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Effects of α-adrenoceptor agonists on cardiac output and its regional distribution in the pithed rat

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1 Cardiac output, its distribution and tissue blood flows were determined with tracer microspheres in pithed rats during pressor responses elicited by either α_1-adrenoceptor agonists (cirazoline, phenylephrine) or α_2-adrenoceptor agonists (xylaxine, B-HT 933). Two doses were used for each of cirazoline and B-HT 933 and phenylephrine was investigated in the presence of propranolol (3 mg kg^{-1}). The rats were pithed under halothane anaesthesia.

2 Cardiac output was increased by xylazine, the higher dose of B-HT 933 and phenylephrine. Heart rate was increased by phenylephrine and the higher doses of both cirazoline and B-HT 933. Stroke volume was greater in those groups given xylazine, phenylephrine and the higher dose of B-HT 933 but was decreased in those animals given the higher dose of cirazoline.

3 Both α_2-adrenoceptor agonists increased the number of microspheres trapped in the lungs and the proportion of the cardiac output passing through the hepatic artery but decreased that flowing through the spleen and gastrointestinal tract. The higher dose of B-HT 933 also decreased the fraction of cardiac output flowing to the kidneys but kidney blood flow was maintained as a result of the increased cardiac output. Also, this treatment reduced blood flow in the epididimal fat pads.

4 Both α_1-adrenoceptor agonists increased the fraction of cardiac output received by the coronary vasculature but the only other effect on distribution common to these agents was an increase in the percentage of the cardiac output passing to the hepatic artery. Cirazoline decreased the proportion of cardiac output distributed to the gastrointestinal tract and spleen but the total fraction of cardiac output passing to the hepatosplanchnic region was maintained as a result of the increase to the hepatic artery.

5 Cirazoline markedly reduced the proportion of the cardiac output received by the kidneys and absolute flow in these organs was only 1.4% of control after the higher dose of this agonist but flow at the lower dose was maintained by the higher cardiac output.

6 It is concluded that there is a significant contribution to the pressor responses elicited by α-agonists resulting from an α-adrenoceptor-mediated increase in cardiac output that may result from greater heart rates or stroke volumes. Also, there is a differential distribution of α-receptor subtypes throughout the vasculature which is especially noticeable in the kidneys.

Introduction

It is now well established that α-adrenoceptors of both α_1- and α_2-subtypes exist postjunctionally in the vasculature of the rat and other species (McGrath, 1982). It is also accepted that stimulation of either population of receptors can bring about vasoconstriction (Digges & Summers, 1983; Yamamoto *et al.*, 1984). The systemic pressor responses mediated by these receptors have been widely described (Drew & Whiting, 1979; Docherty & McGrath, 1980; Flavahan *et al.*, 1985) but few investigations have attempted to elucidate the sites at which these agents cause the individual vasoconstrictions which produce the increased peripheral resistance leading to the development of the pressor response.

However, studies carried out on isolated organ preparations have shown that activation of α_1- and α_2-adrenoceptor subtypes summates to mediate vasoconstriction in a variety of organs including the

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hind limbs of the rat (Yamamoto *et al.*, 1984), cat and dog (Gardiner & Peters, 1982); the cat lung (Hyman & Kadowitz, 1985) and rabbit kidney (Hesse & Johns, 1984; see also Ruffolo *et al.*, 1981; Timmermans & Van Zwieten, 1981). Meanwhile, other investigators have demonstrated a vasoconstriction primarily mediated by α_1-adrenoceptors in the kidneys of the rat (Schmitz *et al.*, 1981), dog (Horn *et al.*, 1982; Wolff *et al.*, 1984) and cat (Drew & Whiting, 1979) while vasoconstriction of the canine coronary vessels appears to be mediated selectively by α_2-adrenoceptors (Kakihana *et al.*, 1985).

Of the range of vascular beds thus studied, uncertainty still exists about the precise nature of the receptors mediating vasoconstriction of the rat superior mesenteric arterial bed. Considerable evidence from studies of the isolated vasculature suggests that the vasoconstriction seen here is mediated entirely by means of α_1-adrenoceptors (Eikenburg, 1984; Yamamoto *et al.*, 1984; Hogestatt & Andersson, 1984; Agrawal & Daniel, 1985: Nichols & Hiley, 1985). Despite this, there is evidence for a mixed population of pharmacologically functional α_1- and α_2-adrenoceptors in this tissue; decreases in cardiac output distribution to this bed occur after administration of either methoxamine (an α_1-adrenoceptor agonist) or UK 14,304 (an α_2-adrenoceptor agonist) to the pithed rat (Hicks & Waldron, 1983; Waldron & Hicks, 1985).

Thus, there is much evidence for the existence of post-junctional adrenoceptors of both subtypes in several vascular beds but little is known about the relative contributions of these discrete vasoconstrictions or changes in cardiac output to the establishment of a pressor response. In view of this lack of knowledge of the co-ordinated haemodynamic responses resulting from the vasoconstrictor and other cardiovascular actions of α-adrenoceptor agonists and the uncertainty that surrounds the role of α_2-adrenoceptors in the rat superior mesenteric arterial vascular bed, we have carried out a study, using radioactive tracer microspheres in the pithed rat, of the haemodynamic changes brought about by the administration of selective α_1- and α_2-adrenoceptor agonists.

Methods

Determination of cardiac output and its distribution

Male Wistar rats weighing 220–250 g (Bantin & Kingman Ltd, Hull) were pithed under halothane anaesthesia by passing a 16 gauge steel needle through the orbit, through the foramen magnum and down into the spinal canal. Immediately after pithing, the rats were respired with air through a tracheal cannula by means of a respiratory pump (BioScience, Sheerness, U.K.) operating at 54 cycles min^{-1} with a volume of 20 ml kg^{-1}.

The right femoral artery was cannulated and connected to a Bell & Howell type 4-422-0001 transducer to measure systemic arterial blood pressure which was recorded on a Grass 79D polygraph. The left femoral artery was also cannulated and connected to a Braun Perfusor IV pump for the withdrawal of blood. With the aid of pressure monitoring, a cannula was passed down the right common carotid artery into the left ventricle. Drugs were administered through a cannula placed in the left external jugular vein and, when a sustained response had been obtained, 60,000–80,000 ^{113}Sn labelled microspheres (15 ± 3 μm; NEN, Boston, MA), suspended by ultrasonication in 0.3 ml saline containing 0.01% Tween 80, were injected into the ventricle over 20 s. Blood was withdrawn from the left femoral artery at a rate of 0.5 ml min^{-1} during and for 70 s after the microsphere injection. The circulation was stopped with an air embolism and the organs dissected out, weighed and placed in scintillation vials for counting in a Packard Autogamma 500 γ-counter. The number of counts in the blood sample was also determined and cardiac output and tissue blood flow were determined as described by McDevitt & Nies (1976).

Blood gases and pH were sampled in 19 animals (including 3 from each experimental group) by removing a sample of 125 μl from a femoral artery cannula 5 min before the administration of agonist or saline and 3 min after the microsphere injection. These samples were then placed into a Corning 166 micro blood gas analyser. The values obtained before and after the microsphere injection respectively were pH 7.41 ± 0.02 and 7.42 ± 0.02; PO_2 78 ± 1 and 78 ± 2 mmHg; PCO_2 33 ± 2 and 32 ± 2 mmHg. There were no significant differences between any of these values when assessed with Student's paired *t* test.

Drugs

All drugs were administered in saline in the form of a bolus injection of 0.5 ml followed by an infusion of 0.1 ml min^{-1}; the details are as follows. Cirazoline (Synthelabo, Paris): lower dose, 0.25 μg bolus, infusion 1 μg min^{-1}; higher dose, 10 μg bolus followed by 2 μg min^{-1}. Phenylephrine (Sigma, Poole, Dorset): 5 μg bolus, 0.4 μg min^{-1} infusion. Xylazine (Bayer U.K., Newbury, Berkshire): 0.5 mg bolus, 100 μg min^{-1} infusion. B-HT 933 (2-amino-6-ethyl-5,6,7,8-tetrahydro-4H-oxazolo-[4,5-d]-azepine dihydrochloride) Boehringer Ingelheim U.K., Bracknell, Berkshire): lower dose, 0.25 mg bolus, 100 μg min^{-1} infusion; higher dose, 1 mg bolus, 100 μg min^{-1} infusion. Control animals received a bolus injection and infusion of physiological saline. Animals which were given phenylephrine were pretreated with

Table 1 Effects of α-adrenoceptor agonists on blood pressure, cardiac index and heart rate in pithed rats

Group	*Diastolic pressure* (mmHg)	*Mean arterial pressure* (mmHg)	*Heart rate* (beats min^{-1})	*Cardiac index* (ml min^{-1} 100g b wt^{-1})	*Stroke volume* (ml)	*TPR* (mmHg ml^{-1} min 100g b wt)
Saline	46 ± 3	52 ± 4	234 ± 8			
	−1 ± 1	−1 ± 2	−4 ± 1	10.6 ± 1.4	0.121 ± 0.012	5.2 ± 0.5
Xylazine	47 ± 2	53 ± 2	249 ± 6			
	47 ± 5***	56 ± 6***	−5 ± 3	14.2 ± 0.7	0.156 ± 0.007*	7.0 ± 0.3
B-HT 933	44 ± 2	50 ± 3	234 ± 6			
(low dose)	52 ± 3***	59 ± 3***	0 ± 0	13.6 ± 1.7	0.162 ± 0.022	8.7 ± 0.9**
B-HT933	44 ± 2	50 ± 3	254 ± 9			
(high dose)	56 ± 4***	63 ± 5***	19 ± 6***	18.5 ± 0.9***	0.165 ± 0.015*	6.2 ± 0.5
Cirazoline	43 ± 2	48 ± 2	251 ± 12			
(low dose)	38 ± 3***	43 ± 3***	3 ± 3	12.0 ± 0.9	0.134 ± 0.009	8.0 ± 0.5*
Cirazoline	48 ± 2	55 ± 3	222 ± 8			
(high dose)	85 ± 5***	103 ± 5***	19 ± 6***	8.6 ± 1.1	0.082 ± 0.011*	21.7 ± 4.1***
Phenylephrine	48 ± 2	57 ± 2	237 ± 15			
and	60 ± 4†††	71 ± 5†††	34 ± 8†††	16.8 ± 1.9†††	0.166 ± 0.012††	8.8 ± 1.6†††
propranolol						
Saline and	44 ± 2	51 ± 3	246 ± 11			
propranolol	−1 ± 1	−2 ± 1	−4 ± 3	10.3 ± 0.6	0.120 ± 0.008	4.9 ± 0.2

Where two values are given in a column, the upper values are those immediately before administration of the agonist or saline. The lower value is the change between the basal value and that at the midpoint of the microsphere injection. Cardiac index is the absolute value determined by the tracer microsphere method. TPR is the total peripheral resistance calculated from cardiac index and mean arterial pressure during the microsphere injection, assuming central venous pressure to be zero. Significant differences between the saline control and the experimental groups were determined by analysis of variance: $*P<0.05$; $**P<0.01$; $***P<0.001$. Significant differences between the group given saline after propranolol and those given phenylephrine after propranolol were also determined by analysis of variance: $††P<0.01$; $†††P<0.001$. There were no significant differences between the two groups given saline. For all groups, $n = 8$.

propranolol (ICI Pharmaceuticals, Macclesfield, Cheshire), at a dose of 3 mg kg^{-1} i.v., 5 min before starting the administration of phenylephrine; these animals were compared with a control group similarly pretreated with propranolol.

The specificity of the agonists was assessed by administering to groups of 3 rats either (for α_1-adrenoceptor agonists) prazosin (50 μg kg^{-1}; Pfizer, Sandwich, Kent) or (for α_2-adrenoceptor agonists) yohimbine (0.75 mg kg^{-1}; Sigma) 5 min before the start of one of the above infusions. When an equilibrium response had been obtained, the second antagonist was administered in order to determine the extent to which the residual response was dependent on cross-stimulation of receptors.

Statistical comparison

All results are given as the mean ± s.e.mean and the statistical significance between groups was assessed by one way, random block, analysis of variance followed by the least significant difference procedure (Snedecor & Cochran, 1980).

Table 2 Percentage of the cardiac output distributed to the various organs after administration of α-adrenoceptor agonists

Group	*Heart*	*Lungs*	*Kidneys*	*Testes*	*Epididimides*
Saline	6.1 ± 1.8	3.7 ± 0.8	14.6 ± 1.5	1.7 ± 0.1	0.23 ± 0.03
Xylazine	7.8 ± 0.6	7.4 ± 1.4**	12.2 ± 0.8	1.3 ± 0.2	0.24 ± 0.02
B-HT 933 (low dose)	6.6 ± 0.9	8.7 ± 1.0**	12.0 ± 0.6	1.0 ± 0.1	0.25 ± 0.03
B-HT 933 (high dose)	7.2 ± 0.6	10.2 ± 1.0***	10.1 ± 0.4*	1.1 ± 0.2	0.23 ± 0.02
Cirazoline (low dose)	9.9 ± 1.5*	2.5 ± 0.3	9.9 ± 1.4***	1.7 ± 0.2	0.24 ± 0.02
Cirazoline (high dose)	31.6 ± 2.9***	4.5 ± 1.0	0.3 ± 0.1***	2.0 ± 0.4	0.24 ± 0.06
Phenylephrine and propranolol	7.4 ± 0.6†	7.1 ± 0.6††	11.8 ± 0.9	1.3 ± 0.1	0.26 ± 0.02
Saline and propranolol	3.9 ± 0.4	3.1 ± 0.6	11.3 ± 0.7*	1.5 ± 0.1	0.24 ± 0.02

	Liver	*Spleen*	*G.I.T.*	*Total hepatosplanchnic*
Saline	4.8 ± 0.5	0.96 ± 0.11	20.0 ± 1.0	26.8 ± 1.1
Xylazine	11.6 ± 0.6***	0.51 ± 0.05***	16.1 ± 0.6**	28.2 ± 0.5
B-HT 933 (low dose)	8.0 ± 0.8*	0.59 ± 0.07***	16.9 ± 0.6**	25.5 ± 0.8
B-HT 933 (high dose)	10.2 ± 0.6***	0.60 ± 0.06***	17.3 ± 0.9*	26.9 ± 1.4
Cirazoline (low dose)	12.6 ± 1.4***	0.45 ± 0.05***	17.1 ± 0.9*	30.8 ± 1.4
Cirazoline (high dose)	6.3 ± 2.0	0.09 ± 0.02***	11.0 ± 1.1***	17.4 ± 0.3***
Phenylephrine and propranolol	8.6 ± 1.1††	0.72 ± 0.06	20.3 ± 0.8	29.8 ± 1.4
Saline and propranolol	4.1 ± 0.3	0.80 ± 0.04	21.7 ± 0.9	26.6 ± 1.0

G.I.T. = gastrointestinal tract

Significant differences between the saline control and the experimental groups were determined by analysis of variance: *$P<0.05$; **$P<0.01$; ***$P<0.001$.

Significant differences between the group given saline after propranolol and those given phenylephrine after propranolol were also determined by analysis of variance: †$P<0.05$; ††$P<0.01$. There were no significant differences between the two groups given saline. For all groups, $n = 8$.

Results

There were no significant differences between the groups in the pre-infusion values of diastolic blood pressure, mean arterial pressure or heart rate. Table 1 shows that all the agonists produced significant increases in both diastolic and mean arterial pressure. The changes brought about by the two doses of B-HT 933 were not significantly different. However, it may be seen from the heart rate data that the higher doses of both B-HT 933 and cirazoline increased heart rate but not to the same extent as the single dose of phenylephrine used. In the experiments to confirm agonist specifity it was found that after 50 $\mu g\,kg^{-1}$ prazosin the increases in diastolic pressure and heart rate were, for phenylephrine, 3.3 ± 0.3 mmHg and 5 ± 3 beats min^{-1}; for the lower dose of cirazoline, 4.3 ± 5.5 mmHg and 3 ± 8 beats min^{-1}; and, for the higher dose of cirazoline, 27.6 ± 2.4 mmHg and 2 ± 13 beats min^{-1} ($n = 3$ for each measurement). Yohimbine at 0.75 $mg\,kg^{-1}$ had no effect on the residual response with the higher dose of cirazoline. After 0.75 $mg\,kg^{-1}$ yohimbine, the changes in diastolic blood pressure and heart rate were, for the lower dose of B-HT 933, 8.0 ± 0.6 mmHg and -3 ± 3 beats min^{-1}; for the higher dose of B-HT 933, 13.0 ± 0.6 mmHg and -7 ± 9 beats min^{-1}; and, for xylazine, 23.8 ± 4.4 mmHg and -6 ± 6 beats min^{-1}. Subsequent administration of prazosin had no effect on the responses to B-HT 933 but reduced the residual response to xylazine by 3.7 ± 2.6 mmHg with no effect on heart rate ($n = 3$ for each group).

It may be seen from Table 1 that, in the absence of antagonists, cardiac index was significantly greater in three groups of animals, that is those given either xylazine (in which it was 34% higher than in the control animals), the higher dose of B-HT 933 (74% higher than control) or phenylephrine (58% greater than control). The mean cardiac index in those animals given the lower dose of B-HT 933 was greater than the control by 28% but the difference was not significant. Table 1 also shows that the stroke volume was significantly greater than control in those animals given xylazine, the higher dose of B-HT 933 and phenylephrine. It is noteworthy that the high dose of cirazoline produced a significant reduction in stroke volume.

Table 2 shows that the two α_2-adrenoceptor agonists had no effect on the percentage of cardiac output passing to the heart itself. However, both compounds apparently increased the fraction of cardiac output passing to the lungs. Both xylazine and B-HT 933 increased the proportion of the cardiac output flowing directly to the liver through the hepatic artery but decreased that passing to the spleen and gastrointestinal tract.

It can also be seen from Table 2 that, apart from a decrease in the fraction passing to the kidneys, propranolol (3 $mg\,kg^{-1}$, i.v.) had no significant effect on the pattern of cardiac output distribution. Both α_1-adrenoceptor agonists, cirazoline and phenylephrine, significantly increased the percentage of the cardiac output received by the heart; in the case of the higher dose of cirazoline, nearly one-third of the microspheres were trapped in the heart and this organ experienced a five fold increase in the fraction of cardiac output it received. Apart from their effects on distribution to the cardiac vascular bed, the only other change brought about in common by the two α_1-adrenoceptor agonists was an increase in the fraction of the cardiac output passing through the hepatic artery; however, it must be pointed out that the increase with cirazoline was not dose-related and did not occur with the higher dose. Cirazoline at both doses reduced the fraction of cardiac output received by the gastrointestinal tract and the spleen in a dose-dependent manner, with the changes in the spleen being the most pronounced. However, because of the increase in hepatic arterial supply the total hepato-splanchnic share of the cardiac output was not significantly different from control in the group treated with the lower dose of cirazoline. The most notable effect of cirazoline was the reduction in the distribution of the cardiac output to the kidneys; with the lower dose there was a reduction to 68% of the control value but with the higher dose the decrease was to 2%.

Table 3 gives details of tissue blood flows and it can be seen that, despite the lower fraction of cardiac output going to the kidneys with the higher dose of B-HT 933, the greater cardiac index resulted in renal blood flow being unchanged. The increased cardiac output also resulted in gastrointestinal blood flow being significantly greater than the control despite the reduction of 2.7% in the proportion of cardiac output passing to this vascular bed. The 74% greater cardiac index also accounts for the increased flow through the epididimides (increased by 69%) and the pectoral skeletal muscle (increased by 72%). The higher dose of B-HT 933 significantly reduced blood flow in the epididimal fat pad and, although it did not reach significance, the mean flow with the lower dose was nearly 50% less than that in the saline control.

Although both doses of cirazoline reduced the fraction of cardiac output passing to the kidneys, it may be seen in Table 3 that renal blood flow was not significantly affected by the lower dose of cirazoline (because the cardiac index was elevated) but the higher dose reduced flow to 1.4% of that observed in the saline control group. Splenic blood flow was only 10% of the control during the pressor response induced by this higher dose of cirazoline and flow in the gastrointestinal tract was decreased by 50%. The only significant decrease in organ blood flow resulting from

Table 3 Organ blood flow (ml min^{-1} g^{-1} organ wt) after administration of α-adrenoceptor agonists

Group	*Heart*	*Lungs*	*Kidneys*	*Testes*	*Epididimides*
Saline	2.31 ± 0.98	0.96 ± 0.23	1.99 ± 0.38	0.16 ± 0.01	0.084 ± 0.008
Xylazine	3.29 ± 0.34	2.29 ± 0.52**	2.15 ± 0.09	0.19 ± 0.01	0.122 ± 0.016
B-HT 933 (low dose)	2.62 ± 0.33	2.51 ± 0.39**	2.06 ± 0.18	0.14 ± 0.02	0.090 ± 0.017
B-HT 933 (high dose)	3.72 ± 0.40	3.90 ± 0.45***	2.18 ± 0.10	0.21 ± 0.05	0.142 ± 0.021**
Cirazoline (low dose)	3.46 ± 0.50	0.66 ± 0.09	1.65 ± 0.25	0.19 ± 0.03	0.088 ± 0.008
Cirazoline (high dose)	7.36 ± 0.73***	0.88 ± 0.30	0.03 ± 0.013***	0.16 ± 0.03	0.06 ± 0.017
Phenylephrine and propranolol	3.98 ± 0.51†††	2.93 ± 0.36†††	2.68 ± 0.23††	0.22 ± 0.02	0.124 ± 0.007†
Saline and propranolol	1.16 ± 0.14	0.69 ± 0.14	1.68 ± 0.10	0.16 ± 0.01	0.075 ± 0.005

	Fat	*Muscle*	*Skin*	*Liver*	*Spleen*	*G.I.T.*
Saline	0.026 ± 0.003	0.053 ± 0.007	0.062 ± 0.006	0.19 ± 0.006	0.31 ± 0.06	0.38 ± 0.06
Xylazine	0.019 ± 0.003	0.079 ± 0.009	0.056 ± 0.004	0.41 ± 0.03*	0.22 ± 0.02	0.46 ± 0.01
B-HT 933 (low dose)	0.014 ± 0.004	0.075 ± 0.020	0.057 ± 0.014	0.39 ± 0.12*	0.27 ± 0.05	0.48 ± 0.07
B-HT 933 (high dose)	0.009 ± 0.002*	0.091 ± 0.010*	0.109 ± 0.017*	0.43 ± 0.04**	0.38 ± 0.06	0.64 ± 0.06***
Cirazoline (low dose)	0.018 ± 0.002	0.063 ± 0.007	0.68 ± 0.008	0.39 ± 0.05*	0.18 ± 0.03*	0.46 ± 0.03
Cirazoline (high dose)	0.015 ± 0.011	0.032 ± 0.006	0.024 ± 0.006	0.14 ± 0.05	0.03 ± 0.01***	0.19 ± 0.03***
Phenylephrine and propranolol	0.017 ± 0.002	0.075 ± 0.009	0.124 ± 0.038†	0.39 ± 0.06†	0.52 ± 0.06†††	0.77 ± 0.04††
Saline and propranolol	0.017 ± 0.003	0.069 ± 0.008	0.068 ± 0.007	0.10 ± 0.01	0.27 ± 0.03	0.47 ± 0.03

G.I.T. = gastrointestinal tract.
Significant differences between the saline control and the experimental groups were determined by analysis of variance: *$P<0.05$; **$P<0.01$; ***$P<0.001$. Significant differences between the group given saline after propranolol and those given phenylephrine after propranolol were also determined by analysis of variance: †$P<0.05$; ††$P<0.01$; †††$P<0.001$. There were no significant differences between the two groups given saline. For all groups, $n = 8$.

the administration of the lower dose of cirazoline was of 42% occurring in the spleen. This dose of cirazoline increased hepatic arterial blood flow by 105%. Although neither dose of cirazoline significantly affected skin blood flow, phenylephrine increased it by 82% and much of this can be accounted for by the 63% increase in cardiac output. Phenylephrine also increased blood flow in the heart (43%), kidneys (60%), epididimides (65%), hepatic artery (290%), spleen (93%) and the gastrointestinal tract (64%). As with xylazine and B-HT 933, phenylephrine significantly increased the fraction of the injected microspheres trapped in the lungs, in this case by 325%.

Discussion

The α_2-adrenoceptor agonists, xylazine and B-HT 933, both increased cardiac output as did one of the α_1-adrenoceptor agonists, phenylephrine. Gerold & Haeusler (1983) have also found increases in cardiac output in pithed rats with both α-$_1$ and α_2-adrenoceptor agonists. We found that with xylazine, the increase in the stroke volume (29%) was very similar to the increase in cardiac index (34%) as would be expected since heart rate was unchanged by this agent. For the other two compounds, the 36% increases in stroke volume accounted for just under half the 74% increase in cardiac index with the high dose of B-HT 933 and approximately two-thirds of 58% increase in cardiac index given by phenylephrine. Both α_2-adrenoceptor agonists also apparently increased the fraction of cardiac output distributed to the lungs, although it should be noted that the microspheres trapped here include not only those passing through the bronchial arteries but also those passing through peripheral arteriovenous shunts and becoming trapped after returning through the venous system and the right heart. Hence the increased proportion of the injected microspheres trapped in the lungs may represent an increase in shunting. Xylazine and B-HT 933 also increased the fraction of cardiac output flowing through the hepatic artery. These haemodynamic changes, common to both α_2-adrenoceptor agonists, appear to be dose-dependent for B-HT 933.

The two α_2-adrenoceptor agonists also reduced the proportion of the cardiac output delivered to the spleen and gastrointestinal tract. However, the increased hepatic arterial supply compensated for the reduction in the proportion of the cardiac output passing through the hepatic portal vein such that the total fraction of the cardiac output received by the liver was unchanged. These observations are in good agreement with those of Waldron & Hicks (1985) who showed that the α_2-adrenoceptor agonist, UK 14,304, reduced the fractions of the cardiac output reaching only the mesenteric vascular bed and the tail.

It is not easy to reconcile these observations with *in situ* and *in vitro* studies on the perfused mesenteric bed in which α_2-adrenoceptor agonists have been found to be without vasoconstrictor action, even at very high doses. Fiotakis & Pipili (1983) reported that UK 14,304 had no vasoconstrictor effect in isolated tissue perfused with physiological salt solution. Also, we have found only a very small and inconsistent vasoconstriction with xylazine (in doses up to 1 mg), clonidine or B-HT 933 in the *in situ* blood perfused mesenteric bed in intact anaesthetized or pithed rats (Nichols, 1985; Nichols & Hiley, 1985). Redistribution of cardiac output away from a bed without vasoconstriction in that region could only occur if other parts of the vasculature experienced vasodilatation. This does not seem a likely explanation with the agents studied here since calculation of organ resistances, using the mean arterial pressure as inflow pressure and zero as venous outflow pressure (which might not be justified in view of the changes occurring in stroke volume), showed that all the significant changes took the form of increases in resistance with the exception of the increase in coronary flow with the higher dose of cirazoline (see below) and the increases in hepatic arterial flow with xylazine and the lower dose of cirazoline where vascular resistance fell from 397 ± 66 (control) to 247 ± 12 (xylazine) and 260 ± 26 (cirazoline) mmHg min ml^{-1}g tissue. Thus, there do appear to be α_2-adrenoceptors mediating an increase in resistance to flow in the mesenteric vascular bed and it would seem that these are not detectable under the perfusion conditions hitherto used on this bed.

The α_1-adrenoceptor agonists used in this study, cirazoline and phenylephrine, did not produce parallel responses. The kidneys, spleen, gastrointestinal tract and the total hepatosplanchnic arcade were sensitive to vasoconstriction mediated only by cirazoline. With the exception that Hicks & Waldron (1983) also found that methoxamine constricted the skeletal muscle vascular beds, there is general agreement between the studies with these two agonists. It was also apparent that all of the changes in blood flow observed here in response to cirazoline administration were dose-dependent. However, it must be noted that the higher dose of cirazoline caused a generalized vasoconstriction in most of the tissues studied and particularly to the kidneys, where blood flow was reduced to 2% of that in saline-treated controls. In the same group of animals it was also found that 33% of the injected microspheres were trapped in the heart. This may represent sparing of cardiac vasculature by α_1-adrenoceptors and, indeed, calculated cardiac resistance fell from 44.3 (control) to 23.3 mmHg min ml^{-1} g tissue in these rats. In view of the large increase in total peripheral resistance underlying the pressor response seen with the larger dose of cirazoline it is interesting to note that the stroke volume was significantly lower

than in the control animals. However, the trapping of so great a proportion of the injected microspheres in the heart coupled with a massive increase in peripheral resistance is likely to distort the haemodynamic effects and caution must be observed in interpreting these results.

In contrast to the widespread vasoconstriction caused by cirazoline, phenylephrine failed to bring about reductions in the fraction of the cardiac output distributed to any of the tissues studied. The only similarities in the actions of phenylephrine and cirazoline appear to be increases in the proportions of the cardiac output received by the heart and the liver. In their study, Waldron & Hicks (1985) found methoxamine, at a dose giving a mean pressor response of 68 mmHg, caused an increase in the proportion of the cardiac output going to the heart and a decrease in that received by the kidneys, mesentery, skeletal muscle and the spleen. The responses to this agonist thus resemble more closely those we found for cirazoline than for phenylephrine.

It is not clear why there is this lack of parallelism between the effects of the two α_1-adrenoceptor agonists studied here, especially since the lower dose of cirazoline gave rise to a pressor response lower than that given by the single dose of phenylephrine used. Part of the difference might be due to β-adrenoceptor stimulation by phenylephrine underlying the increase in cardiac output observed with the phenethylamine agonist. However, propranolol was present in those animals to which phenylephrine was given at a dose of $3\,mg\,kg^{-1}$ and we found no change in heart rate in animals given phenylephrine after both propranolol and prazosin. Flavahan & McGrath (1981a) reported that $1\,mg\,kg^{-1}$ propranolol abolished the depressor response unmasked by the administration of prazosin to pithed rats and antagonized the increase in heart rate. In a later paper they reported that $1\,mg\,kg^{-1}$ propranolol had no effect on the heart rate responses to phenylephrine at doses equal to, or less than, $10\,\mu g\,kg^{-1}$. Thus it is likely that the responses we obtained to phenylephrine were independent of its potential for activating β-adrenoceptors.

Not only phenylephrine but also cirazoline produced tachycardia in our experiments and α_1-adrenoceptors mediating such effects have been reported (Flavahan & McGrath, 1981b; McGrath *et al.*, 1982). However, α_2-mediated increases in heart rate have not been reported previously and it is possible that the chronotropic responses we observed to the higher dose of B-HT 933 were the consequence of it activating both types of α-receptors with only α_1-adrenoceptors participating in this response. Against this, it should be noted that the higher doses of both B-HT 933 and cirazoline gave identical increases in heart rate, but changes in stroke volume were opposite for the two drugs and the α_2-adrenoceptor agonist gave a much smaller pressor effect. Also, in our pilot experiments to verify agonist specificity, there was no change in heart rate with B-HT 933 in rats previously given yohimbine. Thus, in view of this specificity of B-HT 933 for α_2-adrenoceptors (van Meel *et al.*, 1981), it is unlikely that the chronotropic response is due to activation of α_1-adrenoceptors on the myocardium.

When considering blood flow to various organs it is noticeable that the most widespread changes are seen in response to phenylephrine administration. Except for the heart, the hepatic artery and the spleen, the changes were similar in magnitude to the 58% in cardiac output and thus it is likely that, apart from these flows, most of these increases may be simply attributed to the enhanced cardiac output. Similar considerations apply to the blood flow responses to the higher dose of B-HT 933, a treatment which resulted in an increase in cardiac index (of 74%) somewhat greater than that produced by phenylephrine. There were increases in flow through the epididimides (69%), skeletal muscle (72%), skin (76%), liver (126%) and gastrointestinal tract (68%) and a decrease in flow, of 65%, to the epididimal fat pad. Hence, most of the increases in organ blood flow are a product of the increased cardiac output seen with these drugs. For both, this is a product of a positive chronotropic effect and an increase in stroke volume and, although α_1-adrenoceptors mediating an increase in contractility have been described (Wagner & Brodde, 1978; Schumann, 1980), no such effect has been described for α_2-adrenoceptors. The increases in stroke volume with xylazine and B-HT 933 could result from increased venous return to the heart due to venoconstriction and this explanation has been advanced previously for the increase in cardiac output observed in pithed rat and cats by Kalkman *et al.* (1974) after administration of the α_2-adrenoceptor agonist, B-HT 920. It is interesting to note that these authors did not find any changes in heart rate with either α_1- or α_2-adrenoceptor agonists; their animals were pithed under hexobarbitone anaesthesia and we have found that pithing rats under pentobarbitone anaesthesia blunts the cardiovascular responses obtained relative to those seen in animals pithed under halothane anaesthesia (Hiley, Reid & Thomas, unpublished observations).

In conclusion, we have shown that the patterns of vasoconstriction brought about by α_1- and α_2-adrenoceptor agonists differ in the pithed rat although we found marked differences between the two α_1-adrenoceptor agonists studied. We have also shown that the pressor effects of these compounds are, at least in part, mediated by increases in cardiac output, be it a consequence of chronotropic effects, increases in stroke volume or a combination of both. Thus stimulation of α-adrenoceptor subtypes by systemic administration brings about a complex series of

changes affecting both vascular smooth and cardiac muscle. Further study of this area is essential before a comprehensive profile of the haemodynamic effects of these drugs can be presented.

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