Responses to noradrenaline in human subcutaneous resistance arteries are mediated by both α_1 - and α_2 -adrenoceptors

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1 *In vitro* experiments in a microvascular myograph were designed to characterize postjunctional α -adrenoceptors of human subcutaneous resistance arteries (normalised internal diameter 143–313 μ m).

2 Both the α_1 -selective agonist phenylephrine in the presence of 0.3 μ M yohimbine and the α_2 -selective agonist B-HT 933 in the presence of 0.3 μ M prazosin elicited prominent and concentration-dependent contractions. The maximum response to phenylephrine and B-HT 933 was not different from the response to high K physiological salt solution (125 mM K⁺), and the pD₂ values (–log EC₅₀) were 5.90 and 6.11, respectively.

3 In the presence of the α_2 -selective antagonist yohimbine (0.3 μ M), the α_1 -selective antagonist prazosin competitively antagonised the responses to phenylephrine; the pA₂ of prazosin for the receptor which mediated the response to phenylephrine was 8.41.

4 Blockade of either α_2 -adrenoceptors with 0.1 μ M yohimbine or α_1 -adrenoceptors with 0.1 μ M prazosin caused shifts to the right of the noradrenaline concentration-response curves and the shifts in pD₂ were 0.69 and 0.61, respectively. The combination of the two antagonists at the above-mentioned concentrations caused a marked, parallel shift to the right of the noradrenaline concentration-response curve, the shift of the pD₂ was 2.68.

5 These results suggest that activation of both α_1 - and α_2 -adrenoceptors produces contractions in human subcutaneous resistance arteries, and that responses to noradrenaline in these vessels are mediated by both α -adrenoceptor subtypes.

Introduction

During the last decade it has been established in different animal species that both α_1 - and α_2 -adrenoceptors exist postjunctionally on arteries and can induce vasoconstriction (Timmermans *et al.*, 1979; De Mey & Vanhoutte, 1981; Schumann & Lues, 1983; Skärby *et al.*, 1983; Busija & Leffler, 1987; Faber, 1988). In man the evidence for the presence of postjunctional vascular α_2 -adrenoceptors comes mainly from *in vivo* studies (e.g. Elliot & Reid, 1983; Goldberg & Robertson, 1984; Ekenvall *et al.*, 1988), but a few studies with human isolated arteries have also demonstrated α_2 -adrenoceptor-mediated contractions (Moulds & Jauernig, 1977; Steen *et al.*, 1984a,b; Flavahan *et al.*, 1987). Recently, an inverse relationship has been demonstrated between the magnitude of postjunctional α_2 -adrenoceptor responses and the calibre of human isolated subcutaneous resistance arteries (Nielsen *et al.*, 1987; 1989). In this study, we have examined the same vessel type in an attempt to investigate whether both α_1 - and α_2 -adrenoceptors are present postjunctionally in the smaller of these vessels, and, if so, to determine whether both subtypes of α -adrenoceptors are involved in the responses to noradrenaline.

Methods

Subjects and preparation

Twenty two patients (age 19–68 years, 9 male) undergoing various forms of abdominal surgery served as vessel donors. Informed consent was obtained from all subjects, and the protocol of the study was approved by the local Ethics Committee. All the patients were normotensive (blood pressure not higher than 140/90 mmHg), and none received any regular medication.

During surgery, small pieces (ca. 2 × 1 × 1 cm) of subcutaneous fat from ventral abdominal wall were isolated and placed in cold physiological salt solution (PSS). Within 1 h, small arteries (a total of 39 vessels, normalised internal diameters 143–313 μ m) were dissected from the fat tissue and mounted as ring segments (approximately 2 mm long in an isometric myograph (Mulvany & Halpern, 1977) by threading them onto two stainless steel wires and securing the wires to the supports. After equilibration for ca. 1 h at 37°C, the vessels were set to a normalised internal circumference L₁₀₀, estimated to be 0.9 times the circumference they would maintain if relaxed and exposed to a transmural pressure of 100 mmHg (Mulvany & Halpern, 1977). The chamber was bubbled with 95% O₂, 5% CO₂. At the start of each study the vessels were stimulated 3 times with K-PSS (PSS with 119 mM KCl substituted for NaCl). These served as standardised control responses, and the 5 vessels that failed to produce more than 100 mmHg effective active pressure (equal to pressure against which vessels could contract, Mulvany & Halpern, 1977) were excluded from the study.

Experimental procedure

All the responses to noradrenaline were evoked in normal PSS, and control experiments (see Results) showed no tachyphylaxis of the preparation to this drug. However, earlier experiments have shown that tachyphylaxis of subcutaneous small arteries to B-HT 933 could be overcome by partially depolarising the vessels (Nielsen *et al.*, 1989). Therefore, and for comparison, all responses in this study to B-HT 933 and phenylephrine were elicited in partially depolarising PSS (see below).

Concentration-response curves to agonists were obtained by increasing the concentration cumulatively by half-log increments. When competitive antagonists were used, the vessels were incubated for at least 15 min with the drugs which remained in the solution during exposure to the agonists. All the concentration-response curves were generated in the presence of 3 μ M cocaine and 1 μ M propranolol in order to block neuronal uptake and β -adrenoceptors, respectively.

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Figure 1 Stimulation of α_1 - and α_2 -adrenoceptor subtypes in a human subcutaneous resistance artery with an internal diameter of $184 \mu\text{m}$. The left panel shows the vasoconstriction produced by depolarisation with K-PSS (125 mM K^+). Yohimbine (Yoh, $0.3 \mu\text{M}$) was added 20 min before the generation of the phenylephrine (PE) concentration-response curve, and prazosin (Praz, $0.3 \mu\text{M}$) was added 15 min before the addition of B-HT 933. Drugs were added cumulatively at the indicated minus log molar concentrations.

Calculations

Concentration-response curves based on a Hill-relationship were fitted to individual concentration-response data by a computer programme (GraphPad, Institute for Scientific Information, U.S.A.). Sensitivities to drugs were calculated on the basis of data from individual vessels and are expressed as $\text{pD}_2 = -\log \text{EC}_{50}$, the EC_x being the agonist concentration needed to produce $x\%$ of the maximal response. Antagonist pA_2 -values were determined by Schild analysis (Arunlakshana & Schild, 1959) of data from individual vessels.

Figure 2 Concentration-response curves for (a) phenylephrine (5 vessels) in the presence of yohimbine ($0.3 \mu\text{M}$), and (b) B-HT 933 (6 vessels) in the presence of prazosin ($0.3 \mu\text{M}$) in PSS containing 30 mM K^+ . Values are means normalised to the maximum response to each agonist; s.e.mean is shown by vertical bars.

Figure 3 Effect of prazosin on the phenylephrine concentration-response curve (CRC). The phenylephrine CRCs were generated in partially depolarising PSS with $0.3 \mu\text{M}$ yohimbine present throughout: (○) control; (●) 1 nM prazosin; (□) 3 nM prazosin; (■) 10 nM prazosin. The values are expressed relative to the maximum response to phenylephrine in the control curve; s.e.mean shown by vertical bars (5 vessels).

Statistics

The results are expressed as mean $\pm$ s.e.mean. Statistical differences between two means were determined by two-tailed, paired Student's t test. Differences were accepted as significant at $P < 0.05$.

Drugs and solutions

The composition of PSS was (mM): NaCl 119, KCl 4.7, $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ 2.5, $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 1.17, NaHCO_3 25, KH_2PO_4 1.18, Na_2EDTA 0.026, glucose 5.5. Partially depolarising PSS was obtained by gradually substituting KCl for NaCl until the vessel developed slight tone; usually 30 mM KCl was needed. Stock solutions were prepared daily in distilled water. B-HT 933-2 HCl (2-amino-6-ethyl-4,5,6,7-tetrahydro-6H-oxazolo-(5,4-d)-azepin dihydrochloride) was a gift from Boehringer Ingelheim (West Germany) and prazosin was a gift from Pfizer (U.K.). Noradrenaline-HCl and yohimbine-HCl were obtained from Sigma Chemical Co., phenylephrine (Metaoxedrine) from Danmarks Apotekerforening, cocaine-HCl from the Aarhus City Hospital pharmacy, and propranolol (Frekven) from Ferrosan (Denmark).

Results

α_1 - and α_2 -adrenoceptor agonism

The α_1 -selective agonist phenylephrine, in the presence of the α_2 -selective antagonist yohimbine ($0.3 \mu\text{M}$), constricted the vessels in a concentration-dependent manner (Figures 1 and 2a) and the pD_2 was 5.90 ± 0.15 (5 vessels). Also, the α_2 -selective agonist B-HT 933, in the presence of the α_1 -selective antagonist prazosin ($0.3 \mu\text{M}$), evoked concentration-dependent contractions (Figures 1 and 2b) and the pD_2 was 6.11 ± 0.18 (6 vessels).

The size of the maximal α_1 -adrenoceptor-mediated response (phenylephrine with $0.3 \mu\text{M}$ yohimbine, 5 vessels) was not different from the maximal α_2 -adrenoceptor-mediated response (B-HT 933 with $0.3 \mu\text{M}$ prazosin, 6 vessels): $104 \pm 9\%$ and $100 \pm 11\%$, respectively, of the responses evoked by K-PSS (125 mM K^+).

Prazosin affinity

The generation of 4 consecutive concentration-response curves in partially depolarising PSS, at 20 min intervals with $0.3 \mu\text{M}$ yohimbine present, revealed no tachyphylaxis of the preparation to phenylephrine. The pD_2 values for the first, second, third, and fourth concentration-response curves were: 5.95 ± 0.12 , 5.85 ± 0.13 , 6.03 ± 0.08 and 5.80 ± 0.20 , respectively, and the maximum responses were $2.15 \pm 0.25 \text{ N m}^{-1}$, $2.23 \pm 0.18 \text{ N m}^{-1}$, $2.20 \pm 0.20 \text{ N m}^{-1}$ and $2.08 \pm 0.20 \text{ N m}^{-1}$,

respectively (4 vessels). The α_1 -selective antagonist prazosin competitively antagonised the responses to phenylephrine in the presence of $0.3 \mu\text{M}$ yohimbine (Figure 3). Schild analysis showed a pA_2 for prazosin against phenylephrine of 8.41 ± 0.14 , slope 1.08 ± 0.07 (not significantly different from unity, 4 vessels).

Noradrenaline

Two consecutive noradrenaline concentration-response curves at 15 min intervals were generated and the pD_2 -values for the first and second concentration-response curves were 6.93 ± 0.25 and 6.89 ± 0.17 , respectively. The maximum responses to noradrenaline were $2.44 \pm 0.51 \text{ N m}^{-1}$ and $2.51 \pm 0.40 \text{ N m}^{-1}$, respectively (5 vessels). Therefore, this preparation did not show any tachyphylaxis to noradrenaline.

Prazosin and yohimbine antagonism of noradrenaline responses

The noradrenaline concentration-response curves were shifted to the right by (a) $0.1 \mu\text{M}$ yohimbine, (b) $0.1 \mu\text{M}$ prazosin, and (c) the combination of $0.1 \mu\text{M}$ yohimbine and $0.1 \mu\text{M}$ prazosin (Figure 4). In all three cases the log shifts at the EC_{10} , EC_{50} , and EC_{90} levels were statistically significant. Yohimbine caused a significantly greater log shift at the EC_{10} than at the EC_{90} level. With either prazosin alone or the combination of the two antagonists the log shift at the EC_{10} and EC_{90} levels did not deviate significantly from each other (Table 1).

Discussion

A discrepancy exists as regards the location of post-junctional α_2 -adrenoceptors (Langer & Hicks, 1984; Faber, 1988). α_2 -Adrenoceptor-mediated responses can be readily observed

after α_1 -adrenoceptor blockade in *in vivo* preparations, but it has been more difficult to demonstrate similar responses *in vitro* (Minneman, 1988). In an attempt to reconcile this apparent paradox, it has been hypothesised that postjunctional α_2 -adrenoceptors are confined to smaller resistance vessels (Langer & Hicks, 1984; Alabaster & Davey, 1984). In contrast, it has been suggested that the contribution of α_1 -adrenoceptors to contractile responses decreases in distal arteries (Flavahan *et al.*, 1987; Faber, 1988).

α_1 - and α_2 -adrenoceptor agonism

In the present study on human subcutaneous small arteries both phenylephrine and B-HT 933 evoked well-pronounced responses in the same vessels. Since α_1 -adrenoceptors are much more sensitive than α_2 -adrenoceptors to the α -adrenoceptor agonist, phenylephrine (Starke *et al.*, 1975; Drew, 1977), it is most likely that the responses to phenylephrine in the presence of $0.3 \mu\text{M}$ of the α_2 -selective antagonist yohimbine (Drew, 1985) were evoked by selective stimulation of α_1 -adrenoceptors. *Vice versa*, B-HT 933 is selective for α_2 -adrenoceptors (Timmermans & van Zweiten, 1980), and therefore the most probable explanation for responses to B-HT 933 in the presence of $0.3 \mu\text{M}$ of the highly selective α_1 -antagonist, prazosin (Jones *et al.*, 1987), is stimulation of α_2 -adrenoceptors. These conclusions are supported by the antagonist studies. The competitive antagonism of the responses to phenylephrine in the presence of $0.3 \mu\text{M}$ yohimbine by prazosin and the pA_2 (8.41) of prazosin for the receptor mediating these responses suggest that this adrenoceptor is of the α_1 -subtype. It has previously been shown in these vessels (Nielsen *et al.*, 1989) that yohimbine competitively antagonises α_2 -adrenoceptor-mediated responses to B-HT 933. Therefore, the results of this study and the previous study with the same vessel types (Nielsen *et al.*, 1989) strongly suggest that both α_1 - and α_2 -adrenoceptors exist on human subcutaneous small arteries, and that both subtypes of α -adrenoceptor can bring about vasoconstriction of these vessels.

Both the maximal responses evoked by phenylephrine and the maximal responses elicited by B-HT 933 were of the same size as the vasoconstriction produced by K-PSS. This is in contrast to other studies on human arteries that showed a lower maximal α_2 -adrenoceptor-mediated response compared to the α_1 -adrenoceptor-mediated response (Steen *et al.*, 1984a; Flavahan *et al.*, 1987; Sjöberg *et al.*, 1987). One possible explanation for these observations is that the maximum vasoconstriction mediated by postjunctional α_2 -adrenoceptors seems to increase with diminishing vessel calibre (Nielsen *et al.*, 1989), and the vessels in this study are all relatively small.

Prazosin and yohimbine antagonism of noradrenaline responses

Both the α_1 -antagonist prazosin and the α_2 -antagonist yohimbine antagonised the responses to the endogenous agonist noradrenaline. It is unlikely that the changes in noradrenaline- pD_2 values produced by the two antagonists

Figure 4 The effects of selective α_1 - and α_2 -adrenoceptor antagonists on the noradrenaline concentration-response curves. Control responses ($\circ$) and (a) those after blockade of α_2 -adrenoceptors with $0.1 \mu\text{M}$ yohimbine ($\bullet$, 7 vessels), (b) after blockade of α_1 -adrenoceptors with $0.1 \mu\text{M}$ prazosin ($\blacksquare$, 6 vessels), and (c) after blockade of both α -adrenoceptor subtypes with the $0.1 \mu\text{M}$ yohimbine + $0.1 \mu\text{M}$ prazosin ($\blacktriangle$, 4 vessels). Values are means normalised to the maximum response to noradrenaline in the absence of antagonists; s.e.mean shown by vertical bars.

Table 1 Antagonism by yohimbine and prazosin of noradrenaline concentration-response curves in human subcutaneous resistance vessels

	n	pD_2 with antagonist(s)		EC_{10}	log shifts	
		Absent	Present		EC_{50}	EC_{90}
Yohimbine $0.1 \mu\text{M}$	7	6.92 ± 0.33	6.23 ± 0.25	$0.93 \pm 0.24^{*\dagger}$	$0.69 \pm 0.17^*$	$0.45 \pm 0.12^{*\dagger}$
Prazosin $0.1 \mu\text{M}$	6	7.24 ± 0.17	6.63 ± 0.18	$0.68 \pm 0.21^*$	$0.61 \pm 0.08^*$	$0.57 \pm 0.14^*$
Yohimbine $0.1 \mu\text{M}$ + prazosin $0.1 \mu\text{M}$	4	6.79 ± 0.21	4.11 ± 0.25	$2.80 \pm 0.68^*$	$2.68 \pm 0.63^*$	$2.56 \pm 0.58^*$

* Statistically significant shift caused by antagonist(s).

† Significant difference between the log shifts in EC_{10} and EC_{90} (paired *t* test).

are due to a time-dependent loss of sensitivity in this preparation, since the time-control experiments showed no change in noradrenaline sensitivity or efficacy. Therefore, the antagonism by prazosin and yohimbine indicates that both α -adrenoceptor subtypes contribute to the contraction to noradrenaline in these vessels. However, an important prerequisite for this conclusion is that the above mentioned antagonists are selective for the α -adrenoceptor subtype in question at the concentrations used. Prazosin is known to have an affinity for α_1 -adrenoceptors 3 orders of magnitude greater than for α_2 -adrenoceptors (Jones *et al.*, 1987). Accordingly, it is most likely that the significant antagonism of the responses to noradrenaline by 0.1 μ M prazosin is due to blockade of α_1 -adrenoceptors. Yohimbine has a selectivity for the α_2 -adrenoceptor of more than 10–50 times (Ruffolo, 1984), and a recent study by Faber (1988) demonstrated that 0.1 μ M yohimbine specifically antagonises α_2 -adrenoceptor-mediated responses in rat skeletal muscle microcirculation. Therefore, the concentrations of the antagonists used seem to be specific for each α -adrenoceptor subtype. The statistically significant shifts in noradrenaline-pD₂ values by the two antagonists indicate that noradrenaline produces contraction by activating both α -adrenoceptor subtypes. This conclusion is also supported by the finding, that the combination of both

α -adrenoceptor antagonists produced a shift at the EC₅₀ level (479 fold) that was disproportionately greater than the shifts produced by either α -adrenoceptor antagonist alone (4–5 fold).

The significantly greater log shift at the EC₁₀ than at the EC₉₀ caused by yohimbine alone—but not prazosin alone—can fairly be interpreted as α_2 -adrenoceptor blockade being more effective at low compared to high concentrations of noradrenaline, as earlier suggested by Flavahan *et al.* (1987).

The results of the present study indicate that both α_1 - and α_2 -adrenoceptors are present in smaller subcutaneous resistance arteries in man. Both α_1 - and α_2 -adrenoceptors can bring about a pronounced vasoconstriction. Finally, since the responses to noradrenaline can be antagonised by selective α_1 - and α_2 -adrenoceptor inhibition, these findings strongly suggest that responses to noradrenaline in human subcutaneous resistance arteries are mediated by both α_1 - and α_2 -adrenoceptors.

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