

# Vasodilator responses to dopamine in rat perfused mesentery are age-dependent

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**1** Dose-dependent vasodilator responses to dopamine, isoprenaline, noradrenaline, 3-isobutyl-1-methylxanthine (IBMX) and sodium nitroprusside were obtained in isolated perfused mesentery preparations, taken from reserpine-treated rats of different ages. The preparations were pretreated with phenoxybenzamine (1  $\mu\text{M}$ ) and perfused with physiological salt solution containing cocaine (10  $\mu\text{M}$ ), additional KCl (20 mM) and vasopressin (0.1  $\mu\text{M}$ ).

**2** Vasodilator responses to dopamine were abolished by the dopamine<sub>1</sub> (DA<sub>1</sub>)-selective antagonist SCH 23390 (10 nM) and those to isoprenaline by propranolol (1  $\mu\text{M}$ ), but the vasodilator responses to noradrenaline were abolished only when SCH 23390 and propranolol were used together. This indicated that dopamine was acting via DA<sub>1</sub>-receptors, isoprenaline via  $\beta$ -adrenoceptors and that noradrenaline could act via DA<sub>1</sub>-receptors and  $\beta$ -adrenoceptors in this preparation.

**3** Responses to all the vasodilator drugs decreased in magnitude between the ages of 1 and 2 months. Responses to dopamine declined further in 4 month-old rats and were negligible at 6 or 22–24 months of age. Responses to isoprenaline were well maintained up to 6 months of age, but were negligible at 22–24 months.

**4** It is concluded that, in the rat mesenteric vasculature, there is a non-specific decline in responses to vasodilator drugs during development (1 to 2 months). Subsequently there is a specific decline in DA<sub>1</sub>-receptor-mediated and  $\beta$ -adrenoceptor-mediated responses; the former are lost at an earlier age than the latter. This different time course suggests that age influences receptor numbers, or their coupling to adenylate cyclase, rather than a post-receptor event in the adenylate cyclase/cyclic AMP pathway.

## Introduction

It is well known that  $\beta$ -adrenoceptor-mediated relaxation of isolated arterial preparations declines as the age of the animal increases (Fleisch, 1981). In a previous study on rat isolated pulmonary artery and aorta, relaxant responses to several  $\beta$ -adrenoceptor agonists were reduced in aged rats, whereas responses to the adenylate cyclase activator, forskolin, and to the phosphodiesterase inhibitors, 3-isobutyl-1-methylxanthine (IBMX) and enprofylline, were unchanged (O'Donnell & Wanstall, 1986). These observations suggested that age influenced a  $\beta$ -adrenoceptor-linked event rather than a post-receptor event in the adenylate cyclase/adenosine 3':5'-cyclic monophosphate (cyclic AMP) pathway. The aim of the present study was to determine

whether vascular relaxation mediated by the vascular dopamine receptor (DA<sub>1</sub> subtype) was also age-dependent and, if so, to compare the time course of this age-dependence with that for  $\beta$ -adrenoceptors. The vascular DA<sub>1</sub>-receptor was chosen because, like the  $\beta$ -adrenoceptor, it is linked to adenylate cyclase (Amenta *et al.*, 1984; Alkadhi *et al.*, 1986).

The preparation used in the study was rat isolated perfused mesentery, because dopamine receptors have previously been identified in the mesenteric vasculature of this species (Nichols & Hiley, 1985; Dupont *et al.*, 1987). Preparations were taken from rats ranging in age from 1 month to 2 years enabling the effects both of maturation and of ageing to be assessed. A preliminary account of these data has been presented to the American Society for Pharmacology and Experimental Therapeutics (Wanstall &

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O'Donnell, 1988a) and to the Australasian Society of Clinical and Experimental Pharmacologists (Wanstall & O'Donnell, 1988b).

## Methods

### Perfused mesentery preparations

Male Wistar rats of the following ages and weights were used: 1 month (60–120 g), 2 months (200–310 g), 4 months (430–570 g), 6 months (570–640 g), and 22 to 24 months (340–550 g). The rats were pretreated with reserpine (1 mg kg<sup>-1</sup> i.p. 18–24 h before the experiment) and deprived of food overnight. On the day of the experiment they were anaesthetized with pentobarbitone (60 mg kg<sup>-1</sup> i.p.) and injected with heparin (250 i.u. i.p.). The abdominal cavity was opened, the superior mesenteric artery was cannulated, and the intestine and mesentery removed to a petri dish where the mesentery was carefully teased away from the intestine. The mesenteric vascular bed was then perfused, at 4.5 ml min<sup>-1</sup>, with physiological salt solution (PSS; 95% O<sub>2</sub>/5% CO<sub>2</sub>; 37°C; pH 7.4). The composition of the PSS was (mM): NaCl 118, KCl 5.9, CaCl<sub>2</sub> 1.5, MgSO<sub>4</sub> 0.72, NaHCO<sub>3</sub> 25, glucose 11.7, ascorbic acid 1.14, and it contained 10 μM cocaine to block neuronal uptake. In preliminary experiments it was shown that it was unnecessary to include an extraneuronal uptake inhibitor. Perfusion pressure was recorded with a Statham pressure transducer (P23AC) and displayed on a Grass polygraph.

Bolus injections of drugs, in volumes not greater than 15 μl, were given at 5 min intervals into the perfusing solution immediately proximal to the cannula, by Agla micrometer syringes.

### Experimental protocols

At the commencement of each experiment, constrictor responses to noradrenaline (10 and 30 nmol) were obtained. The preparations were then perfused with 1 μM phenoxybenzamine for 15 min to block α-adrenoceptors irreversibly. After reverting to phenoxybenzamine-free PSS, the above doses of noradrenaline were retested to check that the α-adrenoceptors had been successfully blocked.

The preparations were perfused thereafter with PSS containing 25.9 mM KCl (i.e. an increase of 20 mM, with a corresponding reduction in the NaCl concentration) plus 0.1 μM vasopressin, to elevate the perfusion pressure so that vasodilator responses could be recorded (Figure 1). In preliminary experiments, a sustained rise in perfusion pressure of suffi-

**Table 1** Resting perfusion pressure, and increases in perfusion pressure produced by 20 mM KCl plus 0.1 μM vasopressin, in isolated mesenteric preparations from rats of different ages

Age of rats (months)	n	Resting perfusion pressure (mmHg)	Increase in perfusion pressure (mmHg)
1	16	19 ± 1.6	49 ± 3.7
2	8	17 ± 2.4	38 ± 5.1
4	5	17 ± 2.0	35 ± 3.5
6	4	13 ± 3.4	35 ± 4.6
22–24	9	12 ± 1.2	83 ± 9.0*

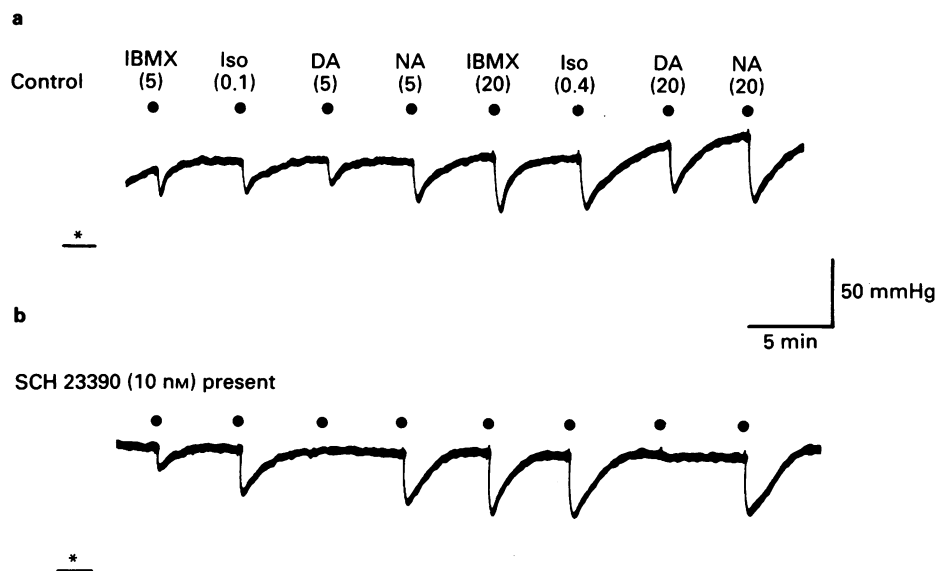
\* Value significantly greater than the value obtained in 2 month-old rats,  $P < 0.001$  (Student's *t* test).

cient magnitude was not obtained with either vasopressin alone or with KCl alone, unless KCl was used in concentrations greater than 40 mM. These higher concentrations of KCl markedly attenuated the vasodilator responses, as noted in other blood vessel preparations (O'Donnell & Wanstall, 1987).

The KCl/vasopressin perfusate caused an initial large increase in perfusion pressure (> 125 mmHg). The pressure subsequently declined, but remained at a level which was above the resting perfusion pressure (Table 1). There were minor fluctuations in the elevated perfusion pressure for the time required to complete an experiment (2–4 h from the commencement of the KCl/vasopressin perfusion). Therefore, for the values quoted in Table 1, the increase in perfusion pressure for any one preparation was taken as the mean of individual values determined immediately before the administration of each dose of vasodilator drug. A mean value ± s.e. was then calculated for the total number of preparations (Table 1). Vasodilator responses obtained during the first hour after the commencement of the KCl/vasopressin perfusion were erratic, and were not used.

Dose-response curves were obtained, on preparations from rats of different ages (*vide supra*), to the following dilator drugs: dopamine (5 to 150 nmol), noradrenaline (5 to 75 nmol), isoprenaline (0.1 to 1.5 nmol), IBMX (5 to 75 nmol) and sodium nitroprusside (0.5 to 4 nmol). Two to five of these drugs (3 to 4 doses per drug) were examined on any one preparation (with IBMX included in every experiment), and responses to the various drugs used on a particular preparation were alternated (Figure 1).

In addition, on preparations from 1 month-old rats, dose-response curves to dopamine, isoprenaline, noradrenaline and IBMX (3 doses per drug) were



**Figure 1** Responses of a rat isolated perfused mesentery preparation to isobutyl methylxanthine (IBMX), isoprenaline (Iso), dopamine (DA) and noradrenaline (NA). Doses, in nmol, are shown in parentheses. Data in the absence of any antagonist (control, a) and in the presence of 10 nM SCH 23390 (b) are shown. The preparation was treated with phenoxybenzamine ( $1 \mu\text{M}$ ) for 15 min and perfused with PSS containing cocaine ( $10 \mu\text{M}$ ), KCl ( $25.9 \text{ mM}$ ) and vasopressin ( $0.1 \mu\text{M}$ ). The level of the perfusion pressure before changing to the KCl/vasopressin perfusate is shown (\*).

obtained first in the absence of any antagonist, then in the presence of either propranolol ( $1 \mu\text{M}$ ), SCH 23390 ( $10 \text{ nM}$ ) or propranolol ( $1 \mu\text{M}$ ) plus SCH 23390 ( $10 \text{ nM}$ ). The antagonists were present in the perfusate 15 min before, and then during, the agonist dose-response curves, and all four agonists were examined on each preparation. Sometimes propranolol or SCH 23390 caused slight increases in perfusion pressure ( $5\text{--}20 \text{ mmHg}$ ), but these increases were short-lived ( $<10 \text{ min}$ ).

#### Analysis of data

Vasodilator responses were determined as decreases in perfusion pressure, and were expressed as a percentage of the KCl/vasopressin-induced increase in perfusion pressure measured immediately before the administration of each dose of vasodilator drug. Responses, when normalized as described above, were highly reproducible both within and between experiments, regardless of the magnitudes of the increases in pressure. Mean dose-response curves were obtained by calculating mean vasodilator responses (% , as defined above) to each dose of vasodilator drug used.

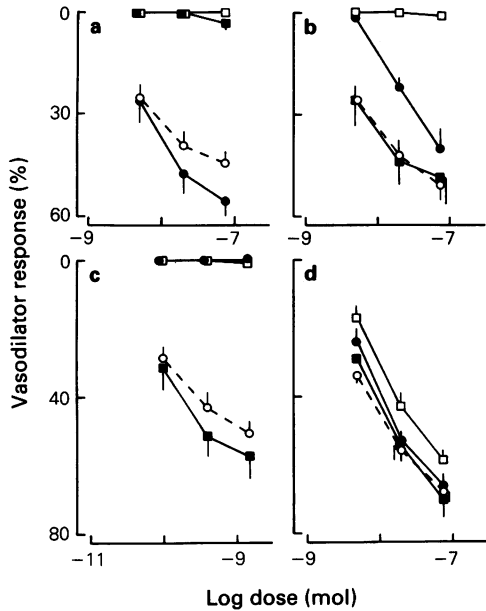
#### Drugs and solutions

Dopamine hydrochloride (3-hydroxy-tyramine, Sigma); heparin sodium (Weddel Pharmaceuticals); 3-isobutyl-1-methylxanthine (IBMX, Sigma); (-)-isoprenaline acid tartrate (Sigma); (-)-noradrenaline acid tartrate (Sigma); pentobarbitone sodium (Nembutal, Ceva Chemicals); propranolol hydrochloride (ICI); reserpine (Serpasil ampoules, Ciba); SCH 23390 ((R)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine, gift from Schering Corporation); sodium nitroprusside (Sigma).

Solutions of dopamine ( $100 \text{ mM}$ ), isoprenaline ( $10 \text{ mM}$ ) and noradrenaline ( $100 \text{ mM}$ ) were prepared in  $10 \text{ mM}$  HCl. IBMX ( $5 \text{ mM}$ ) was prepared in  $10 \text{ mM}$  NaOH, SCH 23390 ( $1 \text{ mM}$ ) in 90% ethanol, and propranolol ( $10 \text{ mM}$ ) and sodium nitroprusside ( $10 \text{ mM}$ ) in deionized water. Dilutions of drugs were prepared in PSS and kept on ice for the duration of the experiment.

#### Statistical analyses

Mean values are quoted together with their standard errors (s.e.). Data from rats aged 1, 4, 6 and 22–24 months have been compared with those from 2



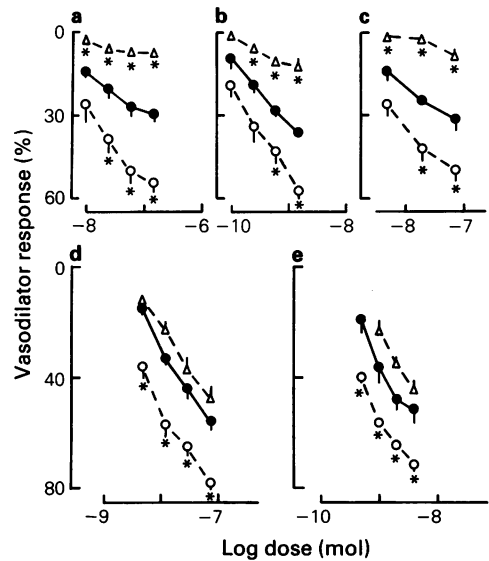
**Figure 2** Mean dose-response curves to (a) dopamine, (b) noradrenaline, (c) isoprenaline and (d) isobutyl methylxanthine (IBMX) on rat isolated perfused mesentery preparations. Data are shown in the absence of antagonist (○---○,  $n = 8$ ) and in the presence of  $1 \mu\text{M}$  propranolol (●—●,  $n = 4$ ),  $10 \text{ nM}$  SCH 23390 (■—■,  $n = 4$ ) or  $1 \mu\text{M}$  propranolol plus  $10 \text{ nM}$  SCH 23390 (□—□,  $n = 4-8$ ). Vasodilator responses (decreases in perfusion pressure) are expressed as a percentage of the increase in perfusion pressure induced by KCl ( $20 \text{ mM}$ ) plus vasopressin ( $0.1 \mu\text{M}$ ). The s.e. of mean responses are shown by the vertical lines, except when smaller than the symbols.

month-old rats by Student's *t* test (for values expressed as mmHg) or by Mann-Whitney U test (for values expressed as %).

## Results

### Establishment of receptor type(s) involved in vasodilator responses to agonists

Dopamine, isoprenaline and noradrenaline all gave dose-related vasodilator responses in rat perfused mesentery preparations. Responses to isoprenaline were abolished by propranolol ( $1 \mu\text{M}$ ) but were unaffected by SCH 23390 ( $10 \text{ nM}$ ), whereas those to dopamine were abolished by SCH 23390 but were unaffected by propranolol (Figures 1, 2a and c). Responses to noradrenaline were abolished only when propranolol and SCH 23390 were both present; SCH 23390 alone had no effect while pro-



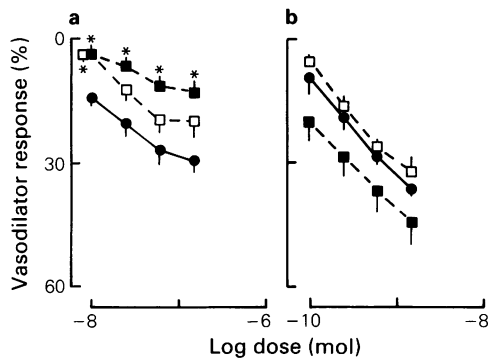
**Figure 3** Mean dose-response curves to (a) dopamine ( $n = 4-5$ ), (b) isoprenaline ( $n = 4-5$ ), (c) noradrenaline ( $n = 4-8$ ), (d) isobutyl methylxanthine (IBMX) ( $n = 8-9$ ) and (e) sodium nitroprusside ( $n = 4$ ) on isolated perfused mesentery preparations from rats aged 1 month (○---○), 2 months (●—●) or 22-24 months (△---△). Vasodilator responses (decreases in perfusion pressure) are expressed as a percentage of the increase in perfusion pressure induced by KCl ( $20 \text{ mM}$ ) plus vasopressin ( $0.1 \mu\text{M}$ ). The s.e. of mean responses are shown by the vertical lines, except when smaller than the symbols. Significant differences ( $P < 0.05$ , Mann-Whitney U test) between responses in 1 or 22-24 month-old rats and those in 2 month-old rats are indicated by an asterisk.

pranolol alone slightly attenuated the responses (Figure 2b). Neither propranolol nor SCH 23390, used singly or together, blocked the dilator responses to IBMX (Figures 1 and 2d), confirming that the action of these antagonists was specific for their respective receptors.

### Effects of age of rats on vasodilator responses

Mean dose-response curves for dopamine, isoprenaline, noradrenaline, IBMX and sodium nitroprusside in preparations from rats of different ages are shown in Figures 3 and 4. For each of these drugs, vasodilator responses in preparations from 2 month old rats were significantly smaller than those in preparations from 1 month old rats (Figure 3). Between 2 months and 2 years of age there was a further decline in responses to the catecholamines dopamine, isoprenaline and noradrenaline, but not to IBMX or sodium nitroprusside (Figure 3).

Dopamine (DA<sub>1</sub>-receptor agonist) and isoprena-



**Figure 4** Mean dose-response curves for (a) dopamine and (b) isoprenaline on isolated perfused mesentery preparations from rats aged 2 months (●—●,  $n = 4$ ), 4 months (□--□,  $n = 5$ ) and 6 months (■--■,  $n = 4$ ). Vasodilator responses (decreases in perfusion pressure) are expressed as a percentage of the increase in perfusion pressure induced by KCl (20 mM) plus vasopressin (0.1  $\mu$ M). The s.e. of mean responses are shown by the vertical lines, except when smaller than the symbols. Significant differences ( $P < 0.05$ , Mann-Whitney U test) between responses in 4 or 6 month-old rats and those in 2 month-old rats are indicated by an asterisk.

line ( $\beta$ -adrenoceptor agonist) were then examined on preparations from rats at two intermediate ages (4 and 6 months). Vasodilator responses to dopamine were reduced at 4 and 6 months of age, when compared with data from 2 month old rats (Figure 4a). There was no reduction in responses to isoprenaline (Figure 4b) on the same preparations.

## Discussion

This study has shown that, on rat perfused mesentery, dilator responses mediated by  $DA_1$ -receptors, as well as those mediated by  $\beta$ -adrenoceptors, declined in magnitude as the age of the rats increased. However the time course for this decline differed for these two receptor types. Other workers have shown a decrease in dopamine-stimulated adenylate cyclase activity in the central nervous system with increasing age (Cimino *et al.*, 1984; Nomura *et al.*, 1985), but an effect of age on dopamine receptor-mediated responses in the periphery has not previously been described.

In the vasculature, dopamine can cause contraction of vascular smooth muscle via  $\alpha$ -adrenoceptors (Hughes *et al.*, 1988), relaxation of vascular smooth muscle via  $\beta$ -adrenoceptors (Kohli, 1968; Cohen & Berkowitz, 1975) and/or  $DA_1$ -receptors (Schmidt & Imbs, 1980; Nichols & Hiley, 1985), inhibition of the neuronal release of noradrenaline via prejunctional

$DA_2$ -receptors (Cavero *et al.*, 1982) and, *in vivo*, inhibition of ganglionic transmission via ganglionic  $DA_1$ - and/or  $DA_2$ -receptors (Cavero *et al.*, 1982; Alkadhi *et al.*, 1986; Van der Niepen *et al.*, 1987). Under the experimental conditions used in the present study (reserpine pretreated rats; preparations treated with phenoxybenzamine and cocaine), it can be assumed that the vasodilator responses to dopamine represented only the direct effects of this amine on receptors in the vascular smooth muscle. These responses appeared to involve  $DA_1$ -receptors, but not  $\beta$ -adrenoceptors, since they were blocked by a low concentration (10 nM) of the selective  $DA_1$ -receptor antagonist, SCH 23390 (Hilditch *et al.*, 1984), but not by propranolol, in a concentration (1  $\mu$ M) which abolished responses to the  $\beta$ -adrenoceptor agonist, isoprenaline.

The studies with rats of different ages showed that this  $DA_1$ -receptor-mediated vasodilatation was age-dependent, in that it occurred only in the first few months of the life span of the rat. Responses to dopamine were most pronounced in 1 and 2 month-old rats, were reduced in 4 month-old rats, and by 6 months of age were negligible. Responses mediated by  $\beta$ -adrenoceptors in rat perfused mesentery were also age-dependent (confirming a preliminary observation of Fleisch & Spaethe, 1981) but, interestingly, the time course for the decline in responses to  $\beta$ -adrenoceptor-agonists differed from that for responses to dopamine. At 6 months of age, in preparations in which responses to dopamine were negligible, responses to isoprenaline were well maintained. Thus the decline in  $\beta$ -adrenoceptor-mediated responses did not occur until after the rats reached maturity. In this respect, the  $\beta$ -adrenoceptor-mechanisms of rat perfused mesentery resembled those of rat pulmonary artery (O'Donnell & Wanstall, 1984), rather than those of rat aorta, in which responses to isoprenaline are lost during maturation (Hyland *et al.*, 1987).

The small decline in vasodilator responses during development (between 1 and 2 months), seen for both dopamine receptor-mediated and  $\beta$ -adrenoceptor-mediated responses, appeared to be non-specific since it was also seen for the vasodilator responses to the phosphodiesterase inhibitor, IBMX, and to sodium nitroprusside. However, from two months onwards, the effect of age was specific for the receptor-mediated responses, since there was no further decline in responses to IBMX or sodium nitroprusside.

The different time courses for the decline in responses mediated by dopamine receptors and by  $\beta$ -adrenoceptors (*vide supra*) suggest that the influence of age is mainly at the receptor level i.e. age could affect receptor numbers and/or the coupling of the receptors to adenylate cyclase. Any effect of age

on a post-receptor event common to both receptor types, e.g. cyclic AMP-dependent protein kinase activation (Tsujimoto *et al.*, 1986), must be of minor importance or occur after the age of 6 months.

It was noted that the increase in perfusion pressure induced by the combination of 20 mM potassium and 0.1  $\mu$ M vasopressin was the same in all age groups except the aged (22–24 month-old) rats, where it was significantly greater. The reason for this increased pressor response in aged rats remains to be established. Nevertheless, the vasodilator responses (when expressed as a percentage of the increases in pressure, see Methods) did not appear to be related to the absolute magnitude of the induced pressor response in that: (i) the reduction in vasodilator responses in the aged rats occurred for only some of the vasodilator drugs *viz.* the catecholamines; (ii) responses to all the vasodilator drugs were reduced between 1 and 2 months of age, when there was no change in the increase in perfusion pressure; (iii) responses to dopamine were already negligible in 6 month-old rats, when there was no change in the increase in perfusion pressure.

An additional finding from these studies was that, in the dose range used, noradrenaline could act as a DA<sub>1</sub>-receptor agonist, as well as a  $\beta$ -adrenoceptor agonist, in rat mesentery. The results of previous studies with this amine on vascular dopamine receptors have been conflicting. Toda & Goldberg (1975) and Goldberg *et al.* (1978) concluded that noradrenaline was inactive on dopamine receptors in canine coronary arteries and renal vascular bed, whereas the data of Crooks & Martin (1979) and Toda (1976) indicated a possible action of noradrenaline on dopamine receptors in rabbit splenic artery and canine cerebral arteries, respectively. An action of noradrenaline on dopamine receptors in rat mesentery is supported by the observation that, in the presence of propranolol (1  $\mu$ M), the isomeric potency ratio for (–)-noradrenaline: (+)-noradrenaline was only 5:1 (compared with >50:1 on  $\beta$ -adrenoceptors) (Wanstall & O'Donnell, 1988a). A low isomeric potency ratio is predicted for activation

of dopamine receptors, but not  $\beta$ -adrenoceptors (Patil *et al.*, 1975).

Agonists for DA<sub>1</sub>-receptors have been proposed as a new class of antihypertensive agents (Cavero *et al.*, 1982), but one can only speculate as to the relevance of the present findings to the clinical use of these drugs. It could be argued that, if dopamine receptor-mediated vasodilatation is age-dependent in the renal vasculature (where the effects of dopamine receptor agonists are particularly important with respect to hypertension), and the age-dependence should extend to man, then the use of these drugs as antihypertensive agents may be most beneficial in younger patients. The above possibilities cannot be ascertained from the clinical trials carried out so far with dopamine and the DA<sub>1</sub>-receptor agonist, fenoldopam, since these have largely been carried out on relatively young patients (19–40 years, Hughes *et al.*, 1986; mean 30.6 years, Harvey *et al.*, 1985; mean 32 years, Mousdale *et al.*, 1988; mean 49 years, Caruana *et al.*, 1987) and the data have not been analysed with respect to age.

In summary, this study has shown that, in the rat mesenteric vasculature, the age-dependence of receptor-mediated vasodilatation is not restricted to  $\beta$ -adrenoceptors, but extends to at least one other receptor type linked to adenylate cyclase, namely DA<sub>1</sub>-receptors albeit with a different time course. Noradrenaline could act via dopamine receptors as well as  $\beta$ -adrenoceptors in this preparation. Since dopamine receptor-mediated responses were virtually lost by the age of 6 months, whereas those mediated by  $\beta$ -adrenoceptors were not, any involvement of DA<sub>1</sub>-receptors in the dilator responses to noradrenaline would presumably be confined to young rats.

This work was supported by a grant from the National Health and Medical Research Council of Australia and this aid is gratefully acknowledged. J.C.W. is an NH&MRC Research Scientist. We would like to thank Miss Kerry Anderson for her excellent technical assistance, and the Schering Corporation for a gift of SCH 23390.

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(Received February 6, 1989

Revised April 10, 1989

Accepted May 3, 1989)