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Postjunctional α_2-adrenoceptors mediate venoconstriction in the hindquarters circulation of anaesthetized cats

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1 A study was made of the subtypes of postjunctional α-adrenoceptors which mediate arterial and venous constriction in the hindquarters circulation of anaesthetized cats, as measured by changes in perfusion pressure and vena cava blood flow, respectively.

2 It was found that, while noradrenaline caused constriction in both the arterial and venous compartments, methoxamine caused only arterial constriction. Clonidine and B-HT 920 also caused arterial and venous constriction although autodesensitization to both drugs occurred.

3 The ability of either prazosin or yohimbine to antagonize the constrictor effects of noradrenaline was also examined. It was found that the combination of both antagonist drugs abolished both the arterial and venous constrictor effects of noradrenaline. However, there was a greater prazosin-resistant response to noradrenaline in the venous compartment as compared with the arterial effects of noradrenaline. Yohimbine caused approximately equal reductions in the effect of noradrenaline in both arteries and veins, which was greater than that observed with prazosin.

4 These results suggest that, in the cat hindquarters, both α_1- and α_2-adrenoceptors are present in the arterial circulation, whereas there are mainly α_2-adrenoceptors in the venous circulation.

Introduction

It is now generally accepted that both α_1- and α_2-adrenoceptors which mediate vasoconstriction are located at postjunctional sites in the vasculature (McGrath, 1982; Langer & Hicks, 1984).

Most of the *in vivo* data used to classify α-adrenoceptors have been derived from experiments that examine changes in either systemic blood pressure in intact or pithed animals, or perfusion pressure of a particular vascular bed. Blood pressure measurements indicate changes predominantly in resistance and cardiac function, the latter of which could be due to either intrinsic cardiac factors (e.g. heart rate, contractility) or changes in venous return (Gerold & Haeusler, 1983). However, the relative contribution of each component cannot be readily determined, although the measurement of perfusion pressure (under constant flow) will indicate changes in only resistance function. In contrast, there are very few studies on the α-adrenoceptor subtypes in the venous circulation. This is surprising in light of *in vitro* results which have suggested that the venous smooth muscle contains a greater proportion of α_2- compared to α_1-adrenoceptors than does arterial smooth muscle (De Mey & Vanhoutte, 1981; Vanhoutte, 1982; Glusa & Markwardt, 1983). Moreover, recent studies, also *in vitro*, using electrophysiological methods have claimed that only α_2-adrenoceptors are present in guinea-pig renal (Makita, 1983), dog mesenteric (Suzuki, 1984) and rat saphenous (Cheung, 1985) veins, and the neuroeffector transmission in the human saphenous vein is mediated predominantly by postjunctional α_2-adrenoceptors (Docherty & Hyland, 1985).

We have recently developed a technique for measuring the venous return from the hindquarters of anaesthetized animals in which the input of blood to this region was under control of a constant-flow perfusion pump, and was thus independent of drug-induced changes in cardiac output. In this way, both arterial and venous function can be recorded simultaneously (Bentley *et al.*, 1986). It was shown that intra-arterial injections of both noradrenaline and adrenaline into the cat hindquarters elicited marked arterial and venous constriction, as seen by increases in perfusion pressure and vena cava blood flow (VCBF), respectively (Bentley *et al.*, 1986). Therefore, the aim

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of the present study was to investigate the subtypes of α-adrenoceptors in the venous circulation of the cat hindquarters.

Methods

Cat autoperfused hindquarters preparation

The measurements of arterial and venous haemodynamics in the cat hindquarters were performed as described previously (Bentley *et al.*, 1986). Briefly, cats of either sex weighing 3.5–5.0 kg were anaesthetized with 80 mg kg^{-1} α-chloralose given intravenously following induction with halothane and nitrous oxide. Arterial blood pressure was recorded from the right brachial artery using a Statham P23AC pressure transducer and the right brachial vein was cannulated for intravenous (i.v.) injections.

The abdominal aorta was cannulated just proximal to the inferior mesenteric artery and blood was passed through a constant-flow perfusion pump and back again to the aorta just distal to the first cannulation. Perfusion pressure was measured by a Statham P23AC pressure transducer connected to the perfusion circuit close to its re-entry into the aorta, and was set equal to the systemic blood pressure by adjusting the blood flow to the perfused region. Heparin was given intravenously (500 units kg^{-1}). In addition, VCBF was recorded by placing an electromagnetic flow probe (1.5 mm i.d., Biotronex) around the inferior vena cava, and mean blood flow measured on a blood flow meter (Biotronex). After placement of the flow probe, all variables, displayed on a Grass polygraph (Model 7D) were similar to initial levels.

All visible arterial and venous side-branches in the exposed region were ligated. Thus, since the arterial inflow was controlled entirely by the pump, changes in perfusion pressure reflected changes in peripheral resistance while changes in VCBF reflected changes in capacitance.

Experimental design

At the beginning of each experiment pentolinium 0.75 mg kg^{-1} was injected to minimize reflex autonomic effects. Originally, it was planned to use selective α_1- and α_2-adrenoceptor agonists; however, these were found to be inappropriate (see Results). Therefore, only the ability of the non-selective α-adrenoceptor agonist noradrenaline to cause arterial and venous constriction, and its antagonism by prazosin (α_1-selective) or yohimbine (α_2-selective), was examined. For this purpose, the method described by Drew & Whiting (1979) for the arterial circulation was used.

Submaximal doses of noradrenaline (0.5 μg), representing about 60–75% of the maximum response to noradrenaline, were injected intra-arterially (i.a.). After responses to noradrenaline were constant, prazosin or yohimbine (0.01–1.0 mg kg^{-1}) was infused intravenously, after which the injection of 0.5 μg noradrenaline was given again 15 min later. Thereafter, doses of the antagonist were administered in a cumulative fashion and the effect of a single dose of noradrenaline was retested at each dose level.In this way, the percentage change from control (i.e. pre-antagonist) of the effect of noradrenaline was calculated after each dose of antagonist (Drew & Whiting, 1979). This was done for responses obtained simultaneously in the arterial (using perfusion pressure) and venous (using VCBF) circulations of the hindquarters. The time between subsequent antagonist injections was approximately 20 min, which should maintain constant equilibrium conditions throughout the experiments. Where appropriate, the concentration of the antagonist which depressed the effect of noradrenaline by 50% (ID_{50} value) was determined for each experiment in both arterial and venous circulations. In experiments in which prazosin was initially administered, yohimbine was injected after the final concentration of prazosin, while in other experiments, the reverse order was used.

Drugs

The following drugs were used: B-HT 920 (6-allyl-2-amino-5,6,7,8-tetrahydro-4H-thiazolo-[4,5-d]azepin dihydrochloride; Boehringer Ingelheim); α-chloralose (BDH Chemicals); clonidine hydrochloride (Boehringer Ingelheim); halothane (ICI); methoxamine hydrochloride (Burroughs Wellcome); noradrenaline bitartrate (Sigma); pentolinium tartrate (May & Baker); prazosin hydrochloride (Pfizer) and yohimbine hydrochloride (Sigma).

Noradrenaline and adrenaline were dissolved in distilled water at a concentration of 1 mg ml^{-1}, together with sodium metabisulphite ($Na_2S_2O_5$, 1 mg ml^{-1}) and 0.1 ml of 0.1 N HCl (in 10 ml) to prevent oxidation. Prazosin was suspended in glycerol and then dissolved in 5% (w/v) dextrose solution to give a concentration of 0.4 mg ml^{-1}, while all other drugs were dissolved in distilled water.

Final dilutions of all constrictor drugs were made immediately before use in a 0.9% NaCl solution containing 20 μg ml^{-1} EDTA and 10 μg ml^{-1} ascorbic acid. These were injected in 0.1–0.5 ml volumes into the perfusion circuit, while prazosin and yohimbine were both infused intravenously over 1–2 min in 0.2–7.0 ml and 0.3–3.5 ml volumes respectively, according to the required concentration. All concentrations refer to the base.

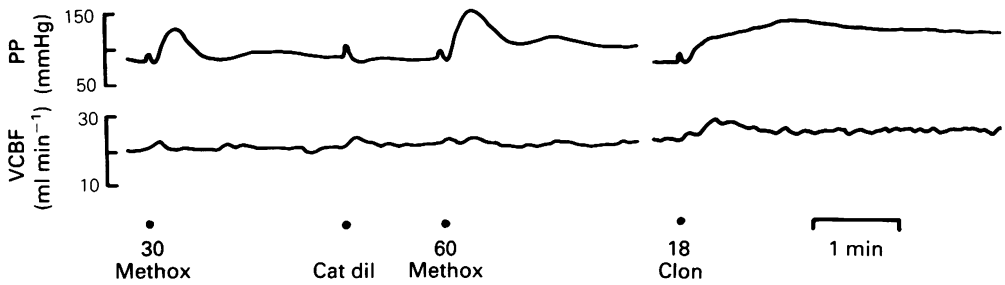


Figure 1 Recording from a chloralose-anaesthetized cat with autoperfused hindquarters. Effect of doses of methoxamine (Methox), clonidine (Clon) and vehicle (Cat dil) on perfusion pressure (PP) and vena cava blood flow (VCBF) in the same preparation. All doses are in μg and were injected intra-arterially. Flow rate to the hindquarters (delivered by the perfusion pump) was 18 ml min^{-1}.

Results

Agonists

Pilot studies were performed in 4 cats in which noradrenaline, as well as the α_1-adrenoceptor agonist methoxamine and the α_2-adrenoceptor agonists clonidine and B-HT 920, were injected i.a. into the hindquarters. It was found that noradrenaline always caused consistent increases in both perfusion pressure and VCBF, indicating arterial and venous constriction, respectively. Methoxamine, at doses up to 100 μg failed to cause venoconstriction, as seen by lack of effect on VCBF. However, at the same time, it caused dose-dependent arterial constriction, as seen by increases in perfusion pressure (see Figures 1 and 2). Both clonidine (18 μg) and B-HT 920 (32 μg) produced constriction in the arterial and venous circulations, although this was less pronounced than with noradrenaline and, unlike noradrenaline, showed marked autodesensitization, so that the effects of subsequent doses of the two drugs were progressively smaller. The first dose of clonidine, tested in 4 cats, increased perfusion pressure by 55 ± 14 mmHg and increased VCBF by 4.5 ± 0.6 ml min^{-1}. B-HT 920 was tested in 2 cats with the initial effect being to increase perfusion pressure by 33 and 30 mmHg and to increase VCBF by 3.5 and 4.5 ml min^{-1}, respectively, in the 2 animals. However, it was not possible to use these selective α_2-adrenoceptor agonists to cause constriction of a reproducible nature in both arterial and venous circuits. This, together with the finding that methoxamine failed to cause any venoconstriction, precluded the use of these drugs in antagonist studies. Thus, only the ability of the non-selective α-agonist noradrenaline to cause arterial and venous constriction, and its susceptibility to α-blockade, was examined further.

Antagonists

Nine cats were used in these studies and resting values are listed in Table 1. Pentolinium, infused in a volume of 0.75 ml kg^{-1} over 1 min, produced reductions in all baseline variables which remained significantly below resting levels for the duration of the experiment (Table 1).

Prazosin Noradrenaline (0.5 μg) was injected intra-arterially at least twice before prazosin to ensure that stable responses were obtained. In 5 experiments,

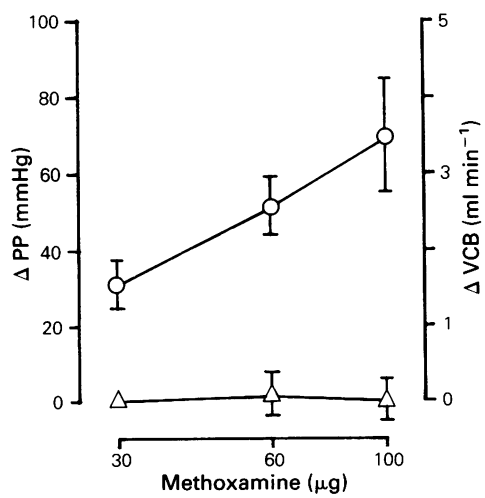
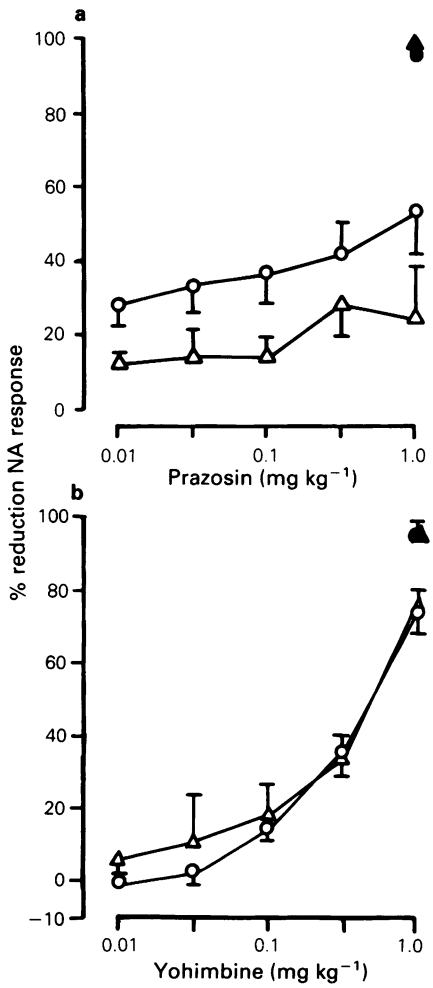


Figure 2 Log dose-response curves showing the effect on perfusion pressure (PP; O) and vena cava blood flow (VCBF; Δ) of methoxamine injected intra-arterially. Each point represents the mean of 4 experiments and vertical lines show s.e.mean.

Table 1 Changes in mean arterial pressure (MAP), heart rate (HR), hindquarter perfusion pressure (PP), arterial inflow (AIn) and mean vena cava blood flow (VCBF) of chloralose-anaesthetized cats with autoperfused hindquarters in response to intravenous (i.v.) pentolinium

Treatment	*Variable*	*Initial value*	*Change*	*% change*
Pentolinium	MAP	113 ± 8.0	−29 ± 6.5*	−24 ± 5.0
0.75 mg kg^{-1} i.v.	(mmHg)			
(n = 9)	HR	180 ± 12.2	−30 ± 8.7*	−15 ± 3.7
	(beats min^{-1})			
	PP	105 ± 4.6	−12 ± 2.9*	−11 ± 2.4
	(mmHg)			
	AIn	23.2 ± 2.3	—	—
	(ml min^{-1})			
	VCBF	22.8 ± 3.0	−2.4 ± 0.6*	−9.9 ± 2.3
	(ml min^{-1})			

Data shown are means ± s.e.mean.
−, Indicates decreases in the appropriate variable.
*, Significantly different from control levels, $P < 0.05$, paired t test.



0.5 μg noradrenaline increased perfusion pressure by 63 ± 6.7 mmHg and increased VCBF by 7.4 ± 0.4 ml min^{-1}. Both variables had returned to control levels within 2–4 min. Prazosin (0.01–1.0 mg kg^{-1}) was then given intravenously in a cumulative regimen, and 15 min later, noradrenaline was tested at every dose level of the antagonist drug. In each experiment, the percentage reduction in the effect of noradrenaline as compared with control responses caused by each dose of prazosin was determined. At doses of 0.01–0.1 mg kg^{-1}, prazosin had negligible effects on blood pressure, perfusion pressure and VCBF, although the two largest doses used, 0.3 and 1.0 mg kg^{-1}, caused transient increases (1–2 min) in these variables which were presumably due to the larger injection volumes required.

The effect of prazosin on the arterial and venous constriction produced by noradrenaline is shown in Figure 3. This indicates that, in both the arterial and venous circulations, there was a considerable prazosin-resistant component of the effect of noradrenaline. In these experiments, it was not valid to calculate the concentration of prazosin required to reduce either the arterial or venous response of

Figure 3 Log-dose response curves for the antagonism by (a) prazosin and (b) yohimbine of the increase in perfusion pressure (○) and vena cava blood flow (△) in response to 0.5 μg noradrenaline (NA) injected intra-arterially. Each point represents the mean of (a) 5 or (b) 4 experiments; vertical lines show s.e.mean. In (a) the closed symbols indicate the effect of the subsequent intravenous injection of 1.0 mg kg^{-1} yohimbine in 4 experiments. In (b) the closed symbols indicate the effect of the subsequent intravenous injection of 0.1 mg kg^{-1} prazosin.

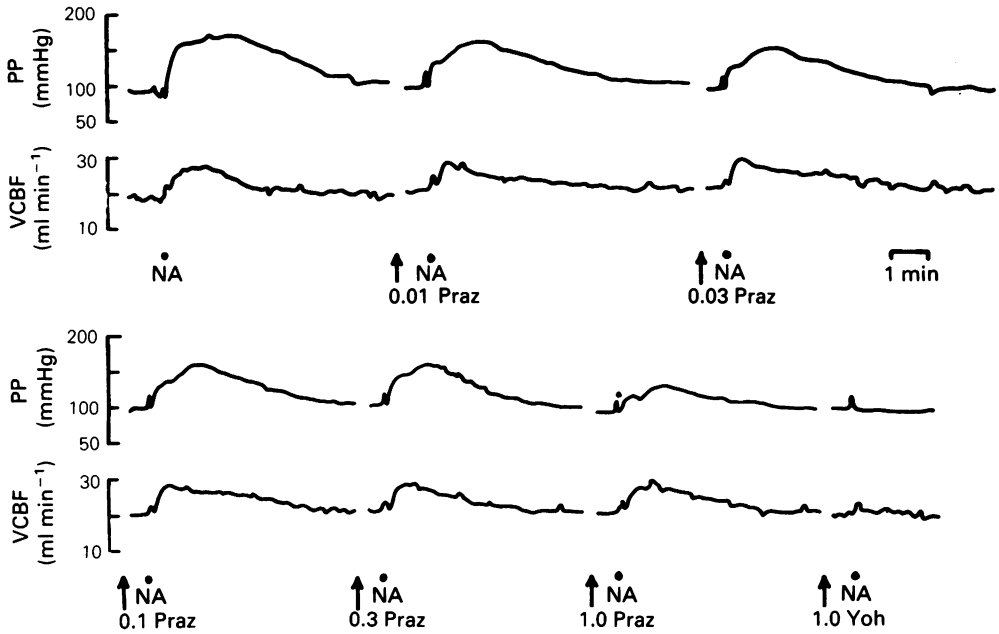


Figure 4 Recording from a chloralose-anaesthetized cat with autoperfused hindquarters. Effect of intra-arterial injection of 0.5 μg noradrenaline (NA) and its subsequent antagonism by increasing doses of prazosin (Praz), followed by yohimbine (Yoh), on perfusion pressure (PP) and vena cava blood flow (VCBF). Doses of prazosin listed are cumulative concentrations and both prazosin and yohimbine doses are in mg kg^{-1}. Flow rate to the hindquarters (delivered by the perfusion pump) was 22 ml min^{-1}.

noradrenaline by 50% (ID_{50}) because there was considerable variation in the results. However, the maximum inhibition of noradrenaline-induced increases in perfusion pressure produced by prazosin (1.0 mg kg^{-1}) averaged 54%, although in individual experiments, the maximum inhibition was 79, 57, 13, 55 and 65%. While this represented a large prazosin-resistant component to noradrenaline in the arterial circulation, the lack of effect of prazosin was even more marked in the venous circulation, since this drug caused a mean maximum inhibition of the noradrenaline-induced increases in VCBF of only 28%. The maximum inhibition was 54, 15, 39, 0 and 33% in the individual experiments (these values are given in the same order of experiments as for perfusion pressure). Moreover, this occurred with 0.3 mg kg^{-1} prazosin and, unlike perfusion pressure responses, 1.0 mg kg^{-1} prazosin caused no further inhibition of noradrenaline-induced venoconstriction (Figure 3). However, due to the variability of prazosin in both circulations, the maximum inhibition caused by this drug was not significantly different in the arteries and veins.

Following the cumulative administration of 1 mg kg^{-1} prazosin, yohimbine, 1 mg kg^{-1}, was then injected intravenously to four cats. This abolished the prazosin-resistant fractions of the response to noradrenaline in both the arterial and venous circulations (see Figure 3). A trace showing the effect of prazosin and yohimbine on the response to noradrenaline is reproduced in Figure 4.

Yohimbine The effect of the cumulative addition of yohimbine on the response to noradrenaline was examined in four cats. Yohimbine (0.01–1.0 mg kg^{-1}) had a negligible effect on all baseline variables, except in one cat in which the largest concentrations of this drug (0.3, 1.0 mg kg^{-1}) briefly reduced blood pressure, perfusion pressure and VCBF.

Before the administration of yohimbine, 0.5 μg noradrenaline increased perfusion pressure by 60 ± 6.7 mmHg ($n = 4$) and increased VCBF by 8.1 ± 2.3 ml min^{-1} ($n = 4$). After giving increasing doses of yohimbine, both the arterial and venous components of noradrenaline were depressed to approximately the same extent, although there were still yohimbine-resistant components which comprised about 25% of the control response (see Figure 3). Mean ID_{50} values (± s.e.mean) for yohimbine in the arterial and venous circulations were 0.51 ± 0.15 mg kg^{-1} ($n = 4$) and 0.49 ± 0.10 mg kg^{-1}

($n = 4$), respectively.

Prazosin 0.1 mg kg^{-1} injected intravenously following yohimbine completely abolished the yohimbine-resistant fractions of the response to noradrenaline in both arteries and veins (see Figure 3).

Discussion

The advantages of the experimental technique used in the present study over more conventional methods of recording venous function have been discussed previously (see Bentley *et al.*, 1986). These include the measurement of active changes in venous smooth muscle simultaneously with, but independently of, changes in arterial resistance.

In the present study, it was found that, while i.a. methoxamine caused arterial constriction, it was completely ineffective in the venous circulation. In contrast, the partial α_2-adrenoceptor agonist clonidine and the more selective α_2-adrenoceptor agonist B-HT 920 caused both arterial and venous constriction, although this was complicated by the fact that smaller responses were obtained with subsequent injections of both drugs. This is consistent with a recent *in vitro* study which suggested that desensitization occurs to α_2-adrenoceptor, but not α_1-adrenoceptor, responses (Cheung, 1986). It is possible that the autodesensitization observed to both these drugs may be minimized by increasing the time between doses, although this would preclude the testing of other agonists in the same preparation. However, i.a. noradrenaline consistently caused constrictor responses in both the arterial and venous circulations of the cat hindquarters, although it appears that different α-adrenoceptor subtypes are involved in these responses.

Prazosin, in doses which had little effect on baseline variables, produced only a partial and variable blockade of the noradrenaline-induced arterial constriction, as has been described by other workers for this preparation (Drew & Whiting, 1979; Langer *et al.*, 1985). The fact that both prazosin and yohimbine, given in either order, were needed to abolish noradrenaline-induced arterial constriction suggests the presence of both α_1- and α_2-adrenoceptors in arterial smooth muscle. This is consistent with other *in vivo* studies using hindquarter preparations of cats, dogs and rabbits, in which β-adrenoceptor blockade was either present (Drew & Whiting, 1979; Langer *et al.*, 1980; 1985; Gardiner & Peters, 1982; Horn *et al.*, 1982) or absent (Drew & Whiting, 1979; Langer *et al.*, 1980; Madjar *et al.*, 1980).

However, at the same time, the maximum antagonism of noradrenaline-induced venoconstriction caused by prazosin was approximately half that of its effect in the arterial circulation. Taken together with the findings that both clonidine and B-HT 920, but not methoxamine, caused constrictor responses in the venous compartment, this suggests that noradrenaline elicited venoconstriction mainly by the stimulation of postjunctional α_2-adrenoceptors. This is supported by the finding that the residual (but larger) component of the venoconstrictor effect of noradrenaline could be abolished by the subsequent administration of yohimbine.

Similar conclusions have also been reached recently by Greenway and co-workers, using conventional plethysmographic techniques to measure hepatic venous blood volume in cats. From these studies it has been suggested that the insensitivity towards prazosin observed in the hepatic venous vasculature (Greenway, 1979) indicates the presence of only α_2-adrenoceptors in this preparation (Patel *et al.*, 1981). This was confirmed for the hepatic blood volume responses to both sympathetic stimulation and catecholamine infusions (Segstro & Greenway, 1986). However, unlike the present study, arterial responses were not determined in the same vascular compartment, although systemic arterial constrictor responses were mediated by both α_1- and α_2-adrenoceptors (Greenway, 1979; Patel *et al.*, 1981; Segstro & Greenway, 1986).

In light of the present results, it might have been expected that yohimbine would produce a preferential blockade of the venous effect of noradrenaline. In fact, a tendency towards this effect was observed only with low doses of yohimbine, although similar ID_{50} values for yohimbine were calculated for both circulations. This discrepancy may relate to the relative selectivities of the two antagonists used in this study. Prazosin is considered to be the most selective α_1-adrenoceptor antagonist available (see Langer & Hicks, 1984). This is supported by the results of the present study, in that increasing the dose of prazosin from 0.3 to 1.0 mg kg^{-1} did not increase further the venous block of noradrenaline. Yohimbine is the antagonist most widely used in studies characterizing α_2-adrenoceptors. However, under certain conditions its α_2-adrenoceptor selectivity may be reduced (see Goldberg & Robertson, 1983). Therefore, a preferential block or noradrenaline-induced venoconstriction may only be identified using newer more selective α_2-adrenocepor antagonists (e.g. idazoxan) and by the construction of full dose-response curves to noradrenaline, to enable the calculation of dose-ratios.

Thus, on the basis of growing evidence demonstrating the presence of α_2-adrenoceptors in venous smooth muscle (Makita, 1983; Suzuki, 1984; Cheung, 1985; Docherty & Hyland, 1985), it is reasonable to assume that the results obtained in the present study indicate that both α_1- and α_2-adrenoceptors are present in the arterial circulation of the cat hindquarters, while there was an exclusive, or at least predominant, α_2-adrenoceptor population in the venous circulation. These

findings are consistent with others (De Mey & Vanhoutte, 1981; Vanhoutte, 1982; Glusa & Markwardt, 1983) which indicate that venous smooth muscle contains a greater proportion of α_2-adrenoceptors than does arterial smooth muscle, although all previous evidence was based on *in vitro* data.

However, these results are not in complete agreement with those from other *in vivo* studies, in which an increase in cardiac output in pithed animals has been used as a measure of venoconstriction (Gerold & Haeusler, 1983). From those studies, it appears that there are α_2-adrenoceptors in the systemic venous circulation of pithed rats (Gerold & Haeusler, 1983; Kalkman *et al.*, 1984), although it has been suggested that there are no functional α_2-adrenoceptors in the systemic venous circulation of pithed cats (Kalkman *et al.*, 1984) or spinalized, ganglion-blocked dogs (Zandberg *et al.*, 1984). This was because neither B-HT 920 nor B-HT 933 elevated cardiac output in these preparations. In contrast, it has been found that, in conscious areflexic dogs, neither noradrenaline, phenylephrine nor B-HT 920 increased cardiac output, although all drugs caused similar increases in left ventricular end-diastolic pressure (Woodman & Vatner, 1986).

It is difficult to explain the differences between the results of these previously mentioned studies and the present findings, although it is possible that these discrepancies may be related both to species differences as well as to the different techniques used and regions studied. In the present study, only the hindquarters vascular region was examined and this was under controlled flow conditions. However, in the studies measuring changes in cardiac output, the results provide information on the overall changes in venous blood flow and so the effect in an individual vascular bed may be masked. Furthermore, arterial blood flow cannot be adequately controlled, especially since all α-adrenoceptor agonists simultaneously increased arterial resistance. Therefore, it is possible that changes in cardiac output do not adequately reflect venoconstriction.

In addition, the influence of blood gases on the results of this and other studies may play a role in α-adrenoceptor-mediated constrictor responses. Although blood gas measurements were not taken in the present study, recent data have indicated that α_1- and α_2-adrenoceptor-mediated arterial pressor responses in pithed rats could be modified by altering the blood gas levels, as a result of varying the experimental conditions (e.g. ventilation rate) (McGrath *et al.*, 1982; Grant *et al.*, 1985). Therefore, the possibility that α_2-adrenoceptors exist under more optimal conditions in the venous circulation cannot be discounted.

In conclusion, the results from the present study support the concept that there may be a greater proportion of α_2-adrenoceptors, relative to α_1-adrenoceptors, in veins as compared with arteries (De Mey & Vanhoutte), 1981; Glusa & Markwardt, 1983; Segstro & Greenway, 1986).

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References

BENTLEY, G.A., CULLEN, L.K., REYNOLDSON, J.A. & WIDDOP, R.E. (1986). The effect of clonidine on venous haemodynamics in cats and dogs. *Br. J. Pharmac.*, **88**, 161–171.

CHEUNG, D.W. (1985). An electrophysiological study of α-adrenoceptor mediated excitation-contraction coupling in the smooth muscle cells of the rat saphenous vein. *Br. J. Pharmac.*, **84**, 265–271.

CHEUNG, D.W. (1986). Desensitization of the vascular contractile response to cumulative doses of α_2-adrenoceptor agonists. *Can. J. Physiol. Pharmac.*, **64**, 1343–1345.

DE MEY, J. & VANHOUTTE, P.M. (1981). Uneven distribution of postjunctional alpha$_1$ and alpha$_2$-like adrenoceptors in canine arterial and venous smooth muscle. *Circulation Res.*, **48**, 875–884.

DOCHERTY, J.R. & HYLAND, L. (1985). Evidence for neuroeffector transmission through postjunctional α_2-adrenoceptors in human saphenous vein. *Br. J. Pharmac.*, **84**, 573–576.

DREW, G.M. & WHITING, S.B. (1979). Evidence for two distinct types of postsynaptic α-adrenoceptor in vascular smooth muscle *in vivo*. *Br. J. Pharmac.*, **67**, 207–215.

GARDINER, J.C. & PETERS, C.J. (1982). Postsynaptic α_1 and α_2-adrenoceptor involvement in the vascular responses to neuronally released and exogenous noradrenaline in the hindlimb of the dog and cat. *Eur. J. Pharmac.*, **84**, 189–198.

GEROLD, M. & HAEUSLER, G. (1983). α_2-Adrenoceptors in rat resistance vessels. *Naunyn-Schmiedebergs Arch. Pharmac.*, **322**, 29–33.

GLUSA, E. & MARKWARDT, F. (1983). Characterization of postjunctional α-adrenoceptors in isolated human femoral veins and arteries. *Naunyn-Schmiedebergs Arch. Pharmac.*, **323**, 101–105.

GOLDBERG, M.R. & ROBERTSON, D. (1983). Yohimbine: a pharmacological probe for study of the α_2-adrenoceptor. *Pharmac. Rev.*, **35**, 143–180.

GRANT, T.L., McGRATH, J.C. & O'BRIEN, J.W. (1985). The influence of blood gases on α_1- and α_2-adrenoceptor-mediated pressor responses in the pithed rat. *Br. J. Pharmac.*, **86**, 69–77.

GREENWAY, C.V. (1979). Effects of sodium nitroprusside, isosorbide dinitrate, isoproterenol, phentolamine and prazosin on hepatic venous responses to sympathetic nerve stimulation in the cat. *J. Pharmac exp. Ther.*, **209**, 56–61.

HORN, P.T., KOHLI, J.D., LISTINSKY, J.J. & GOLDBERG, L.I. (1982). Regional variation in the alpha-adrenergic receptors in the canine resistance vessels. *Naunyn-Schmiedebergs Arch. Pharmac.*, **318**, 166–172.

KALKMAN, H.O., THOOLEN, M.J.M.C., TIMMERMANS, P.B.M.W.M. & VAN ZWIETEN, P.A. (1984). The influence of α_1- and α_2-adrenoceptor agonists on cardiac output in rats and cats. *J. Pharm. Pharmac.*, **36**, 265–268.

LANGER, S. Z., DUVAL, N. & MASSINGHAM, R. (1985). Pharmacologic and therapeutic significance of α-adrenoceptor subtypes. *J. cardiovasc. Pharmac.*, **7** (Suppl. 8), S1–S8.

LANGER, S.Z. & HICKS, P.E. (1984). Alpha-adrenoreceptor subtypes in blood vessels: physiology and pharmacology. *J. cardiovasc. Pharmac.*, **6**, S547–S558.

LANGER, S.Z., MASSINGHAM, R. & SHEPPERSON, N.B. (1980). Presence of postsynaptic α_2-adrenoreceptors of predominantly extrasynaptic location in the vascular smooth muscle of the dog hindlimb. *Clin. Sci.*, **59**, 225S–228S.

MADJAR, H., DOCHERTY, J.R. & STARKE, K. (1980). An examination of pre- and postsynaptic α-adrenoceptors in the autoperfused rabbit hindlimb. *J. cardiovasc. Pharmac.*, **2**, 619–627.

MAKITA, Y. (1983). Effects of adrenoceptor agonists and antagonists on smooth muscle cells and neuromuscular transmission in the guinea-pig renal artery and vein. *Br. J. Pharmac.*, **80**, 671–679.

McGRATH, J.C. (1982). Evidence for more than one type of postjunctional α-adrenoceptor. *Biochem. Pharmac.*, **31**, 467–484.

McGRATH, J.C., FLAVAHAN, N.A. & McKEAN, C.E. (1982). α_1- and α_2-adrenoceptor-mediated pressor and chronotropic effects in the rat and rabbit. *J. cardiovasc. Pharmac.*, **4**, S101–S107.

PATEL, P., BOSE, D. & GREENWAY, C. (1981). Effects of prazosin and phenoxybenzamine on α- and β-receptor-mediated responses in intestinal resistance and capacitance vessels. *J. cardiovasc. Pharmac.*, **3**, 1050–1059.

SEGSTRO, R. & GREENWAY, C. (1986). Alpha adrenoceptor subtype mediating sympathetic mobilization of blood from hepatic venous system in anaesthetized cats. *J. Pharmac. exp. Ther.*, **236**, 224–229.

SUZUKI, H. (1984). Adrenergic transmission in the dog mesenteric vein and its modulation by α-adrenoceptor antagonists. *Br. J. Pharmac.*, **81**, 479–489.

VANHOUTTE, P.M. (1982). Heterogeneity of postjunctional vascular α-adrenoceptors and handling of calcium. *J. cadiovasc. Pharmac.*, **4**, S91–S96.

WOODMAN, O.L. & VATNER, S.F. (1986). Cardiovascular responses to the stimulation of alpha-1 and alpha-2 adrenoceptors in the conscious dog. *J. Pharmac exp. Ther.*, **237**, 86–91.

ZANDBERG, P., TIMMERMANS, P.B.M.W.M. & VAN ZWIETEN, P.A. (1984). Haemodynamic profiles of methoxamine and B-HT 933 in spinalized ganglion-blocked dogs. *J. cardiovasc. Pharmac.*, **6**, 256–262.

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