injection of doses of 10^{-7}–10^{-5} M in a volume of 0·1 ml into the perfusion fluid at a point just proximal to the artery. In each experiment, the test dose of noradrenaline was selected so as to produce approximately 50% of the maximal vasoconstrictor responses.

Vascoconstrictor responses, measured as increases in perfusion pressure, were obtained to sympathetic nerve stimulation and noradrenaline before, during and after infusion of dopamine and apomorphine.

Drugs. Dopamine hydrochloride (Sigma), apomorphine hydrochloride (Sigma), (−)-noradrenaline bitartrate (Sigma), phentolamine hydrochloride (Ciba), haloperidol (Seranase, Searle), yohimbine hydrochloride (Martindale Samoore Ltd), cocaine hydrochloride (Sigma), and 5-hydroxytryptamine creatinine sulphate (Sigma).

Statistical analysis. The unpaired Student's *t*-test was used. Probability levels less than 0·05 were taken to indicate significant differences between group means.

RESULTS

Rat mesenteric artery

Nerve stimulation produced an increase in perfusion pressure varying between 30–210 mm Hg (mean ± s.e. 112 ± 16·7 mm Hg, n = 15) in different preparations.

Infusion of dopamine (10^{-7}, 5×10^{-7} and 10^{-6} M) or apomorphine (5×10^{-7} and 5×10^{-6} M) did not affect the responses of the artery to added noradrenaline but reduced the responses to nerve stimulation in a dose-dependent manner (Table 1, Fig. 1). The inhibition of neurogenic vasoconstriction both by dopamine and apomorphine was reversible and reproducible. Concentrations of dopamine higher than 10^{-6} M inhibited the responses to added noradrenaline. This inhibition was slow in onset and difficult to reverse even with prolonged washing.

The dopamine receptor antagonist haloperidol (3×10^{-7} M) had no effect on responses to nerve stimulation or to added noradrenaline but reduced the inhibitory effect of dopamine and apomorphine on neuronally mediated vasoconstriction. In contrast, yohimbine (3×10^{-7} M), a relatively selective prejunctional α-adrenoceptor antagonist, produced a 10–15% increase in responses to nerve stimulation but did not affect the inhibitory effect of dopamine or apomorphine (Table 1, Fig. 1).

Injection of dopamine (0·1 ml volume) in concentrations of 10^{-5}– 5×10^{-4} M caused direct vasoconstriction which was blocked by 3×10^{-7} M phentolamine.

In preparations previously contracted by infusion of 10^{-7} M 5-hydroxytryptamine (5-HT), injection of

Table 1. Inhibition by dopamine and apomorphine of adrenergic nerve mediated constrictor responses of isolated perfused mesenteric artery of rat, rabbit and mouse, and the effect on this of haloperidol and yohimbine. The magnitude of the effect of dopamine and apomorphine is expressed in terms of percentage reduction of control response.

	Rat mesenteric artery % inhibition ± s.e.			Rabbit mesenteric artery % inhibition ± s.e.			Mouse mesenteric artery % inhibition ± s.e.		
		In presence of			In presence of			In presence of	
	Control	Haloperidol 3×10^{-7} M	Yohimbine 3×10^{-6} M	Control	Haloperidol 3×10^{-7} M	Yohimbine 3×10^{-6} M	Control	Haloperidol 3×10^{-7} M	Yohimbine 3×10^{-6} M
Dopamine									
10^{-7} M	17·5 ± 1·0 (12)	2·1 ± 0·6** (0)	—	21·3 ± 0·8 (10)	6·8 ± 0·6* (6)	—	6·2 ± 0·4 (6)	7·3 ± 0·8 (3)	0 (2)
5×10^{-7} M	31·3 ± 1·3 (12)	5·3 ± 0·5** (6)	29·6 ± 1·2 (5)	41·4 ± 1·7 (10)	15·4 ± 0·9* (6)	38·4 ± 1·2 (6)	15·8 ± 0·9 (5)	19·5 ± 1·3 (3)	2·6 ± 1·1* (4)
10^{-6} M	46·6 ± 1·1 (12)	11·2 ± 1·1** (6)	41·9 ± 1·6 (5)	56·3 ± 1·5 (10)	29·2 ± 3·2* (6)	57·8 ± 2·2 (6)	31·6 ± 1·5 (5)	38·4 ± 2·0 (3)	9·3 ± 3·8* (3)
Apomorphine									
5×10^{-7} M	9·2 ± 0·7 (8)	2·6 ± 0·7* (4)	—	13·7 ± 1·3 (8)	8·6 ± 0·5* (5)	—	0 (2)		
10^{-6} M	16·7 ± 1·07 (8)	7·9 ± 1·3* (4)	19·2 ± 1·6 (4)	29·5 ± 0·9 (8)	13·3 ± 1·2* (5)	31·2 ± 2·0 (3)	3·2 ± 1·1 (4)	4·7 ± 1·6 (2)	0 (2)
5×10^{-6} M	34·4 ± 1·3 (8)	19·5 ± 1·9* (4)	29·6 ± 2·05 (3)	44·6 ± 1·4 (8)	26·7 ± 1·4* (4)	40·3 ± 1·5 (3)	4·5 ± 1·25 (4)	5·2 ± 2·2 (2)	2·8 ± 0·8 (2)

* $P < 0·05$ compared with control.
** $P < 0·01$ compared with control.

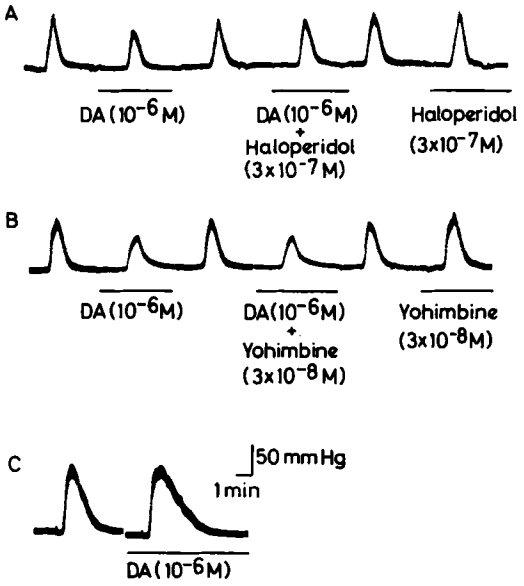

FIG. 1. Constrictor responses of rat isolated perfused mesenteric artery to periarterial nerve stimulation (20 Hz, 10 V, 1 ms for 30 s) (Panel A & B) and to 0·1 ml of 10^{-7} M noradrenaline (Panel C). Infusion of 10^{-6} M dopamine (DA) produced depression of the responses to nerve stimulation (Panel A & B) which was reversed on washing with perfusion fluid free of dopamine. Haloperidol (3×10^{-7} M) prevented the effect of dopamine, but did not affect the responses to nerve stimulation (Panel A). Yohimbine (3×10^{-8} M) did not affect the responses to dopamine, but slightly potentiated the responses to nerve stimulation (Panel B). Infusion of 10^{-6} M DA did not influence responses to 0·1 ml of 10^{-7} M noradrenaline (Panel C).

0·1 ml acetylcholine 5×10^{-8} to 10^{-7} M produced a large fall in perfusion pressure reflecting vasodilatation, but injection of 0·1 ml dopamine 10^{-7} to 5×10^{-6} M had no effect on the perfusion pressure.

Rabbit mesenteric artery

Nerve stimulation produced an increase in perfusion pressure varying from 25–180 mm Hg (mean ± s.e. 95 ± 21·6 mm Hg, n = 10). Infusion of dopamine (10^{-7}–10^{-6} M) and apomorphine (5×10^{-7}–5×10^{-6} M) resulted in an immediate depression of the vasoconstrictor responses to nerve stimulation, which was reversible on washing. These concentrations of dopamine and apomorphine did not affect the responses to added noradrenaline (Fig. 2).

Haloperidol, 3×10^{-7} M had no effect on responses to nerve stimulation or to added noradrenaline but reduced the inhibitory effects of both dopamine and apomorphine (Table 1, Fig. 2).

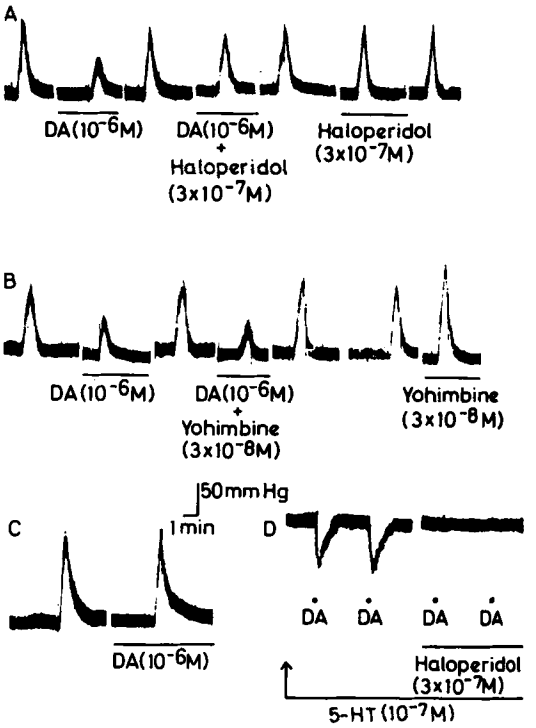

FIG. 2. Panels A, B and C. Constrictor responses of rabbit isolated perfused mesenteric artery to periarterial nerve stimulation (20 Hz, 10 V, 1 ms, 15 s) (Panel A & B) and to 0·1 ml of 10^{-7} M noradrenaline (Panel C). Infusion of dopamine (10^{-6} M) inhibited the responses to nerve stimulation (Panel A & B). Haloperidol (3×10^{-7} M) blocked the inhibitory responses of dopamine, while itself did not affect responses to nerve stimulation (Panel A). Yohimbine (3×10^{-8} M) did not influence the inhibitory effect of dopamine but itself potentiated the responses to nerve stimulation (Panel B). Infusion of 10^{-6} M dopamine did not affect responses to 0·1 ml of 10^{-7} M noradrenaline (Panel C). Panel D: Vasodilator responses of isolated perfused rabbit mesenteric artery, previously contracted by 10^{-7} M 5-hydroxytryptamine. Injection of 0·1 ml of 5×10^{-6} M dopamine produced vasodilatation which was abolished by infusion of 3×10^{-7} M haloperidol.

Yohimbine (3×10^{-8} M) on the other hand, produced a 5–10% increase in responses to nerve stimulation but did not affect the inhibitory effect of dopamine or apomorphine (Fig. 2).

Injection of dopamine (0·1 ml volume) in concentrations between 10^{-5} and 5×10^{-4} M produced a direct vasoconstriction which was blocked by 3×10^{-7} M phentolamine.

In preparations previously contracted by 10^{-7} M 5-HT, and in the presence of 10^{-6} M phentolamine, injection of 0·1 ml of dopamine in concentrations between 10^{-6}–10^{-4} M, produced concentration-

dependent vasodilatation, which was not affected by propranolol (10^{-6} M) but was blocked by haloperidol (3×10^{-7} M) (Fig. 2D).

Mouse mesenteric artery

Nerve stimulation produced an increase in perfusion pressure varying from 15–85 mm Hg (mean ± s.e. 35 ± 10·5 mm Hg, n = 6).

Infusion of dopamine (10^{-7}–10^{-6} M) and apomorphine (5×10^{-7} – 5×10^{-6} M) produced a reversible depression of vasoconstrictor responses to nerve stimulation but not of added noradrenaline. Yohimbine (3×10^{-8} M) blocked the inhibitory effects of dopamine and apomorphine but haloperidol (3×10^{-7} M) did not (Fig. 3, Table 1). Such concentrations of yohimbine and haloperidol had no depressant effect on the responses to nerve stimulation in the absence of dopamine.

Injection of dopamine (volume of 0·1 ml) in concentrations between 10^{-6} and 10^{-4} M produced vasoconstriction, which was blocked by 3×10^{-7} M phentolamine.

In preparations previously contracted by infusion of 10^{-7} M 5-HT and in presence of 10^{-6} M phentolamine, injection of 0·1 ml dopamine 10^{-7} to 10^{-5} M produced no vasodilatation.

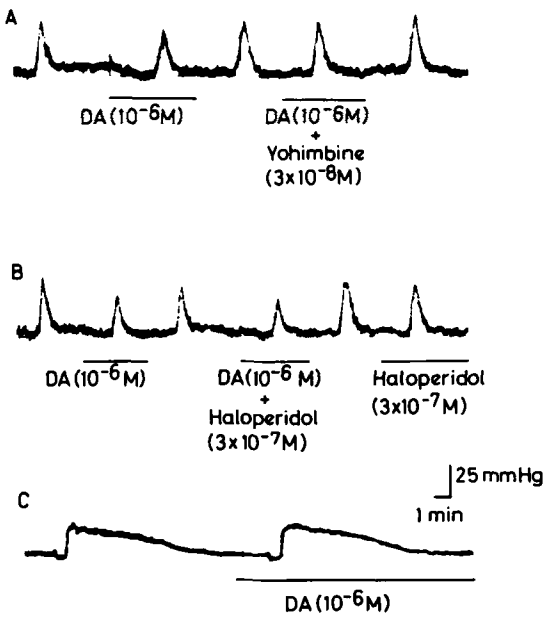

FIG. 3. Constrictor responses of mouse isolated perfused mesenteric artery to periarterial nerve stimulation (20 Hz, 10 V, 1 ms for 30 s) (Panel A & B) and to 0·1 ml of 10^{-7} M noradrenaline (Panel C). Infusion of 10^{-6} M dopamine produced reversible inhibition of responses to nerve stimulation (Panel A & B), which was blocked by 3×10^{-8} M yohimbine (Panel A) but not by 3×10^{-7} M haloperidol (Panel B). Haloperidol (3×10^{-7} M) alone did not affect the responses to nerve stimulation (Panel B). Infusion of dopamine (10^{-6} M) did not affect the responses to 0·1 ml of 10^{-7} M noradrenaline (Panel C).

DISCUSSION

The vasoconstrictor responses to sympathetic nerve stimulation were inhibited by infusion of dopamine and apomorphine in concentrations that did not affect responses to exogenous noradrenaline in all three species studied. In high concentrations, dopamine produced a direct vasoconstrictor effect which involved postjunctional α-adrenoceptors in all three species, since their action could be blocked by phentolamine.

Dopamine which has less than 2% of the potency of noradrenaline as a vasoconstrictor in rabbit ear artery (de la Lande & Harvey 1965) has been shown to be equipotent with noradrenaline in inhibiting stimulation-induced release of transmitter noradrenaline from rabbit ear artery (McCulloch et al 1973), cat spleen and nictitating membrane (Enero & Langer 1975).

Our results indicate that in both rat and rabbit mesenteric artery preparations the inhibition by dopamine and apomorphine of neurogenic vasoconstrictor responses may be mediated through a specific prejunctional inhibitory dopamine receptor, since these effects of dopamine and apomorphine can be blocked by haloperidol and not by yohimbine. We however obtained no evidence of prejunctional dopamine receptors in mouse mesenteric artery. In this tissue the inhibitory action of dopamine and apomorphine may be mediated solely through the activation of prejunctional α-adrenoceptors, as it was antagonized by yohimbine but remained unaffected by haloperidol. This agrees with the results obtained by Hurst et al (1979) on the mouse vas deferens.

We have also examined the possibility that inhibition of neurogenic vasoconstrictor action could occur if dopamine activated the vasodilator postjunctional dopamine receptors on vascular muscle cells. This does not seem to be a possible explanation in rat and mouse mesenteric arteries, as a direct relaxant effect of dopamine or apomorphine could not be demonstrated in these preparations. However, in rabbit mesenteric artery, direct relaxant effects were observed with both dopamine and apomorphine, these effects persisted in the presence of propranolol but were greatly

reduced by haloperidol. The relaxant effects of dopamine and apomorphine were therefore mediated through a specific postjunctional dopamine receptor. However, it is unlikely that such a postjunctional action contributed to the inhibition by dopamine of neurogenic responses, since the concentration of dopamine that inhibited the neurogenic response failed to stimulate the postjunctional dopamine receptors.

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