J. Pharm. Pharmacol. 1985, 37: 110–115
Received June 28, 1984

Identification of adrenoceptors and dopamine receptors mediating vascular responses in the superior mesenteric arterial bed of the rat

A. J. NICHOLS AND C. R. HILEY*

Department of Pharmacology, University of Cambridge, Hills Road, Cambridge CB2 2QD, UK

The nature of the adrenoceptors and dopamine receptors mediating vascular responses in the in-situ blood perfused superior mesenteric arterial bed of the rat have been studied. α_1-Adrenoceptor agonists produced vasoconstriction but α_2-agonists had no significant effect on vascular resistance. The vasoconstrictor effects of noradrenaline were antagonized by low doses of prazosin (26 nmol kg^{-1} i.v.). Isoprenaline and salbutamol produced vasodilation when the vasculature was preconstricted with arginine vasopressin. The responses to isoprenaline were potently antagonized by propranolol (1·69 μmol kg^{-1} i.v.) and weakly but significantly reduced by practolol (3·75 μmol kg^{-1} i.v.) whereas the responses to salbutamol were unaffected by the same dose of practolol. After preconstriction of the vasculature and α-adrenoceptor blockade, dopamine and apomorphine produced dilator responses with both compounds producing the same maximal response and apomorphine being 1·8 times more potent than dopamine. The dopamine responses were present after the animals had been pithed and were resistant to spiperone (506 nmol kg^{-1} i.v.) but were antagonized by *cis*-α-flupenthixol (460 nmol kg^{-1} i.v.). These results suggest that this vascular bed possesses vasoconstrictor α_1- but not α_2-adrenoceptors, vasodilator β_1- and β_2-adrenoceptors and vasodilator dopamine receptors which appear similar to the D_1-type found centrally.

The splanchnic circulation receives approximately one fifth of the cardiac output and contains a similar proportion of the blood volume. Hence it has the potential to play a major role in the control and maintenance of systemic blood pressure. As a result of its position between the gastrointestinal tract and the liver, this vascular bed is also important in the control of absorption of drugs from the gut and their subsequent metabolism. Thus, any change in arteriolar resistance in this vascular bed can produce significant effects on systemic blood pressure and also the pharmacokinetics of drugs.

Most studies on the pharmacological properties and cardiovascular importance of adrenoceptors and dopamine receptors in the mesenteric vascular bed have been performed using the cat and dog with very few studies being made in the rat (see review by Granger et al 1980) despite the increasing use of this species in cardiovascular pharmacology. It is clearly important that results obtained in canine and feline studies are not extrapolated to other species and, subsequently, to man without verification, should that be possible.

The aim of the present investigation was to study the actions of adrenoceptor and dopamine receptor agonists and antagonists in the intact blood perfused superior mesenteric arterial bed of the rat in order to identify the receptors mediating the responses. The preparation used was similar to that described by Jackson & Campbell (1980) and was chosen since it contained all the elements of the vasculature unlike the isolated perfused mesenteric artery preparation such as used by Fiotakis & Pipili (1983).

* Correspondence.

METHODS

Mesenteric arterial perfusion. Male Wistar rats, 200–220 g (Bantin & Kingman, Hull), were starved for 16–20 h before operative procedures but allowed free access to water.

The animals were anaesthetized with sodium pentobarbitone (60 mg kg^{-1} i.p.; Sagatal, May & Baker) and anaesthesia was maintained by giving supplementary doses of anaesthetic, diluted to 10 mg ml^{-1} in saline, into a lateral tail vein. The trachea was cannulated to allow the animals to breathe room air spontaneously and the left jugular vein was cannulated for the injection of drugs and infusion of saline. The right common carotid artery was cannulated and connected to a Bell & Howell type 4-422-0001 pressure transducer which was used to record systemic arterial pressure on a Grass model 79D polygraph. The heart rate was derived from the arterial pressure wave by means of a Grass tachograph preamplifier. Rectal temperature was measured and maintained at 37 ± 1 °C by means of a homeothermic blanket (BioScience, Sheerness).

The animals were prepared for in-situ blood perfusion of the superior mesenteric arterial bed

essentially as described by Jackson & Campbell (1980) with the modifications we have described (Hiley et al 1985). Briefly, the animals were given heparin (1000 units kg^{-1} i.v.) 20 min after the abdominal aorta just distal to the left renal artery and the superior mesenteric artery had been prepared for cannulation. Cannulae were then inserted to allow perfusion of the superior mesenteric arterial bed with blood withdrawn from the aorta. Perfusion was carried out at a rate of 2 ml min^{-1} using a Harvard type 2903 servo-controlled peristaltic pump. Perfusion pressure was determined with the aid of another Bell & Howell transducer placed in the extracorporeal circuit shortly before the point at which the cannula entered the superior mesenteric artery. The preparation was allowed to stabilize for 20 min before a 120 μl carotid arterial blood sample was taken for analysis of pO_2, pCO_2 and pH in a Corning 166 micro blood gas analyser and determination of haematocrit. At the end of the experiment a second arterial blood sample was taken for analysis and any animals which showed severe deterioration were excluded from the study since it has been shown that α-adrenoceptor responsiveness can be altered by changes in pCO_2 and pH (Wiegman et al 1979; Grant et al 1984).

When it was desired to examine the effects of drugs in the absence of sympathetic vasomotor tone, animals were pithed 20 min before heparin was given, by passing a 16 g needle through the orbit into the spinal canal. The animals were maintained by connecting a respiration pump (Miniature Ideal Pump, BioScience) to the tracheal cannula.

Agonist drugs were injected into the extracorporeal circuit after the perfusion pump in volumes of 50 μl or less. Antagonists were injected i.v. and the effects studied after 10 min had elapsed. Control injections of the vehicle for both agonists and antagonists were made in all experiments.

Investigations of vasoconstrictor responses were carried out at normal vascular tone (perfusion pressure of 20–25 mm Hg) but for vasodilator responses the vascular tone was increased by the infusion of arginine vasopressin (0·2 units ml^{-1}; Pitressin, Parke Davis) into the perfusion circuit at rates of less than 0·1 ml min^{-1}. The initial rate of vasopressin administration was 0·5 units h^{-1} which was usually sufficient to give a rise in perfusion pressure of 20–25 mm Hg, but the rate was adjusted, if necessary, to give increases of this magnitude.

Drugs. (−)-Noradrenaline bitartrate (Koch-Light), dopamine hydrochloride (Koch-Light), (−)-phenylephrine hydrochloride (Sigma) and (−)-isoprenaline bitartrate (Sigma) were made up in 0·9% NaCl (w/v) containing 1 mg ml^{-1} ascorbic acid. Amidephrine mesylate (Mead Johnson), xylazine (Bayer UK), clonidine (Boehringer Ingelheim), salbutamol sulphate (Glaxo Research), phentolamine mesylate (CIBA-Geigy) and propranolol hydrochloride (ICI Pharmaceuticals) were used in saline. Solutions of prazosin (Pfizer), spiperone (spiroperidol, Janssen), practolol (ICI Pharmaceuticals), *cis*-α-flupenthixol (Lundbeck) and haloperidol (Searle) were made up at a concentration of 1 mg ml^{-1} in saline containing 0·04 M lactic acid (BDH). Apomorphine hydrochloride (Sigma) was made up immediately before use in warm saline, rapidly cooled and protected from light. Bromocriptine mesylate (Sigma) was made up in 100% ethanol which was subsequently diluted to 30% with saline. All solutions were made fresh daily.

Statistics. Control log dose/response curves to agonists were obtained in each animal before the administration of antagonists and all values are given as the mean ± standard error of the mean. Comparisons of agonists were also carried out by determining log dose/response curves for each pair of drugs in the same animals. Means were compared for statistical significance by Student's paired *t*-test.

RESULTS

Noradrenaline produced dose-related increases in perfusion pressure over the range $1·57 \times 10^{-10}$ to $1·57 \times 10^{-7}$ mol with an increase in pressure at the highest dose of 189 ± 10 mmHg (n = 10). Very seldom were systemic effects observed at doses less than $1·57 \times 10^{-8}$ mol. Phenylephrine also produced dose-related increases in perfusion pressure but had a molar ratio of 4·4 ± 0·6 (n = 7) relative to noradrenaline. The responses to noradrenaline were stable and reproducible for up to 2 h and all experiments were completed within this time. Responses to phenylephrine frequently showed marked diminution with time. Amidephrine ($1·47 \times 10^{-9}$ to $2·94 \times 10^{-8}$ mol) was used in two animals and it gave dose-related increases in perfusion pressure of a much longer duration (up to 10 min) and had marked systemic effects. When doses of amidephrine were given less than 20 min apart the systemic effects cumulated and, therefore, the number of doses given was limited to 5 or 6 per experiment. Consequently, only responses to noradrenaline were studied further.

Prazosin, at a dose of 26 nmol kg^{-1}, produced a

parallel rightward shift of the noradrenaline log dose/response curve with a dose ratio of 22·3 ± 6·2 (n = 5) and reduced resting perfusion pressure by 7 ± 1 mmHg. It may be seen from Fig. 1 that increasing the dose of prazosin to 131 nmol kg^{-1} produced a further shift in the curve and it should be noted that a dose of 2·61 μmol kg^{-1} abolished the responses to noradrenaline given at up to 1·57 × 10^{-7} mol. These two higher doses of prazosin did not further reduce resting perfusion pressure.

Xylazine produced small and inconsistent pressor responses in which an increase in perfusion pressure of less than 10 mmHg was produced by 4·54 × 10^{-6} mol, a dose approximately 3000 times greater than that of noradrenaline required to increase perfusion pressure by 50 mmHg. However, this high dose of xylazine produced a fall in mean arterial pressure of 34 ± 4 mmHg and a bradycardia of 92 ± 6 beats min^{-1} (n = 7). Experiments in pithed rats showed xylazine to be about 1000 times less potent than noradrenaline at increasing blood pressure by 50 mmHg, the responses to xylazine being unaffected by 26 nmol kg^{-1} prazosin. Clonidine (2·17 × 10^{-7} mol) also gave similar inconsistent increases in perfusion pressure of approximately 10 mmHg. This dose was sufficient to reduce systemic blood pressure by 50 ± 6 mmHg and lower heart rate by 120 ± 10 beats min^{-1} (n = 4). The mesenteric responses to xylazine and clonidine were not modified by pithing the rats before perfusion was begun. Repetition of the high doses of xylazine and clonidine elicited either very much smaller or no response and thus it was not possible to determine whether or not they were sensitive to blockade by prazosin.

After resting perfusion pressure had been elevated by an infusion of arginine vasopressin into the extracorporeal circuit, isoprenaline gave consistent dose-related reductions in perfusion pressure without, over the range 1·38 × 10^{-11} to 2·77 × 10^{-10} mol, any systemic effects. Fig. 2A shows that the responses were antagonized by 1·69 μmol kg^{-1} propranolol, given i.v., with a dose ratio of 25·4 ± 3·0

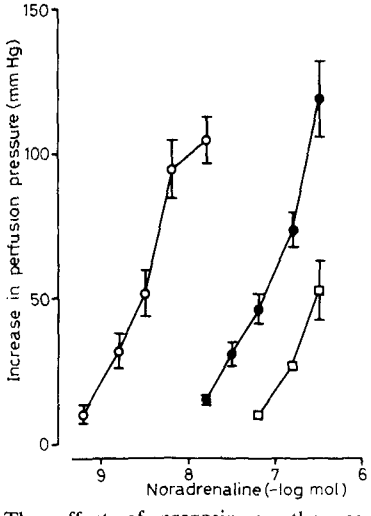

FIG. 1. The effect of prazosin on the responses to noradrenaline on the in-situ rat mesentery at resting tone. (○) Control reponses, (●) responses after 26 nmol kg^{-1} i.v. prazosin and (□) responses after 131 nmol kg^{-1} prazosin. The points are the mean ± s.e.m. of 9 observations.

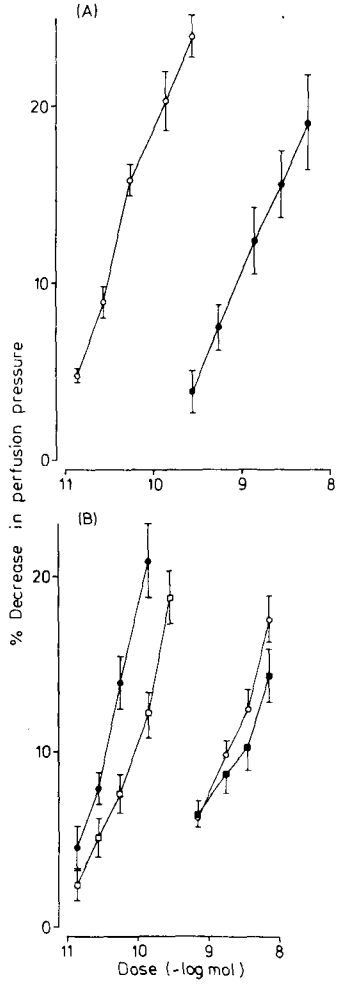

FIG. 2. The effect of β-adrenoceptor agonists and antagonists on the α-receptor blocked mesentery with elevated tone. (A) Responses to isoprenaline in the absence (○) and the presence of propranolol, 1·69 μmol kg^{-1} i.v. (●) shown as the mean ± s.e.m. (n = 7). (B) Control responses to isoprenaline (●) and to salbutamol (○) and responses to isoprenaline (□) and to salbutamol (■) after 3·75 μmol kg^{-1} i.v. practolol. The points are the mean and the error bars represent 1 s.e.m. (n = 8).

(n = 7). Salbutamol also reduced perfusion pressure in a dose-dependent manner (Fig. 2B) but was approximately 150 times less potent than isoprenaline. Practolol (3·75 μmol kg^{-1}) significantly reduced the responses to isoprenaline at each dose used with a mean dose ratio of 2·28 ± 0·30 (n = 8) whereas the responses to salbutamol were not significantly affected. Experiments in intact anaesthetized rats showed that this dose of practolol produced a dose ratio of 13 ± 2 (n = 4) against the effects of isoprenaline on heart rate but did not significantly affect the reductions in diastolic blood pressure given by the agonist.

With the vascular bed at normal tone (20–25 mmHg perfusion pressure), dopamine (2·64 × 10^{-8} to 2·64 × 10^{-6} mol) increased perfusion pressure in a dose-related manner with maximum recorded increases of approximately 30 mmHg. These pressor responses were sometimes followed by depressor responses of up to 5 mmHg which became consistent if the vasculature was preconstricted with vasopressin. α-Adrenoceptor blockade with 3·55 μmol kg^{-1} phentolamine abolished the pressor response to these doses of dopamine and slightly enhanced the depression of perfusion pressure.

Smaller doses of dopamine, in the range 1·06 × 10^{-10} to 1·06 × 10^{-8} mol, consistently lowered perfusion pressure after blockade of α-adrenoceptors with phentolamine (3·55 μmol kg^{-1}) and preconstriction of the vascular bed with vasopressin (Fig. 3A). Apomorphine had a similar effect and was 1·8 ± 0·3 (n = 5) times more potent than dopamine. There was no significant difference in the slopes of the linear parts of the log dose/response curves for the two agonists and the maximum responses, when obtained, were also not different. The magnitude of the responses to both agonists remained constant during the period of the experiments. Similar results were obtained in pithed rats and neither drug produced any systemic haemodynamic effects over the range of doses used. The dilator responses to dopamine were affected neither by β-adrenoceptor blockade with 1·69 μmol kg^{-1} propranolol (n = 6) nor by spiperone (506 nmol kg^{-1}; n = 6). They were antagonized by 2·66 μmol kg^{-1} haloperidol with a mean dose ratio of 4·84 ± 0·82 (n = 6). However, *cis*-α-flupenthixol, at a dose of 460 nmol kg^{-1}, significantly antagonized the dopamine vasodilator responses as shown in Fig. 3B with a dose ratio of 10·7 ± 2·1 (n = 6).

Bromocriptine did not produce any dilator response in the preconstricted vasculature at doses up to 6·66 × 10^{-8} mol although the vehicle alone (30% ethanol in saline) did produce very small

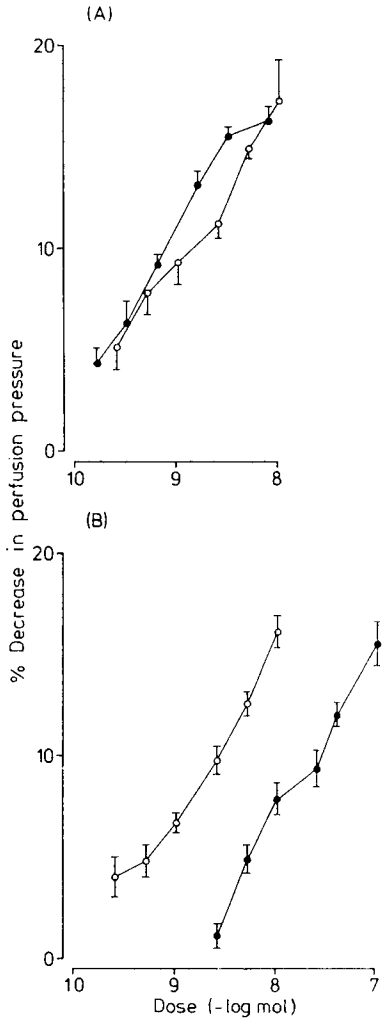

FIG. 3. The effects of dopamine receptor agonists and antagonists on the rat mesentery after α-adrenoceptor blockade and elevation of tone. (A) Dilator responses to dopamine (○) and to apomorphine (●) shown as the mean of 5 observations. The error bars show 1 s.e.m. (B) Control responses to dopamine (○) and responses to dopamine after *cis*-α-flupenthixol, 460 nmol kg^{-1} i.v. (●) shown as the mean ± 1 s.e.m. (n = 6).

decreases in perfusion pressure which tended to lessen on repetition. On occasions, 3·33 to 6·66 × 10^{-8} mol bromocriptine actually increased perfusion pressure by up to 10 mmHg.

DISCUSSION

In this preparation we have shown that noradrenaline, a relatively non-selective α-adrenoceptor agonist, and phenylephrine, an agonist selective for α_1-adrenoceptors, produce vasoconstrictor

responses which are thus mediated at least in part by the α_1-subtype. Moreover, amidephrine which is a more selective but less potent α_1-agonist than phenylephrine (McGrath 1982), also produces vasoconstrictor responses. However, the postjunctional α-adrenoceptors which mediate vasoconstrictor responses in pithed rats have been shown to include both the α_1- and α_2-subtypes (McGrath 1982) but the evidence obtained in the present study suggests that only α_1-adrenoceptors are present in the superior mesenteric vascular bed.

Thus, prazosin, a selective α_1-antagonist (Cambridge et al 1977), at a low dose of 26 nmol kg^{-1} produced a 22-fold shift of the noradrenaline log dose/response curve and 131 nmol kg^{-1} produced a further shift. In pithed rats, Drew & Whiting (1979) showed that more than 261 nmol kg^{-1} prazosin was required to give a dose ratio of 10 when it was used to antagonize the systemic pressor response to noradrenaline, and Kobinger & Pichler (1981) reported the dose required to be 1·44 μmol kg^{-1} whereas the amounts required to produce similar shifts in the responses to phenylephrine were given as 34 and 157 nmol kg^{-1} respectively in the same studies. Therefore the potency of prazosin against noradrenaline in the superior mesenteric arterial bed is very similar to that against α_1-responses and much greater than against combined α_1- and α_2-responses in pithed rats.

The view that only α_1-adrenoceptors are present is supported by our observations with xylazine, a relatively selective α_2-agonist and clonidine, a more potent but less selective α_2-agonist (Docherty & McGrath 1980). Neither drug gave reproducible pressor responses even at doses which, although given into the superior mesenteric artery, activated central α_2-receptors to give systemic hypotension and bradycardia. Also, when sympathetic influence was removed by pithing, neither compound produced significant vasoconstrictor responses in the mesenteric vascular bed, showing that the lack of response in the intact preparations was not due to the inhibition of sympathetic tone. However, the same doses of xylazine given i.v. to pithed rats did produce marked α_2-mediated pressor responses which were not affected by 26 nmol kg^{-1} prazosin. There is not, therefore, a significant population of postjunctional, vasoconstrictor α_2-adrenoceptors in the superior mesenteric vascular bed. This is in contrast to the same vascular bed in the dog in which there has been shown to be both subtypes of α-adrenoceptor (Shepperson et al 1982) but is in agreement with other studies which have demonstrated the presence of only α_1-adrenoceptors in the in-vitro perfused mesentery of the rat (Hepburn & Bentley 1982; Fiotakis & Pipili 1983; MacPherson et al 1984). The present results show that the absence of α_2-receptors reported in these latter studies was not the result of the excision from the preparation of the vessels contained in the intestinal wall.

Borkowski & Porter (1983) have shown that there are β-adrenoceptors mediating vasodilation in the mesenteric bed of the rat and their observations are supported by ours. The non-selective β-adrenoceptor agonist isoprenaline produced vasodilator responses in the blood perfused superior mesenteric bed which were blocked by the non-selective antagonist propranolol. At least some of these responses may be of the β_2-type since salbutamol, a selective β_2-agonist (Brittain et al 1968) also produced dilator responses. β_1-Adrenoceptors which mediate relaxation of vascular smooth muscle in the rat have been reported to occur in the jugular vein (Cohen & Wiley 1978), uterine arterioles (Koo 1981) and pulmonary artery (O'Donnell & Wanstall 1981). Thus there may also be β_1-adrenoceptors in the superior mesenteric arterial vasculature which are activated by isoprenaline. This possibility is supported by the effects of the antagonist practolol which is reported to be selective for β_1-adrenoceptors at the dose of 3·75 μmol kg^{-1} which was used in this study (Campbell & Parratt 1983). This amount of practolol produced a small but significant antagonism of the responses to isoprenaline but had no effect on those elicited with salbutamol. Therefore, it seems likely that this vascular bed contains not only β_2- but also β_1-adrenoceptors mediating vasodilatation.

Studies of the mesenteric vasculature in the cat (Richardson 1974) and the dog (Taira et al 1977) in-vivo have not produced evidence to suggest the presence of both types of β-adrenoceptor in these species. Thus the rat may differ from the cat and the dog in its population of both α- and β-adrenoceptors.

Dopamine and apomorphine both produce vasodilatation in previously constricted, α-adrenoceptor blocked preparations with apomorphine being slightly more potent than dopamine. This is similar to the dog in which apomorphine is approximately 15 times less potent than dopamine and is also a full agonist but is insensitive to blockade by *cis*-α-flupenthixol (Hilditch & Drew 1984). Apomorphine is a partial agonist on central D_1-dopamine receptors (Kebabian & Calne 1979) but in our preparation and in the dog it is a full agonist. It is possible that an apomorphine-sensitive receptor similar to that in the dog mesenteric vascular bed also occurs in the rat.

An alternative would be that there are no dopamine receptors and that the vasodilatation observed was mediated by β-adrenoceptors. This possibility may be ruled out since blockade of β-receptors with propranolol had no effect on the responses to dopamine. It is also unlikely that the responses to either agonist are the result of presynaptic actions since the vasodilatation was still present after α-blockade and pithing. Such mechanisms of action have been proposed for the canine hindlimb (Bogaert & De Schaepdryver 1967) and renal (Lokhandwala & Jandhyala 1979) vascular beds.

In order to determine whether or not the dopamine receptors mediating vasodilatation could be classified in a similar manner to those in the central nervous system, their sensitivity was assessed towards spiperone and haloperidol, which are relatively selective for the D_2-receptor (Seeman 1980), and also towards *cis*-α-flupenthixol, a relatively non-selective dopamine receptor antagonist (Seeman 1980). At the dose used in this study, 506 nmol kg^{-1} i.v., spiperone labels striatal dopamine receptors of the D_2-subtype (Laduron et al 1978) and produces an almost complete inhibition of spontaneous locomotor activity (Leysen & Niemegeers 1981). However, we did not observe any attenuation of the dopamine responses despite a probable complete block of D_2-receptors. Haloperidol was only a weak antagonist of the dopamine responses at the high dose used. Therefore, it is unlikely that receptors similar to the central D_2-type are involved in this response. Non-selective dopamine receptor blockade with *cis*-α-flupenthixol caused a significant antagonism of the dopamine responses. Thus it is likely that the receptor mediating the dilator response to dopamine in this preparation is somewhat similar to the D_1-receptor found centrally. There does not appear to be a receptor mediating vasodilatation similar to the central D_2-receptors in the rat mesenteric vascular bed since there was no response to bromocriptine, a D_2-receptor agonist (Kebabian & Calne 1979). These results are generally compatible with those reported for the mesenteric arterial beds of the dog (Hilditch & Drew 1984) and the cat (Lippton et al 1981) in which dopamine was found to act on dopamine receptors resembling the D_1-subtype.

In conclusion, the in-situ blood perfused superior mesenteric arterial bed of the rat has been shown to possess vasoconstrictor α_1- but not α_2-adrenoceptors, vasodilator β-adrenoceptors probably of both β_1- and β_2-subtypes and vasodilator dopamine receptors resembling the D_1-type found centrally.

Acknowledgements

A. J. N. thanks the Medical Research Council for a Research Studentship. This work was supported by the British Heart Foundation. We are indebted to the pharmaceutical companies named for their kind gifts of drugs.

REFERENCES

Bogaert, M. G., De Schaepdryver, A. F. (1967) Arch. Int. Pharmacodyn. 166: 203–207

Brittain, R. T., Farmer, J. B., Jack, D., Martin, L. E., Simpson, N. T. (1968) Nature 219: 862–863

Borkowski, K. R., Porter, M. (1983) Br. J. Pharmacol. 80: 508P

Cambridge, D., Davy, M. J., Massingham, R. (1977) Br. J. Pharmacol. 59: 514P–515P

Campbell, C. A., Parratt, J. R. (1983) Ibid. 79: 939–946

Cohen, M. L., Wiley, K. S. (1978) Life Sci. 23: 1997–2006

Docherty, J. R., McGrath, J. C. (1980) Naunyn Schmiedeberg's Arch. Pharmacol. 312: 107–116

Drew, G. M., Whiting, S. B. (1979) Br. J. Pharmacol. 67: 207–215

Fiotakis, D., Pipili, E. (1983) Ibid. 79: 234P

Granger, D. N., Richardson, P. D. I., Kvietys, P. R., Mortillaro, N. A. (1980) Gastroenterology 78: 837–863

Grant, T. L., McGrath, J. C., O'Brien, J. W. (1984) Br. J. Pharmacol. 82: 216P

Hepburn, E. R., Bentley, G. A. (1982) J. Cardiovasc. Pharmacol. 4: 297–302

Hilditch, A., Drew, G. M. (1984) J. Cardiovasc. Pharmacol. 6: 460–469

Hiley, C. R., Nichols, A. J., Wilson, A. C. (1985) J. Pharm. Pharmacol. March issue

Jackson, E. K., Campbell, W. B. (1980) Eur. J. Pharmacol. 66: 217–224

Kebabian, J. W., Calne, D. B. (1979) Nature (Lond.) 277: 93–96

Kobinger, W., Pichler, L. (1981) Eur. J. Pharmacol. 73: 313–321

Koo, A. (1981) Br. J. Pharmacol. 74: 941P–942P

Laduron, P. M., Janssen, P. F. M., Leysen, J. E. (1978) Biochem. Pharmacol. 27: 317–321

Leysen, J. E., Niemegeers, C. J. E. (1981) Br. J. Pharmacol. 72: 487P–488P

Lippton, H. L., Meyer, R. L., Parey, S. E., Hyman, A. L., Kadowitz, P. J. (1981) Arch. Int. Pharmacodyn. 251: 136–149

Lokhandwala, M. F., Jandhyala, B. S. (1979) J. Pharm. Exp. Ther. 210: 120–126

MacPherson, G. A., Coupar, I. M., Taylor, D. A. (1984) J. Pharm. Pharmacol. 36: 338–340

McGrath, J. C. (1982) Biochem. Pharmacol. 31: 467–484

O'Donnell, S. R., Wanstall, J. C. (1981) Br. J. Pharmacol. 74: 547–552

Richardson, P. D. I. (1974) Ibid. 52: 481–498

Seeman, P. (1980) Pharmacol. Rev. 32: 229–313

Shepperson, N. B., Duval, N., Langer, S. Z. (1982) Eur. J. Pharmacol. 81: 627–635

Taira, N., Yabuuchi, Y., Yamashita, S. (1977) Br. J. Pharmacol. 59: 577–583

Wiegman, D. L., Miller, F. N., Harris, P. D. (1979) Eur. J. Pharmacol. 57: 307–315