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Influence of the dopamine receptor agonists fenoldopam and quinpirole in the rat superior mesenteric vascular bed

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1 The effect of local administration of the dopamine$_2$ (DA_2)-receptor agonist quinpirole and of the DA_1-receptor agonist fenoldopam was studied in the *in situ*, constant flow autoperfused, superior mesenteric vascular bed of the rat.

2 Local infusion of quinpirole (30 $\mu g\,kg^{-1}\,min^{-1}$ for 5 min) had no effect on baseline perfusion pressure; it reduced the pressor responses to electrical stimulation (4 Hz, 1 ms, supramaximal voltage) of the periarterial sympathetic nerves to 45.6 ± 2.1% of its original value but did not modify similar pressor responses produced by locally administered noradrenaline.

3 The inhibitory effect of quinpirole was antagonized by the selective DA_2-receptor antagonist domperidone (10 $\mu g\,kg^{-1}$) but not by the selective DA_1-receptor antagonist SCH 23390 (50 $\mu g\,kg^{-1}$).

4 Local infusion of fenoldopam (30 $\mu g\,kg^{-1}\,min^{-1}$ for 5 min) reduced baseline perfusion pressure to 89.9 ± 1.9%, increased the pressor response to electrical stimulation (4 Hz, 1 ms, supramaximal voltage) of the periarterial nerves to 134.7 ± 14.0%, but reduced the pressor response to locally administered noradrenaline to 37.2 ± 8.2%. Similar pressor responses induced by the selective α_1-adrenoceptor agonist phenylephrine were also reduced by fenoldopam (to 38.4 ± 6.4%), but responses to locally administered angiotensin II were not modified.

5 Pretreatment with SCH 23390 (50 $\mu g\,kg^{-1}$) antagonized the effect of fenoldopam on baseline perfusion pressure, but had no influence on the effect of fenoldopam on responses to electrical stimulation or to noradrenaline.

6 Pretreatment with the selective α_2-adrenoceptor antagonist rauwolscine (100 $\mu g\,kg^{-1}$) had no effect on the reduction in baseline perfusion pressure induced by fenoldopam nor on its inhibitory effect on the response to noradrenaline, but it antagonized the stimulatory effect of fenoldopam on the response to electrical stimulation.

7 The results show that quinpirole inhibits neurogenic vasoconstriction in the rat superior mesenteric vascular bed through stimulation of presynaptic DA_2-receptors while fenoldopam stimulates postsynaptic vasodilatory DA_1-receptors. In addition, our results suggest that the inhibitory effect of fenoldopam on the vasoconstrictor response to noradrenaline may be due to an antagonistic action at postsynaptic α_1-adrenoceptors, while its potentiating effect on neurogenic vasoconstriction is due to blockade of presynaptic α_2-adrenoceptors.

Introduction

Nichols & Hiley (1985) have recently identified postsynaptic vasodilator dopamine receptors in the superior mesenteric arterial bed of the rat. We have demonstrated that, *in vivo*, the dopamine receptor agonist apomorphine inhibits neurogenic vasoconstriction in the superior mesenteric vascular bed of the rat by interaction with presynaptic inhibitory dopamine receptors on sympathetic nerves (Dupont *et al.*, 1986a). This inhibitory effect of apomorphine is antagonized by the selective DA_2-receptor antagonist domperidone, but not by the selective DA_1-receptor antagonist SCH 23390, indicating that these presynaptic dopamine receptors can be classified as DA_2-receptors (Dupont *et al.*, 1986b).

We found it of interest to study the effect of local administration of recently developed, more selective,

dopamine receptor agonists on baseline perfusion pressure, on neurogenic vasoconstriction and on vasoconstriction induced by exogenous noradrenaline in the *in situ* autoperfused superior mesenteric vascular bed of the rat. The agonists used were the selective DA_1-receptor agonist, fenoldopam (Hahn *et al.*, 1982; Ohlstein *et al.*, 1984; Sengupta & Lokhandwala, 1985), which has been reported to possess also α_1- and α_2-adrenoceptor antagonist activities (Ohlstein *et al.*, 1985; Nakamura *et al.*, 1986) and the selective DA_2-receptor agonist, quinpirole (Hahn & McDonald, 1984).

Preliminary results of these experiments have been presented (Dupont *et al.*, 1987).

Methods

Animals and general procedures

The experiments were done in anaesthetized (pentobarbitone sodium; 40 mg kg^{-1}, i.p.) normotensive Wistar rats of either sex weighing 320–430 g. The animals breathed room air spontaneously through a tracheal tube. An external jugular vein was cannulated for i.v. administration of drugs. A carotid artery was cannulated for blood pressure measurement using a Statham P23I or P23AA pressure transducer and a Gould type 8400 S or a Beckman Dynograph type R recorder. The animals were kept warm using a heating operating table with circulating water at 39°C.

The rats were prepared for *in situ* autoperfusion of the superior mesenteric vascular bed, as described previously (Jackson & Campbell, 1980; Dupont *et al.*, 1986a). The superior mesenteric artery was ligated at its aortic origin and perfused with blood withdrawn from the abdominal aorta using an extracorporeal circuit and a constant flow Minipuls 2 Gilson or Sigma-motor pump. The distal portion of the circuit was connected to a Statham P23I or P23AA pressure transducer for measurement of the perfusion pressure which was recorded on a Gould type 8400 S or a Beckman Dynograph type R recorder. At the beginning of the experiment, flow was adjusted so that perfusion pressure was equivalent to systemic pressure. As flow was kept constant during the whole experiment (2.0–2.8 ml min^{-1}), changes in perfusion pressure reflect changes in vascular resistance. Drugs were administered locally through the distal cannula by bolus injection of 10 µl maximum with a Hamilton microsyringe (701 N, 10 µl) or by infusion of a volume of 0.1 ml min^{-1} with a Braun infusion pump. A small bipolar electrode was applied periarterially, just distally to the cannulation point, to stimulate the mesenteric sympathetic nerves, which were proximally ligated. Electrical stimulation was with square wave pulses from a Grass or Palmer Bioscience 100 stimulator having the same stimulation characteristics (4 Hz, 1 ms, supramaximal voltage) as used in previous experiments (Dupont *et al.*, 1986a) in which we have shown with hexamethonium that predominantly postganglionic nerve fibres are activated. Electrical stimulation was applied until the pressure response was maximal. In all experiments heparin (5 mg kg^{-1}) and atropine (1 mg kg^{-1}) were administered i.v. before the perfusion was started.

Effect of quinpirole on increases in perfusion pressure by electrical stimulation and noradrenaline

Preliminary experiments were performed to determine the appropriate dose of quinpirole: 5 min after starting an infusion of either 1 µg kg^{-1} min^{-1} ($n = 2$) or 10 µg kg^{-1} min^{-1} ($n = 2$), the stimulation-induced pressor responses were reduced to 92.1% and 64.6% of the control values, respectively. A dose of 30 µg kg^{-1} min^{-1} of quinpirole was used in further experiments. In 6 rats the influence of quinpirole, at a dose of 30 µg kg^{-1} min^{-1} administered i.a., was studied both on increases in perfusion pressure evoked at 5 min intervals by electrical stimulation at 4 Hz and by local injection of noradrenaline. The doses of noradrenaline needed to induce increases in perfusion pressure similar to those obtained with electrical stimulation ranged from 0.30 to 0.70 µg kg^{-1}. After a first sequence, consisting of electrical stimulation followed by noradrenaline, infusion of quinpirole (30 µg kg^{-1} min^{-1}) was started and after 5 min the sequence, electrical stimulation/noradrenaline, was repeated. The infusion of quinpirole was then stopped and 5 min later the sequence, electrical stimulation/noradrenaline, was repeated once again. In half of the experiments, the administration of noradrenaline preceded the electrical stimulation. Previous experiments during which saline was infused instead of quinpirole had confirmed the reproducibility of the pressor responses to electrical stimulation and to exogenous noradrenaline in this preparation (Dupont *et al.*, 1986a).

Influence of SCH 23390 and domperidone on the effect of quinpirole

The influence of SCH 23390 (50 µg kg^{-1}) and of domperidone (10 µg kg^{-1}) on the effect of quinpirole was studied in 18 rats randomized into 3 groups of 6. In the 3 groups, the perfusion pressor response to electrical stimulation at 4 Hz was studied 4 times at 5 min intervals; a quinpirole infusion (30 µg kg^{-1} min^{-1}) was started immediately after the second stimulation and stopped immediately after the third stimulation. In the first group of rats no antagonist was administered, but in the second and third groups either SCH 23390 or domperidone was injected locally immediately after

the first stimulation. The dose of domperidone ($10\,\mu g\,kg^{-1}$) used antagonizes the inhibitory effect of apomorphine on neurogenic vasoconstriction in this preparation (Dupont *et al.*, 1986b). In preliminary experiments it was shown that lower doses of domperidone failed to antagonize the effect of quinpirole. The dose of SCH 23390 ($50\,\mu g\,kg^{-1}$) used has been shown to antagonize, on intravenous administration, the blood pressure lowering effect of fenoldopam in the rat (Sengupta & Lokhandwala, 1985).

Effect of fenoldopam in the preconstricted mesenteric vascular bed

In these experiments the mesenteric vascular tone was increased to 170–180 mmHg by local infusion of vasopressin ($0.01-0.05\,u\,kg^{-1}\,min^{-1}$) to facilitate the study of vasodilator responses. In preliminary experiments, it was observed that bolus injections of fenoldopam $3\,\mu g\,kg^{-1}$ ($n = 4$) and $10\,\mu g\,kg^{-1}$ ($n = 4$) had no consistent effects on perfusion pressure. A series of 16 rats was then used to study the effect of 30 and $100\,\mu g\,kg^{-1}$ fenoldopam. In each rat, bolus injections of saline, fenoldopam 30 $\mu g\,kg^{-1}$ and $100\,\mu g\,kg^{-1}$ were given at 5 min intervals; this sequence was repeated again after a recovery period of 10 min. Five minutes before this second sequence SCH 23390 ($50\,\mu g\,kg^{-1}$) was administered locally in 6 rats and domperidone ($10\,\mu g\,kg^{-1}$) in 6 other rats. The solvents of each antagonist were both administered in 2 rats. Based on the results of these experiments, a dose of $30\,\mu g\,kg^{-1}$ was used in all further experiments with fenoldopam.

Effect of fenoldopam on increases in perfusion pressure by electrical stimulation, noradrenaline and angiotensin II

In a first series of experiments, 6 rats were used to study the effect of local administration of fenoldopam ($30\,\mu g\,kg^{-1}\,min^{-1}$) on increases in perfusion pressure evoked both by electrical stimulation at 4 Hz and by local injection of noradrenaline (0.2 to $0.70\,\mu g\,kg^{-1}$), with a protocol identical to that described for the experiments with quinpirole.

A series of 18 rats was then used to study the effect of locally administered fenoldopam ($30\,\mu g\,kg^{-1}\,min^{-1}$) on baseline perfusion pressure and on pressor responses of similar amplitude induced by electrical stimulation at 4 Hz, locally injected noradrenaline ($0.30-0.60\,\mu g\,kg^{-1}$) and locally injected angiotensin II ($0.30-0.65\,\mu g\,kg^{-1}$). Electrical stimulation and the injections of noradrenaline and of angiotensin II were separated by intervals of at least 5 min so that a full return of the perfusion pressure to its control level was possible. The sequence electrical stimulation/ noradrenaline/ angiotensin II was repeated 4 times; infusion of fenoldopam was started after the second sequence and stopped after the third sequence. The rats were randomized into 3 groups of 6. In the first group of 6 rats no antagonist was administered; in the second group the α_2-adrenoceptor antagonist rauwolscine ($100\,\mu g\,kg^{-1}$) was given and in the third group SCH 23390 ($50\,\mu g\,kg^{-1}$) was administered locally immediately after the first sequence electrical stimulation/noradrenaline/angiotensin II.

Preliminary experiments, during which only saline was infused ($n = 6$), confirmed the reproducibility of the pressor responses to electrical stimulation, to noradrenaline and to angiotensin II.

Effect of fenoldopam on increases in perfusion pressure by noradrenaline and phenylephrine

Preliminary experiments showed that the selective α_2-adrenoceptor agonists clonidine ($n = 4$) and UK-14, 304-18 ($n = 4$), both in doses up to $500\,\mu g\,kg^{-1}$, failed to produce vasoconstriction in the superior mesenteric vascular bed. In 6 rats, the effects of local administration of fenoldopam ($30\,\mu g\,kg^{-1}\,min^{-1}$) on increases in perfusion pressure by locally injected noradrenaline ($0.30-0.70\,\mu g\,kg^{-1}$) and phenylephrine ($1\,\mu g\,kg^{-1}$) were studied following the protocol described for the study of the effect of quinpirole on stimulation- and noradrenaline-induced increases in perfusion pressure. The doses of noradrenaline and phenylephrine were chosen to induce increases in perfusion pressure of similar magnitude to those obtained by electrical stimulation at 4 Hz in the previous experiments. Because of the stability of the pressor responses to noradrenaline and phenylephrine, the protocol could be repeated; saline was now infused instead of fenoldopam. In 3 of the 6 rats, saline was infused first.

Drugs

The sources of the drugs used were as follows: angiotensin II (Ciba, Brussels, Belgium), atropine sulphate (Federa, Brussels, Belgium), clonidine hydrochloride (Boehringer Ingelheim, Brussels, Belgium), domperidone (Janssen Pharmaceutica, Beerse, Belgium), fenoldopam (Smith Kline and French Laboratories, Philadelphia, U.S.A.), heparin (Roche, Brussels, Belgium), (−)-noradrenaline bitartrate (Winthrop, Brussels, Belgium), phenylephrine (Winthrop), quinpirole hydrochloride (Lilly Research Laboratories, Indianapolis, U.S.A.), rauwolscine hydrochloride (Carl Roth, Karlsruhe, FRG), SCH 23390 [(**R**)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine] (Schering Corporation, Bloomfield, U.S.A.), UK-14,304-18 [5-bromo-6-(2-imidazolin-2-ylamino)-quinoxaline] (Pfizer, Sandwich, Kent), vasopressin (Sandoz, Basel, Switzerland). For atropine, domperidone, heparin,

noradrenaline, phenylephrine and vasopressin, the commercially available ampoules were used. When required, dilutions were made with saline. The other drugs were available as powder and were dissolved in saline, except for SCH 23390, which was dissolved in 0.1 ml of 0.1 N HCl and made up to volume with distilled water.

Analysis of results

Increases in perfusion pressure were always measured from baseline perfusion pressure, even when the latter was lowered by a previous administration of fenoldopam.

All results are expressed as mean ± s.e.mean. The signed-ranks test was used to assess statistical significance. Differences were considered significant when $P < 0.05$.

Results

Preliminary experiments showed that electrical stimulation at 4 Hz of the periarterial mesenteric sympathetic nerves produced increases in perfusion pressure of 94.6 ± 7.8 mmHg ($n = 4$). When electrical stimulations at 4 Hz were repeated at 5 min intervals, the induced perfusion pressor responses remained stable for at least 1 h.

Effect of quinpirole on increases in perfusion pressure by electrical stimulation and noradrenaline

Local infusion of quinpirole (30 $\mu g\,kg^{-1}\,min^{-1}$) into the superior mesenteric vascular bed had no effect on systemic blood pressure nor on perfusion pressure *per se* (112.3 ± 6.8 mmHg), but significantly reduced the pressor response elicited by electrical stimulation ($n = 6$, $P < 0.05$; Figure 1). Electrical stimulation at 4 Hz before, during and after infusion of quinpirole, increased perfusion pressure by 96.1 ± 8.7 mmHg, 43.8 ± 6.2 mmHg and 70.6 ± 10.7 mmHg, respectively. Equivalent increases of perfusion pressure induced by noradrenaline were not modified by quinpirole (95.0 ± 7.4 mmHg, 89.4 ± 6.8 mmHg and 93.0 ± 9.1 mmHg before, during and after quinpirole infusion, respectively).

Influence of SCH 23390 and domperidone on the effect of quinpirole

The influence of pretreatment with SCH 23390 and with domperidone on the effect of quinpirole is shown in Figure 2. Local injection of SCH 23390 (50 $\mu g\,kg^{-1}$) and domperidone (10 $\mu g\,kg^{-1}$) had no effect on systemic blood pressure, on perfusion pressure *per se* or on the perfusion pressor response to electrical stimulation. The inhibitory effect of quinpirole on neurogenic vasoconstriction was not antagonized by SCH 23390; the response to stimulation during quinpirole infusion after pretreatment with SCH 23390 was comparable to that obtained in the group not treated with an antagonist. In contrast, pretreatment with domperidone antagonized the inhibitory effect of quinpirole (Figure 2).

Effect of fenoldopam in the preconstricted mesenteric vascular bed

After preconstriction of the superior mesenteric vascular bed (176.4 ± 3.6 mmHg), fenoldopam 30 $\mu g\,kg^{-1}$ and 100 $\mu g\,kg^{-1}$ produced similar reductions in perfusion pressure, while bolus injections of saline had no effect on perfusion pressure. After either dose, per-

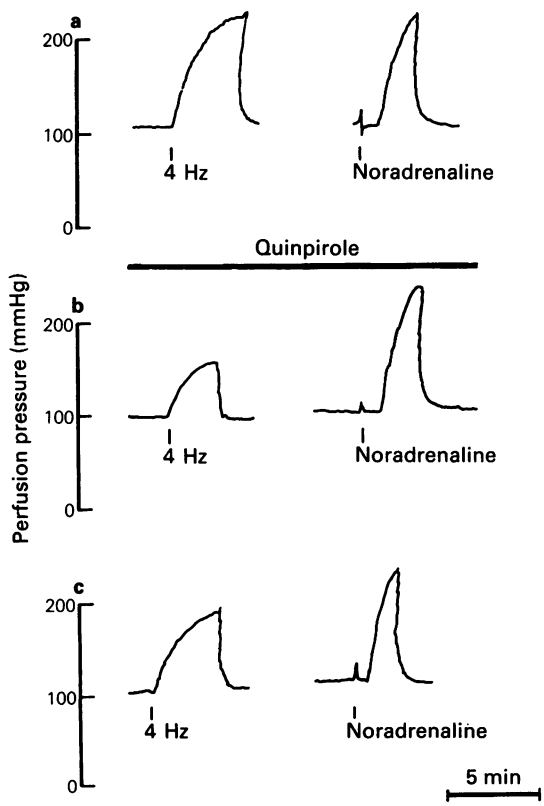

Figure 1 *In situ* autoperfused rat superior mesenteric vascular bed: perfusion pressure responses to electrical stimulation of the periarterial mesenteric sympathetic nerves (supramaximal voltage, 1 ms, 4 Hz) and to locally administered noradrenaline (0.5 $\mu g\,kg^{-1}$); (a) before, (b) during and (c) after quinpirole infusion (30 $\mu g\,kg^{-1}\,min^{-1}$).

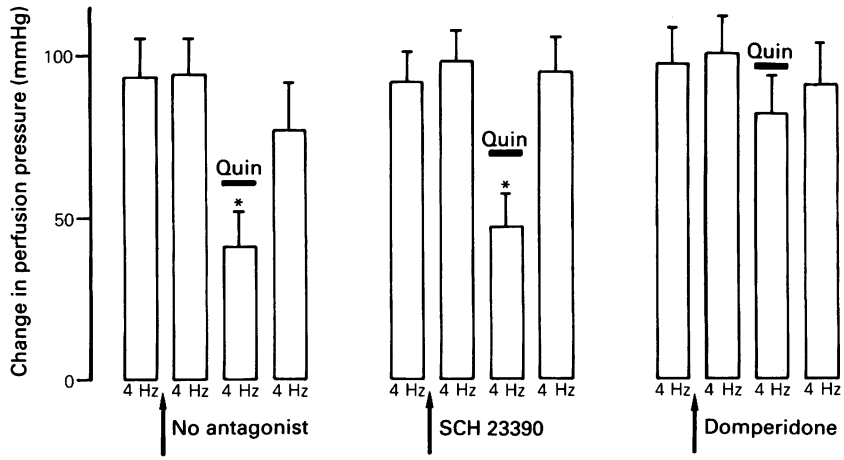

Figure 2 *In situ* autoperfused rat superior mesenteric vascular bed: effect of quinpirole (Quin, 30 $\mu g\,kg^{-1}\,min^{-1}$) on the perfusion pressure responses (mmHg; mean values, s.e.mean shown by vertical lines) to electrical stimulation at 5 min intervals (supramaximal voltage, 1 ms, 4 Hz) in control rats ($n = 6$), in rats pretreated with SCH 23390 (50 $\mu g\,kg^{-1}$, $n = 6$) and in rats pretreated with domperidone (10 $\mu g\,kg^{-1}$, $n = 6$).
*$P < 0.05$: significant difference from the pressure response to the first stimulation.

fusion pressure returned to baseline within 1 min. The results are shown in Table 1. The experiments in which the solvents of SCH 23390 or of domperidone were given showed that the vasodilator effect of fenoldopam was reproducible. Neither SCH 23390 nor domperidone had any effect on baseline perfusion pressure. The vasodilator effect of fenoldopam was markedly reduced by SCH 23390 but was not influenced by pretreatment with domperidone.

Table 1 Reduction of baseline perfusion pressure in rat superior mesenteric vascular bed induced by bolus injections of fenoldopam

		Fenoldopam ($30\,\mu g\,kg^{-1}$)	*Fenoldopam* (*100* $\mu g\,kg^{-1}$)
Before	solvent	19.8 ± 2.8	20.1 ± 2.6
After		21.0 ± 2.6	21.5 ± 2.6
Before	SCH 23390	20.9 ± 2.0	20.6 ± 2.4
After		7.7 ± 2.9*	7.1 ± 2.4*
Before	domperidone	20.9 ± 2.5	19.0 ± 2.9
After		18.1 ± 3.2	17.5 ± 3.0

Fenoldopam, 30 and 100 $\mu g\,kg^{-1}$ in bolus, was given before and after local administration of SCH 23390 (50 $\mu g\,kg^{-1}$; $n = 6$), domperidone (10 $\mu g\,kg^{-1}$; $n = 6$) or their solvent ($n = 4$). Values (in mmHg) are given as the mean ± s.e.mean.
*$P < 0.05$: significantly different from the effect before administration of the antagonist.

Effect of fenoldopam on increases in perfusion pressure by electrical stimulation, noradrenaline and angiotensin II

An experiment during which the effects of local infusion of fenoldopam (30 $\mu g\,kg^{-1}\,min^{-1}$) were studied on perfusion pressure responses both to electrical stimulation at 4 Hz and to locally administered noradrenaline, is shown in Figure 3. These experiments ($n = 6$) indicated that fenoldopam decreased baseline perfusion pressure and markedly potentiated the pressor response to electrical stimulation; furthermore, it decreased the pressor response to noradrenaline.

Therefore, in a subsequent series of experiments, the effect of local infusion of fenoldopam was studied on the responses to stimulation, to noradrenaline and to angiotensin II; the results of these experiments are summarized in Table 2. Local infusion of fenoldopam had no effect on systemic blood pressure, but it significantly reduced baseline perfusion pressure from 114.6 ± 4.8 to 103.0 ± 6.1 mmHg ($n = 6$, $P < 0.05$), with a subsequent return to its control level within 2 min after stopping the fenoldopam infusion. Furthermore, fenoldopam significantly enhanced the pressor response to electrical stimulation to 134.7 ± 14.0% of the control response; this effect was reversible. In contrast, fenoldopam reduced the response to locally administered noradrenaline to 37.2 ± 8.2% of that obtained just before the fenoldopam infusion; this response had recovered partially 5 min after withdrawal of the agonist. The pressor response to locally

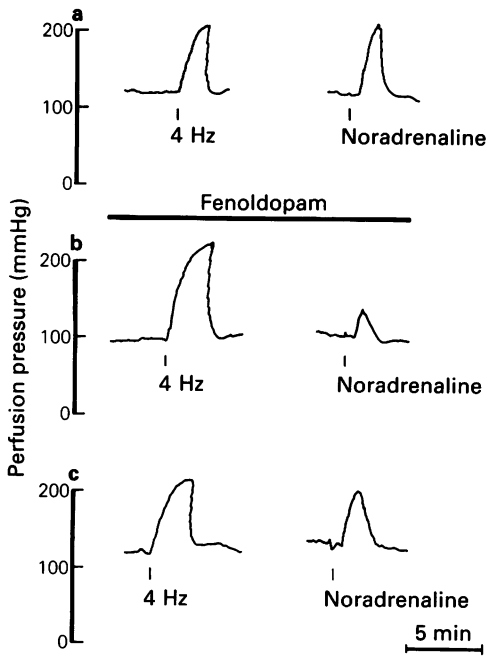

Figure 3 *In situ* autoperfused rat superior mesenteric vascular bed: perfusion pressure responses to electrical stimulation of the periarterial mesenteric sympathetic nerves (supramaximal voltage, 1 ms, 4 Hz) and to locally administered noradrenaline (0.7 $\mu g\,kg^{-1}$), (a) before, (b) during and (c) after fenoldopam infusion (30 $\mu g\,kg^{-1}\,min^{-1}$).

administered angiotensin II was not affected by the infusion of fenoldopam (94.6 ± 8.2% of the response obtained just before the fenoldopam infusion). Rauwolscine (100 $\mu g\,kg^{-1}$, locally) had no effect on the baseline perfusion pressure but it significantly ($P<0.05$) enhanced the pressor response to electrical stimulation. It did not affect the reduction of baseline perfusion pressure (from 117.1 ± 6.2 to 104.2 mmHg; $n = 6$, $P<0.05$) induced by fenoldopam, nor did it affect the inhibitory effect of the agonist on the response to noradrenaline. However, it antagonized the stimulatory effect of fenoldopam on the pressor response to stimulation: the response to stimulation during infusion with fenoldopam was not different from the response obtained after the administration of rauwolscine but just before the fenoldopam infusion. Local administration of the DA_1-receptor antagonist SCH 23390 alone had no effect on baseline pressure or on the pressor responses to stimulation, noradrenaline or angiotensin II, but it antagonized the effect of fenoldopam on baseline perfusion pressure; the baseline perfusion pressure during infusion with fenoldopam (110.9 ± 6.3 mmHg; $n = 6$) was not significantly different from the control level (113.7 ± 6.1 mmHg). Pretreatment with SCH 23390 had no effect on the enhancement of the response to electrical stimulation or on the reduction of the response to noradrenaline induced by fenoldopam.

Effect of fenoldopam on increases in perfusion pressure by noradrenaline and phenylephrine

The pressor responses to noradrenaline and phenylephrine were of similar magnitude and were comparable with the responses to electrical stimulation observed in previous series of experiments; they were not altered by infusion of saline, thus confirming their reproducibility. In this series, local infusion of fenoldopam again reduced baseline perfusion pressure (from 118.6 ± 7.9 mmHg to 103.0 ± 9.2 mmHg; $n = 6$, $P<0.05$). Before, during and after fenoldopam infusion, increases in perfusion pressure of 90.1 ± 4.9 mmHg, 31.4 ± 6.1 mmHg and 92.1 ± 5.6 mmHg were induced by bolus injections of noradrenaline and of 89.6 ± 4.6 mmHg, 34.4 ± 7.1 mmHg and 87.8 ± 5.9 mmHg by bolus injections of phenylephrine.

Discussion

The superior mesenteric arterial bed of the rat contains both postsynaptic dopamine receptors (Nichols & Hiley, 1985) and presynaptic dopamine receptors on the sympathetic nerve endings (Dupont *et al.*, 1986a). In the present study, we therefore assessed the effects of local administration of both fenoldopam and quinpirole, selective agonists for DA_1- and DA_2-receptors respectively, in this vascular bed.

The experiments were done after pretreatment with atropine to exclude cholinergic effects. The electrical stimulation of the periarterial mesenteric sympathetic nerves produced frequency-dependent and reproducible increases in perfusion pressure (results not shown); as in our previous experiments with apomorphine in this vascular bed (Dupont *et al.*, 1986a), a stimulation frequency of 4 Hz was chosen to study the effects of quinpirole and fenoldopam on neurogenic vasoconstriction.

The effect of quinpirole was similar to that observed previously with the less selective dopamine receptor agonists, apomorphine and pergolide (Dupont *et al.*, 1986a): quinpirole significantly reduced the pressor responses evoked by electrical stimulation at 4 Hz, but it did not reduce the pressor responses to exogenous noradrenaline. This suggests that the inhibitory effect of the DA_2-receptor agonist quinpirole is due to interaction with presynaptic receptors which leads to a reduction in the noradrenaline release during stimulation. The absence of effect of quinpirole on resting

Table 2 Influence of fenoldopam on increases in perfusion pressure by electrical stimulation (ES), noradrenaline (NA) and angiotensin II (AII)

			Fenoldopam	
ES	96.4 (± 7.6)	102.0 (± 9.6)	129.9* (± 12.1)	107.2 (± 10.8)
NA	92.3 (± 4.1)	91.8 (± 8.2)	34.1* (± 8.9)	69.0* (± 10.2)
AII	79.4 (± 9.1)	71.4 (± 8.9)	67.6 (± 9.2)	65.8 (± 9.4)
	Rauwolscine		*Fenoldopam*	
ES	92.3 (± 8.1)	153.9* (± 10.2)	155.4* (± 13.6)	142.8* (± 13.7)
NA	89.5 (± 3.4)	92.5 (± 6.2)	43.3* (± 4.1)	74.8 (± 7.2)
AII	81.0 (± 9.2)	72.9 (± 10.6)	82.7 (± 12.1)	74.8 (± 10.2)
	SCH 23390		*Fenoldopam*	
ES	94.7 (± 6.2)	99.3 (± 6.4)	132.7* (± 8.3)	111.4 (± 14.9)
NA	102.7 (± 3.9)	103.5 (± 3.7)	54.8* (± 6.9)	89.8 (± 7.8)
AII	82.1 (± 7.1)	79.5 (± 8.2)	74.5 (± 7.6)	71.6 (± 7.9)

Four sequences of electrical stimulation (ES, supramaximal voltage, 1 ms, 4 Hz)/noradrenaline (NA) /angiotensin II (AII) were performed, the third during the infusion of fenoldopam (30 $\mu g\,kg^{-1}\,min^{-1}$). In the first group of rats ($n = 6$) no antagonist was given; in the second group, rauwolscine (100 $\mu g\,kg^{-1}$, $n = 6$) and in the third group SCH 23390 (50 $\mu g\,kg^{-1}$, $n = 6$), were administered locally immediately after the first sequence. Values (in mmHg) are given as the mean ± s.e.mean.

*$P < 0.05$: significantly different from the first pressor response induced by this stimulus.

perfusion pressure may be explained by the fact that the resting sympathetic tone to the superior mesenteric vascular bed is low, due to the proximal ligation of the periarterial sympathetic nerves; this observation further suggests that quinpirole does not interact with the postsynaptic dopamine receptors reported to be present in this vascular bed (Nichols & Hiley, 1985).

In order to characterize the presynaptic receptors involved in the inhibitory effect of quinpirole, we studied the influence of pretreatment with the selective DA_1-receptor antagonist SCH 23390 (Hilditch *et al.*, 1984; Goldberg *et al.*, 1984) and with the selective DA_2-receptor antagonist domperidone (Kohli *et al.*, 1983; Hilditch & Drew, 1985). SCH 23390, in a dose (50 $\mu g\,kg^{-1}$) reported to antagonize, on intravenous administration, the blood pressure lowering effect of fenoldopam in the rat (Sengupta & Lokhandwala, 1985), did not affect the action of quinpirole. In contrast, domperidone, in a dose that had no effect on vascular tone, antagonized the inhibitory action of quinpirole.

In order to verify the selectivity of these antagonists, we studied their effects, after administration of the same dosage, on the vasodilator action of bolus injections of the selective DA_1-receptor agonist fenoldopam after preconstriction of the superior mesenteric vascular bed by local infusion of vasopressin. Bolus injections of 30 $\mu g\,kg^{-1}$ and 100 $\mu g\,kg^{-1}$ of fenoldopam produced reproducible reductions in baseline perfusion pressure which were of similar magnitude. This is in agreement with the findings of Lappe *et al.* (1986) who observed maximal vasodilator effects in the mesenteric vascular bed after intravenous administration of 30 $\mu g\,kg^{-1}$ fenoldopam to conscious spontaneously hypertensive rats. Domperidone, in a dose that antagonized the effect of quinpirole on the pressor responses to electrical stimulation, had no influence on the vasodilator action of fenoldopam. In contrast, SCH 23390, in a dose that did not influence the effect of quinpirole, significantly antagonized the vasodilator action of fenoldopam. The latter was confirmed in the subsequent experiments during which fenoldopam was infused into the superior mesenteric vascular bed without preconstriction. These results suggest that quinpirole inhibits neurogenic vasoconstriction in the rat superior mesenteric vascular bed of the rat through stimulation of presynaptic DA_2-receptors. In contrast, fenoldopam

interacts with postsynaptic vasodilator DA_1-receptors.

The effect of local infusion of fenoldopam on the pressor responses to electrical stimulation and to exogenous noradrenaline is more complex. Fenoldopam significantly reduced the perfusion pressure response to local administration of noradrenaline and significantly potentiated the pressure response to electrical stimulation. The finding that the pressor response to local administration of angiotensin II was not reduced by fenoldopam indicates that its inhibitory effect on the pressure response to noradrenaline is not a non-specific effect on the increased cross-sectional area of the resistance arterioles. Therefore an interaction of fenoldopam with postsynaptic α-adrenoceptors has to be postulated. Fenoldopam has indeed recently been found to display α_1- and α_2-adrenoceptor antagonist activity (Ohlstein *et al.*, 1985; Nakamura *et al.*, 1986).

Local administration of clonidine and of the selective α_2-adrenoceptor agonist UK-14,304-18 (Cambridge, 1981) into the rat superior mesenteric vascular bed failed to induce vasoconstriction. This confirms the results of Nichols & Hiley (1985), who also found no evidence for the presence of postsynaptic α_2-adrenoceptors in the rat superior mesenteric vascular bed. Thus, it appears that the inhibitory effect of fenoldopam on the pressor response to noradrenaline is mediated through an antagonistic effect at postsynaptic α_1-adrenoceptors. This is corroborated by the finding that pressor responses induced by local administration of the selective α_1-adrenoceptor agonist phenylephrine were inhibited by fenoldopam to a similar degree to those induced by noradrenaline. This α_1-adrenoceptor blocking activity of fenoldopam is probably not involved in its vasodilator action; the latter is antagonized to a great extent by the selective DA_1-antagonist SCH 23390, indicating that this vasorelaxant effect is predominantly mediated by postsynaptic DA_1-receptors.

In spite of its inhibitory action on the pressor response to exogenous noradrenaline, fenoldopam markedly potentiated the pressor response to electrical stimulation. This can only be explained by an increased release of noradrenaline during electrical stimulation. Since the same is observed after local administration of the selective α_2-adrenoceptor antagonist, rauwolscine (Dupont *et al.*, 1986a) and as fenoldopam has been shown to be a relatively potent α_2-adrenoceptor blocker (Ohlstein *et al.*, 1985), it is possible that the latter effect of fenoldopam is mediated through an antagonistic action at presynaptic α_2-adrenoceptors. The fact that this effect was attenuated by pretreatment with rauwolscine, in a dose that itself potentiates the response to electrical stimulation (Dupont *et al.*, 1986a), favours this hypothesis.

In summary, these results show that quinpirole inhibits neurogenic vasoconstriction in the rat superior mesenteric vascular bed through stimulation of presynaptic inhibitory DA_2-receptors. Fenoldopam relaxes this vascular bed through stimulation of postsynaptic vasodilator DA_1-receptors; fenoldopam has probably also an antagonistic action at postsynaptic α_1-adrenoceptors and at presynaptic α_2-adrenoceptors in this vascular bed.

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