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α-Adrenergic receptors in human blood vessels

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1 The evidence for the presence of postjunctional α_1- and α_2-adrenoceptor subtypes in human blood vessels is reviewed.

2 Experiments in healthy subjects are described that show that α_1- as well as α_2-adrenoceptor mediated vasoconstriction contribute to vascular smooth muscle tone and that adrenaline and noradrenaline have similar affinities for each subtype. In addition, evidence is presented for a preferential intrajunctional location of α_1-adrenoceptors and a preferential extrajunctional location of α_2-adrenoceptors in human blood vessels.

3 It is concluded that at present postjunctional α-adrenoceptors in human blood vessels can be classified as α_1 and α_2. Despite the fact that both subtypes mediate vasoconstriction, these receptors are likely to subserve different physiological functions.

Keywords α-adrenoceptors catecholamines forearm blood flow human blood vessels

Introduction

In the last decade, knowledge of α-adrenoceptors has expanded enormously. With respect to the cardiovascular system, it is now widely accepted that, apart from classical α_1-adrenoceptor-mediated vasoconstriction, there are at least two other α-adrenoceptors involved in the regulation of vascular smooth muscle tone. First, a presynaptic or prejunctional α_2-adrenoceptor was discovered, located on adrenergic nerve terminals and modulating neurotransmitter release via a negative feedback mechanism (Langer, 1977; 1980; Starke, 1981). This prejunctional α_2-adrenoceptor is pharmacologically different from the classical α_1-adrenoceptor. Subsequently, an additional vasoconstrictor postjunctional α_2-adrenoceptor was identified, with a pharmacological profile similar to the prejunctional α_2-adrenoceptor (Drew & Whiting, 1979; Timmermans & van Zwieten, 1982; McGrath, 1982). Although not all responses to α-adrenoceptor agonists and antagonists fit satisfactorily into this model (McGrath & Reid, 1985), the above-mentioned α_1–α_2 subdivision prevails at present.

The understanding of α-adrenoceptor subtypes has mostly derived from animal experiments. However, it appears that there are considerable species differences in α-adrenoceptor-mediated vascular responses (Langer & Hicks, 1984). It is thus important that the findings of animal experiments be confirmed in humans. This paper deals primarily with vascular postjunctional α-adrenoceptor subtypes in human blood vessels and with some aspects relating to their possible physiological role.

Demonstration of postjunctional α_2-adrenoceptors in human blood vessels

Using isolated post-mortem strips of arteries and veins, Moulds & Jauernig (1977) and Jauernig *et al.* (1978) were the first to describe prazosin-resistant vasoconstrictor α-adrenoceptors in human blood vessels. Although they were unable to classify clearly these receptors as α_1 and α_2, reinterpretation of their data by Flavahan & McGrath (1984) suggested the presence of both α_1- and α_2-adrenoceptors in human vascular smooth muscle. More recently the concept of a mixed population of postjunctional α_1- and α_2-adrenoceptors, mediating vasoconstriction in human blood vessels, has been further investigated in several studies *in vivo*. Table 1 summarizes the studies in which α-adrenoceptor agonists and antagonists of varying selectivity were infused either systemically or locally into the brachial artery.

Originally it had been shown that intra-arterial infusion of the α_2-selective adrenoceptor agonist B-

Table 1 *In vivo* studies on postjunctional α-adrenoceptor subtypes in human blood vessels

Authors	*Year*	*Agonists*	*Antagonists*	*Experimental model (circulation)*
van Brummelen *et al.*	(1983)	B-HT 933 (α_2)	yohimbine (α_2)	forearm
Kiowski *et al.*	(1983)	clonidine ($\alpha_2 > \alpha_1$)	prazosin (α_1) phentolamine ($\alpha_1 + \alpha_2$)	forearm
Bolli *et al.*	(1983)		prazosin (α_1) yohimbine (α_2)	forearm
Elliott & Reid	(1983)	phenylephrine (α_1) α-methylnoradrenaline (α_2) noradrenaline ($\alpha_1 + \alpha_2$)	idazoxan (α_2)	systemic
Jie *et al.*	(1984a)	methoxamine (α_1) B-HT 933 (α_2) guanfacine ($\alpha_2 > \alpha_1$) clonidine ($\alpha_2 > \alpha_1$)	doxazosin (α_1) yohimbine (α_2)	forearm
Jie *et al.*	(1984b)	adrenaline ($\alpha_1 + \alpha_2$) noradrenaline ($\alpha_1 + \alpha_2$)	doxazosin (α_1) yohimbine (α_2)	forearm
Bolli *et al.*	(1984)	adrenaline ($\alpha_1 + \alpha_2$)	prazosin (α_1) yohimbine (α_2)	forearm
Goldberg & Robertson	(1984)	phenylephrine (α_1) adrenaline ($\alpha_1 + \alpha_2$)	prazosin (α_1) yohimbine (α_2)	systemic
Thom *et al.*	(1985)	UK 14304 (α_2?)	doxazosin (α_1) idazoxan (α_2)	forearm

HT 933 resulted in a dose-dependent vasoconstriction, whereas local infusion of the α_2-selective adrenoceptor antagonist yohimbine produced considerable vasodilation (van Brummelen *et al.*, 1983). Using the same model, Kiowski *et al.* (1983) were able to show that clonidine-induced vasoconstriction was not significantly influenced by the α_1-selective adrenoceptor antagonist prazosin but could be abolished by non-selective α-adrenoceptor blockade with phentolamine. These results suggested the presence of postjunctional α_1- and α_2-adrenoceptors in human blood vessels. Further evidence for this concept was provided by studies in which the selective agonists methoxamine (α_1) and B-HT 933 (α_2), and the selective antagonists doxazosin (α_1) and yohimbine (α_2) were used (Jie *et al.*, 1984a). It was found that the methoxamine-induced vasoconstriction was prevented by doxazosin, whereas it was not significantly influenced by yohimbine (Figure 1). On the other hand, B-HT 933-induced vasoconstriction was little influenced by doxazosin but was abolished by yohimbine (Figure 2). In the same study the results obtained with clonidine and guanfacine were in accordance with mixed α_1- and α_2- agonist activity for both drugs (Jie *et al.*, 1984a).

Elliott & Reid (1983) studied the influence of the selective α_2-adrenoceptor antagonist idazoxan (RX 781094) on the pressor response to intravenous infusion of the agonists phenylephrine (α_1), noradrenaline ($\alpha_1 + \alpha_2$) and α-methylnoradrenaline (α_2). Their finding, that only the pressor response to α-methylnoradrenaline was substantially reduced by idazoxan, is in agreement with the presence of postjunctional α_2-adrenoceptors in human blood vessels. A similar conclusion was drawn by Goldberg & Robertson (1984) from studies in which intravenous infusions of the antagonists prazosin (α_1) and yohimbine (α_2) and the agonists phenylephrine (α_1) and adrenaline ($\alpha_1 + \alpha_2$) were given to β-adrenoceptor blocked healthy subjects.

More recently, Thom & Sever (1984) and Thom *et al.* (1985) were unable to confirm the presence of postjunctional α_2-adrenoceptors in human blood vessels on the basis of *in vivo* and *in vitro* studies with the supposed α_2-selective adrenoceptor agonist UK 14304, and the antagonists doxazosin (α_1) and idazoxan (α_2). However, it could well be that their conflicting results were due to the study design used and to partial agonist activity of idazoxan (Dalrymple *et al.*, 1983; Paciorek & Shepperson, 1983). Interestingly, and for unexplained reasons, *in vitro* experiments do not separate α_1 and α_2-adrenoceptor responses to the same degree as *in vivo* experiments (McGrath, 1982; Timmermans & van Zwieten, 1982).

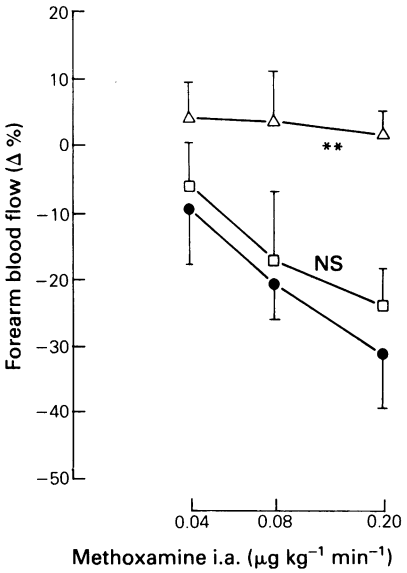

Figure 1 Mean (± s.d.) percentage changes in forearm blood flow during intra-arterial (i.a.) infusion of three cumulative doses of methoxamine in the presence of saline (● 0.4 ml min^{-1}, $n = 6$), yohimbine (□ 1.0 μg kg^{-1} min^{-1}, $n = 6$) and doxazosin (△ 0.1 μg kg^{-1} min^{-1}, $n = 4$). Each dose of the agonist was given for 3 min and the infusions of saline, yohimbine and doxazosin were started 3 min before the methoxamine infusion. Forearm blood flow was measured by venous occlusion plethysmography immediately before starting the infusions, during the last 90 s of the single infusion of saline, yohimbine and doxazosin, and subsequently during the last 90 s of each dose step of the agonist. Significant differences between the infusion with the antagonist and saline: $^{**}P < 0.01$; NS = not significant. After Jie *et al.* (1984a); reproduced with permission from *Circ. Res.*, **54**, 447–452.

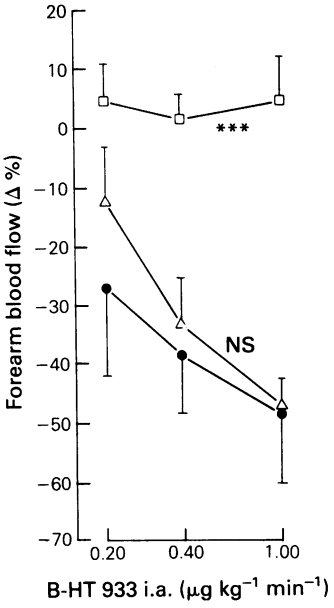

Figure 2 Mean (± s.d.) percentage changes in forearm blood flow during i.a. infusion of 3 cumulative doses of B-HT 933 in the presence of saline (● 0.4 ml min^{-1}, $n = 6$), yohimbine (□ 1.0 μg kg^{-1} min^{-1}, $n = 6$) and doxazosin (△ 0.1 μg kg^{-1} min^{-1}, $n = 5$). For details see legend to Figure 1. $^{***}P < 0.001$. After Jie *et al.* (1984a); reproduced with permission from *Circ. Res.*, **54**, 447–452.

On the basis of the evidence available, there remains little doubt that, as with various animal species (McGrath, 1982; Timmermans & van Zwieten, 1982), human blood vessels have a mixed population of postjunctional α_1- and α_2-adrenoceptors, which both mediate vasoconstriction when stimulated.

Contribution of postjunctional α-adrenoceptor subtypes to basal vascular tone in humans

Since systemic administration of α-adrenoceptor antagonists is invariably accompanied by changes in sympathetic activity (either indirectly via baroreflex mechanisms or directly via blockade of α-adrenoceptors in the central nervous system), the contribution of postjunctional α-adrenoceptors to vascular tone in humans has been studied almost exclusively in the forearm vascular bed. More than 40 years ago it was shown that complete sympathetic blockade (by deep nerve blockade) approximately doubled forearm blood flow in normal subjects, indicating the existence of vasoconstriction mediated by sympathetic nervous activity (Barcroft *et al.*, 1943). Later, the relevance of α-adrenoceptors to vascular tone was established in studies in which the non-selective α-adrenoceptor antagonists phenoxybenzamine and phentolamine were shown to produce vasodilation when infused into the brachial artery (Lowe & Robinson, 1964; Abboud *et al.*, 1968; Kiowski *et al.*, 1981).

Similarly, it has been demonstrated more recently that selective α_1-adrenoceptor blockade by prazosin (Amann *et al.*, 1981; Bolli *et al.*, 1983, 1984) or doxazosin (Jie *et al.*, 1984a, b; Thom *et al.*, 1985) as well as selective α_2-adrenoceptor blockade by yohimbine (van Brummelen *et al.*, 1983; Bolli *et al.*, 1983, 1984; Jie *et al.*, 1984a, 1985) caused vasodilation, indicating that both α-adrenoceptor subtypes contribute to vascular tone in basal conditions. Unlike the response to yohimbine, the

response to intra-arterial infusion of idazoxan is extremely variable and in the lower dose range even causes vasoconstriction (Thom *et al.*, 1985). It is clear that this response cannot be solely explained by blockade of postjunctional α_2-adrenoceptors, but preferential blockade of prejunctional α_2-adrenoceptors, and/or partial agonist activity of idazoxan on postjunctional α-adrenoceptors (Dalrymple *et al.*, 1983; Paciorek & Shepperson, 1983) could account for these results.

Although the evidence for participation of both α_1- and α_2-adrenoceptor mediated vasoconstriction to basal vascular tone is convincing, the relative contribution of each subtype is more difficult to establish. Complete dose–response curves for highly selective antagonists would be required to elucidate this. Unfortunately, in the human forearm this is not possible since higher doses of drug will produce systemic haemodynamic effects resulting in stimulation of homeostatic reflexes. Furthermore, the available drugs, especially the α_2-adrenoceptor antagonists, will lose selectivity when used in higher doses, and their affinity for prejunctional α_2-adrenoceptors will also hamper interpretation of the results. Nevertheless, from the various studies (van Brummelen *et al.*, 1983; Bolli *et al.*, 1983; Jie *et al.*, 1984a) it can be concluded that α_2-adrenoceptor mediated vasoconstriction contributes substantially to vasoconstrictor tone in healthy subjects.

Catecholamines and α-adrenoceptor subtypes

It is well established from pharmacological experiments in animals that both adrenaline and noradrenaline have affinity for α_1- and α_2-adrenoceptors (Timmermans & van Zwieten, 1982; McGrath, 1982; Langer & Hicks, 1984) and this has subsequently been confirmed in healthy volunteers (Elliott & Reid, 1983; Jie *et al.*, 1984b; Bolli *et al.*, 1984; Goldberg & Robertson, 1984; van Brummelen *et al.*, 1985).

Probably more relevant for unravelling the physiological role of α-adrenoceptors subtypes are experiments comparing the effectiveness of highly selective α-adrenoceptor antagonists in blocking the responses to exogenous noradrenaline and endogenously released neurotransmitter. In these studies it was invariably found that the effects of neuronally released noradrenaline were highly sensitive to α_1-adrenoceptor blockade whereas the effects of infused noradrenaline were more sensitive to α_2- than to α_1-adrenoceptor blockade (see Langer & Hicks, 1984 and references cited therein). These results were interpreted as evidence for innervation of α_1-adrenoceptors with noradrenaline being the natural agonist for this receptor subtype, and for an extrajunctional location of the postjunctional α_2-adrenoceptor. Since this evidence was exclusively based on experiments in animals or animal tissues, we have recently performed similar

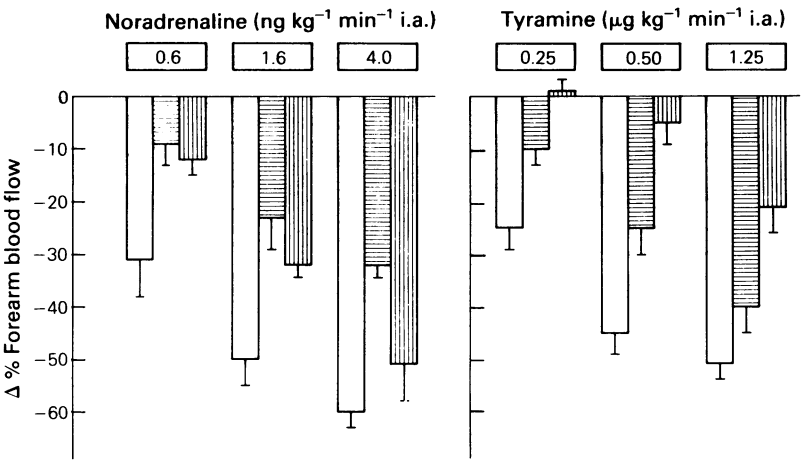

Figure 3 Mean percentage changes (± s.e. mean) in forearm blood flow during i.a. infusion of 3 cumulative doses of noradrenaline and tyramine in the presence of saline (□), yohimbine (▤ 1.0 μg kg^{-1} min^{-1}) and doxazosin (▥ 0.1 μg kg^{-1} min^{-1}). Each dose of noradrenaline was given for 3 min, each dose of tyramine for 5 min. The infusions of yohimbine and doxazosin started 10 min before the agonists. Forearm blood flow was measured by plethysmography, immediately before each infusion of an agonist and during the last 90 (noradrenaline) and 120 (tyramine) s of each dose step (Jie *et al.*, 1985).

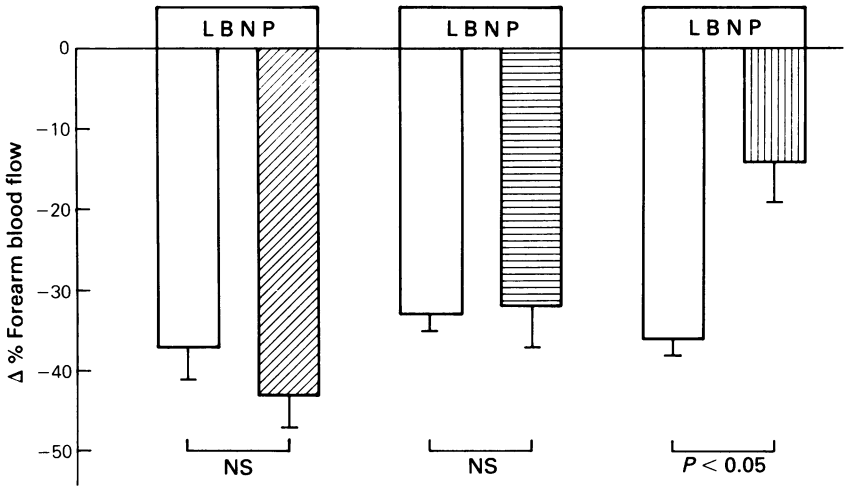

Figure 4 Mean percentage changes (± s.e. mean) in forearm blood flow in the control (□) and experimental arms during 5 min of lower body negative pressure (LBNP) -40 mmHg. Three i.a. infusions were used: saline (▨), yohimbine (▤ 1.0 μg kg^{-1} min^{-1}) and doxazosin (▥ 0.1 μg kg^{-1} min^{-1}). Forearm blood flow was measured simultaneously in both arms by plethysmography (Jie *et al.*, 1985).

studies in the forearm of healthy volunteers (Jie *et al.*, 1986).

In these studies, release of endogenous noradrenaline was stimulated by lower body negative pressure or intraarterial infusion of tyramine. It was shown that the vasoconstriction induced by exogenous noradrenaline was more effectively inhibited by the α_2-adrenoceptor antagonist yohimbine, whereas the vasoconstriction due to endogenously released noradrenaline was preferentially blocked by the α_1-adrenoceptor antagonist doxazosin (Figures 3 and 4). These results are in keeping with preferential intrajunctional location of α_1-adrenoceptors and

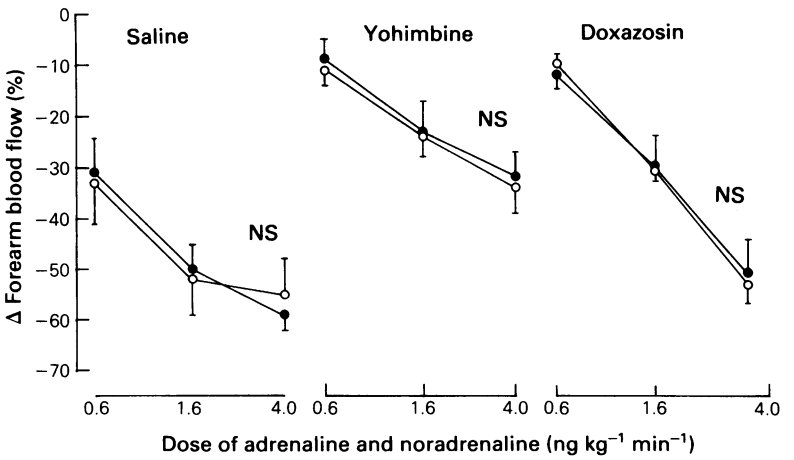

Figure 5 Mean percentage changes (± s.e. mean) in forearm blood flow in six healthy volunteers in response to i.a. infusion of adrenaline (○) and noradrenaline (●) in the presence of saline, yohimbine 1.0 μg kg^{-1} min^{-1} i.a., and doxazosin 0.1 μg kg^{-1} min^{-1} i.a. All infusions were given during local β-adrenoceptor blockade with propranolol 1.0 μg kg^{-1} min^{-1}. Each dose of the catecholamines was given for 3 min and the infusions of yohimbine and doxazosin were started 10 min before the catecholamines. For propranolol this was 3 min. Forearm blood flow was measured by plethysmography immediately before each infusion of a catecholamine and during the last 90 s of each dose step. After van Brummelen *et al.* (1985); reproduced with permission from *Clin. Sci.*, **68 (Suppl. 10)**, 151S–153S.

preferential extrajunctional location of α_2-adrenoceptors.

There is little doubt that noradrenaline is the natural agonist of the α_1-adrenoceptor but what is the natural agonist of the α_2-adrenoceptor? In other words, which catecholamine is responsible for α_2-adrenoceptor mediated vasoconstrictor tone? It has been suggested that circulating adrenaline is primarily responsible for α_2-adrenoceptor mediated vascular smooth muscle contraction (Ariens & Simonis, 1983; Bolli *et al.*, 1985). However, we were unable to find a preferential adrenaline agonism for the α_2-adrenoceptor in the forearm vascular bed of healthy volunteers (van Brummelen *et al.*, 1985). Indeed, during local β-adrenoceptor blockade with propranolol, it was apparent that adrenaline and noradrenaline were equally vasoconstrictor and the contribution of the α_1- and α_2-adrenoceptor was similar for each catecholamine (Jie *et al.*, 1984b; van Brummelen *et al.*, 1985) (Figure 5). In view of the differences in plasma levels between adrenaline and noradrenaline, it seems more likely that under physiological conditions noradrenaline is the agonist responsible for α_2-adrenoceptor vasoconstriction. In agreement with this view is the recent evidence that at physiological concentrations noradrenaline can also act as a cardiovascular hormone (Izzo, 1983).

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