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Review

Subtypes of functional α_1- and α_2-adrenoceptors

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Abstract

In this review, subtypes of functional α_1- and α_2-adrenoceptors are discussed. These are cell membrane receptors, belonging to the seven transmembrane spanning G-protein-linked family of receptors, which respond to the physiological agonists noradrenaline and adrenaline. α_1-Adrenoceptors can be divided into α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors, all of which mediate contractile responses involving $G_{q/11}$ and inositol phosphate turnover. A 4th α_1-adrenoceptor, the α_{1L}-, has been postulated to mediate contractions in some tissues, but its relationship to cloned receptors remains to be established. α_2-Adrenoceptors can be divided into α_{2A}-, α_{2B}- and α_{2C}-adrenoceptors, all of which mediate contractile responses. Prejunctional inhibitory α_2-adrenoceptors are predominantly of the α_{2A}-adrenoceptor subtype (the α_{2D}-adrenoceptor is a species orthologue), although α_{2C}-adrenoceptors may also occur prejunctionally. Although α_2-adrenoceptors are linked to inhibition of adenylate cyclase, this may not be the primary signal in causing smooth muscle contraction; likewise, prejunctional inhibitory actions probably involve restriction of Ca^{2+} entry or opening of K^+ channels. Receptor knock-out mice are beginning to refine our knowledge of the functions of α-adrenoceptor subtypes.

Keywords: α_1-Adrenoceptor; α_2-Adrenoceptor; Prejunctional receptor; Postjunctional receptor

1. Introduction

Adrenoceptors can be defined as the cell membrane receptors, belonging to the seven transmembrane spanning G-protein-linked family of receptors, which respond to the physiological agonists noradrenaline and adrenaline by producing a response in the cell. Adrenoceptors can be divided into two broad categories, α and β, or more correctly into three major sub-categories, α_1, α_2 and β, although this review will concentrate on α_1- and α_2-adrenoceptors. α-Adrenoceptors have been one of the most widely studied families of receptor because of the major physiological importance of these receptors in control of blood pressure and blood flow, neural modulation, digestion, micturition, airways, reproduction, pupil diameter, endocrine and metabolic processes and in behaviour.

Historically, Ahlquist (1948) described two types of adrenoceptor based on the rank order of potency of a series of agonists. The receptor termed β was mainly inhibitory, except in the heart, and the receptor termed α was mainly excitatory, except in the intestine. In Ahlquist's classification, α-adrenoceptors were receptors present on smooth muscle, i.e., postjunctional α-adrenoceptors.

The next major development in adrenoceptor classification did not occur until 1974, but the starting point for this was an article by Brown and Gillespie (1957) which demonstrated that the α-adrenoceptor antagonists dibenamine and phenoxybenzamine increased the release of neurotransmitter from cat spleen. In hindsight, similar observations had been made by Bacq and Frederico in 1934 (Bacq and Frederico, 1934) but were overlooked. These findings were initially explained in terms of potentiation of release of noradrenaline due to blockade of the neuronal noradrenaline transporter (Thoenen et al., 1964), but Starke et al. (1971) demonstrated that the α-adrenoceptor antagonist phentolamine increased stimulation-evoked noradrenaline release by an action distinct from uptake blockade. Since the α-adrenoceptor agonists xylazine (Heise et al., 1971) and clonidine (Starke et al., 1972) were then found to reduce the stimulation-evoked release of noradrenaline from adrenergic nerve terminals, it became clear that these actions of α-adrenoceptor agonists and antagonists were mediated by α-adrenoceptors on the nerve terminals, so called presynaptic or prejunctional receptors (see Starke, 1977). It is now well established that prejunctional receptors for a large number of neurotransmitters

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and neuromodulators are present on many kinds of nerve terminals. Prejunctional α-heteroceptors on non-adrenergic nerves mediate inhibition of transmission in those nerves, but, more interestingly, prejunctional α-autoreceptors on adrenergic nerves mediate a negative feedback whereby released noradrenaline modulates its own further release (for reviews, see Langer, 1974, 1997; Westfall, 1977; Starke, 1977, 1987).

Once the concept of prejunctional and postjunctional α-adrenoceptors had been accepted, it became clear that there were differences between pre- and postjunctional α-adrenoceptors in terms of the relative potencies of a series of agonists and antagonists. This led to the subclassification of α-adrenoceptors into α_1-postjunctional and α_2-prejunctional adrenoceptors (Langer, 1974). Later, when evidence accumulated for α_2-adrenoceptors located postjunctionally, this purely anatomical classification was refined into a pharmacological subclassification, independent of location (Berthelsen and Pettinger, 1977; Starke and Langer, 1979). Perhaps most surprisingly, α_2-adrenoceptors were shown to occur on vascular smooth muscle and to mediate vasoconstrictor responses (Drew and Whiting, 1979; Docherty et al., 1979; Docherty and McGrath, 1980). Initially, it was suggested that these α_2-adrenoceptors may be predominantly extrasynaptic and mediate responses to circulating catecholamines (Langer et al., 1981), but it later became clear that contractions to nerve stimulation in human saphenous vein and other tissues are also α_2-adrenoceptor mediated (Docherty and Hyland, 1985).

Further advances in our understanding of α-adrenoceptors have come from the development of new pharmacological methodologies for the study of receptors. The first of these was the technique of the radioligand binding assay which, beginning in the mid-1980's, began to demonstrate that there were subtypes of both α_1-adrenoceptors (see Morrow and Creese, 1986; Han et al., 1987) and α_2-adrenoceptors (see Bylund, 1985, 1988). However, the relationship between ligand binding sites and functional receptors was not always easy to ascertain (see Docherty, 1989). The study of α-adrenoceptors was revolutionised by the techniques of molecular biology. Six genes for α-adrenoceptors have now been identified and sequenced (α_{1A}, α_{1B}, α_{1D}, α_{2A}, α_{2B}, α_{2C}) and species orthologues have been identified (human α_{2A} and rat α_{2D}: see Bylund et al., 1994; Hieble et al., 1995). Studies of subtypes of receptor have been made easy by transfection of genes into suitable cell lines to produce pure populations of recombinant receptors.

Fig. 1 shows how the subclassification of α-adrenoceptors has developed since 1948.

The object of this short review is to look at functional subtypes of α-adrenoceptors, their physiological roles, and at some problems remaining in terms of subclassification. Rather than discuss α_1- and α_2-adrenoceptors independent of location, I have chosen to investigate pre- and postjunctional receptors separately to allow a more logical consideration of function.

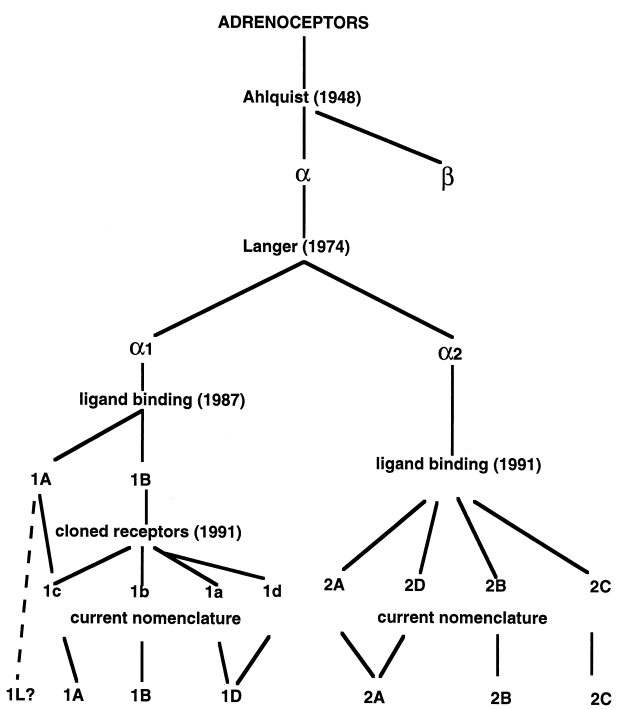

Fig. 1. A simplified representation of the history of the subdivision of α-adrenoceptors. The current classification includes three types of α_1-adrenoceptor (α_{1A}, α_{1B}, α_{1D}) and three types of α_2-adrenoceptor (α_{1A}, α_{2B}, α_{2C}). The status of the α_{1L}-adrenoceptor is unclear, but appears to have links with the α_{1A}.

2. Prejunctional α-adrenoceptors

2.1. Prejunctional α_2-adrenoceptor subtypes

2.1.1. Prejunctional $\alpha_{2A/D}$-adrenoceptors

α_2-Adrenoceptors have been subdivided into three subtypes, α_{2A}-, α_{2B}- and α_{2C}-adrenoceptors, based on ligand binding and molecular cloning studies (Lorenz et al., 1990; Bylund, 1992), and the rat α_{2D}-adrenoceptor is a species orthologue of the human α_{2A}-adrenoceptor (Lanier et al., 1991; Harrison et al., 1991). Functional prejunctional α_2-adrenoceptors in rat submandibular gland (Limberger et al., 1992; Smith et al., 1992a; Smith and Docherty, 1992), rat vas deferens (Smith et al., 1992a; Smith and Docherty, 1992) rat cerebral cortex (Trendelenberg et al., 1993), pithed rat heart (Smith et al., 1995), rat kidney (Bohmann et al., 1993) and mouse atria (Wahl et al., 1996) resemble the α_{2D}-adrenoceptor ligand binding site, whereas those in rabbit cerebral cortex (Trendelenberg et al., 1993), dog mesenteric artery (Daniel et al., 1995), human cerebral cortex (Raiteri et al., 1992) and human saphenous vein (Molderings and Gothert, 1995) resemble the α_{2A}-adrenoceptor.

2.1.2. Prejunctional α_{2C}-adrenoceptors?

However, some studies have produced results suggesting that prejunctional α_2-adrenoceptors may not always be of the $\alpha_{2A/D}$-subtype, or that more than one subtype may be present prejunctionally. Functional prejunctional α_{2C}-adrenoceptors have been reported in human kidney cortex (Trendelenberg et al., 1994) and human right atrium (Rump et al., 1995); however, this identification has been questioned (Trendelenburg et al., 1997). Furthermore, the functional prejunctional α_2-adrenoceptors in rat isolated atrium do not closely resemble the α_{2D}-adrenoceptor (Smith et al., 1992a; see also Limberger et al., 1992) (see Fig. 2). This led to an apparent anomaly that the prejunctional receptor activated by the synthetic α_2-adrenoceptor agonist xylazine in the pithed rat heart closely resembles the rat submandibular α_{2D}-adrenoceptor ligand binding site (see Fig. 2; Smith et al., 1995), whereas the prejunctional receptor activated by endogenous noradrenaline in rat isolated atrium does not (see Fig. 2). Limberger et al. (1992) also found that the prejunctional α_2-adrenoceptor of the rat atrium was difficult to subtype, given that it correlated well with all three subtypes of α_2-adrenoceptor, although, more recently, Trendelenburg et al. (1997) have reported that the inhibitory prejunctional receptor activated by the α_2-adrenoceptor agonist UK 14,304 (5-bromo-6-(2-imidazolin-2-yl-amino) quinoxaline) in rat atrium is an α_{2D}-adrenoceptor.

Due to this discrepancy which might suggest that more than one subtype is present in rat atria, prejunctional α_2-adrenoceptors in rat atrium and rat cerebral cortex were directly compared employing 8 adrenoceptor antagonists (Ho et al., 1998). Only the non selective adrenoceptor antagonist yohimbine and the α_{2D}-adrenoceptor selective adrenoceptor antagonist BRL 44408 (2-((4,5-dihydro-1*H*-imidazol-2-yl)methyl)-2,3-dihydro-1-methyl-1*H*-isoindole) had similar potencies in atria and cortex, suggesting that an

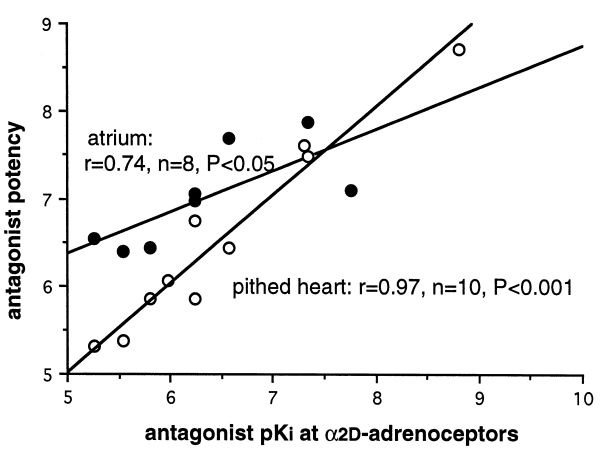

Fig. 2. Correlation between antagonist affinity for α_{2D}-ligand binding sites (rat submandibular gland) and antagonist prejunctional potency in the pithed rat heart (open symbols; $r = 0.97$, $n = 10$, $P < 0.001$) and rat isolated atrium (filled symbols; $r = 0.74$, $n = 8$, $P < 0.05$). Adapted from Smith et al. (1992a, 1995).

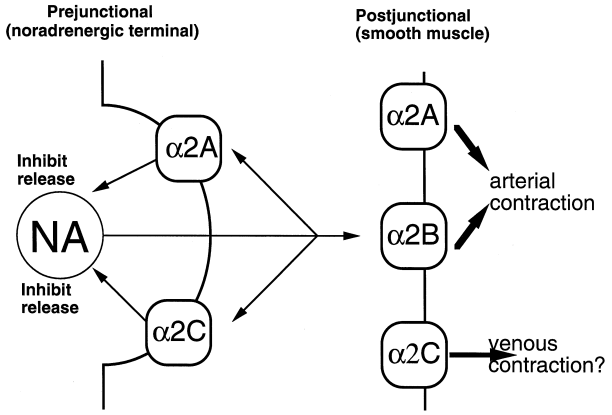

Fig. 3. Summary of the pre- and postjunctional sites of α_2-adrenoceptor subtypes. The predominant prejunctional adrenoceptor on noradrenergic nerve terminals is the α_{2A} (α_{2D} in rat), but α_{2C} may also be present. Postjunctionally, all three subtypes are present on vascular smooth muscle, but the α_{2C} may occur especially in venous smooth muscle.

α_{2D}-adrenoceptor is present in both tissues (Ho et al., 1998). However, the other 6 adrenoceptor antagonists, ARC 239 (2-(2,4-(*o*-methoxyphenyl)-piperazin-1-yl)-ethyl-4,4 dimethyl-1,3-(2*H*,4*H*)-isoquinolindine chloride), HV 723 (α-ethyl-3,4,5-trimethoxy-α-(3-((2-(2-methoxyphenoxy)ethyl)-amino)-propyl)-benzene acetonitrile fumarate), WB 4101 (2-(2′,6′-dimethoxyphenoxyethyl)aminomethyl-1,4-benzodioxan), prazosin, chlorpromazine and abanoquil, which show low affinity for α_{2D}-adrenoceptors in relation to α_{2B}- and/or α_{2C}-adrenoceptors, all significantly increased stimulation-evoked overflow at lower concentrations in rat atrium than rat cerebral cortex (Ho et al., 1998). The results suggest that, in addition to the α_{2D}-adrenoceptor, a second subtype of adrenoceptor is found in the rat atrium but not the cerebral cortex.

We now see that the resemblance of the rat atrial adrenoceptor to any of the α_2-adrenoceptor subtypes is complicated, presumably due to the presence of two subtypes. This probably means that the receptors activated by xylazine to inhibit tachycardia in the pithed rat (Smith et al., 1995) and by UK 14,304 to decrease transmitter release in rat atria (Trendelenburg et al., 1997) are predominantly of the α_{2D}-adrenoceptor subtype, whereas the receptors activated by noradrenaline to inhibit release of transmitter in atria are of two subtypes: α_{2D}-adrenoceptors and either α_{2B} or α_{2C} (Ho et al., 1998). Given the reports of functional prejunctional α_{2C}-adrenoceptors in human kidney cortex (Trendelenberg et al., 1994) and human right atrium (Rump et al., 1995), and that ligand binding studies show both α_{2A}- and α_{2C}-adrenoceptor subtypes in rat cerebral cortex and spinal cord (Uhlen et al., 1992), the evidence may suggest that this second prejunctional adrenoceptor subtype is α_{2C} (Docherty, 1994; see Fig. 3). Studies in α_2-adrenoceptor knockout mice confirm that two subtypes of α_2-adrenoceptor are present prejunctionally (Hein and Kobilka, 1998).

A further point of interest is to speculate on the possible differences in the roles of the two subtypes of prejunctional α_2-adrenoceptor. Both are targets for neurally released noradrenaline (at least when the noradrenaline transporter is blocked; Ho et al., 1998), but are they co-localised or in different locations on the nerve terminal; do they act through the same G-protein/second messenger system; are they internalised/recycled in the same way; does expression alter during development/ageing?

2.1.3. G-proteins and prejunctional α_2-adrenoceptors

G-protein-linked receptors have three possible modes of action in producing prejunctional inhibition: inhibition of Ca^{2+} channels (N or P/Q), activation of presynaptic K^+ channels or direct modulation of components of the vesicle release apparatus (Miller, 1998). The G-proteins involved in α_2-adrenoceptor mediated inhibition have been reported to be *N*-ethylmaleimide sensitive in a number of tissues including rat cerebral cortex (Kitamura and Nomura, 1987), mouse vas deferens (Kaschube and Brasch, 1990), rabbit hippocampus (Allgaier et al., 1986), rat tail artery (Weber, 1989), rabbit renal arteries (Rump et al., 1992), mouse atria (Murphy et al., 1992), rat renal cortex (Browne et al., 1994) and rat vas deferens (Browne et al., 1994). The G-proteins involved in α_2-adrenoceptor mediated inhibition have been reported to be pertussis toxin sensitive in rabbit hippocampus (Allgaier et al., 1986) but pertussis toxin insensitive in mouse atrium (Musgrave et al., 1987) and rat vas deferens (Docherty, 1988a; Borton and Docherty, 1990). However, in cultured rat sympathetic neurones, noradrenaline is reported both to produce voltage dependent, pertussis toxin-sensitive inhibition of N-type Ca^{2+} channels, involving the $\beta\gamma$ subunit of the G-protein (Delmas et al., 1998), and to inhibit release by a pertussis toxin insensitive action which does not involve altering Ca^{2+} entry via N-type channels (Schwartz, 1997). α_2-Adrenoceptor inhibition is sensitive to the K^+ channel blocker 4-aminopyridine in rat vas deferens (Docherty and Brady, 1995) and in the hypothalamus (Feuvrier et al., 1998). These results may suggest two modes of action of α_2-adrenoceptors in producing prejunctional inhibition, presumably opening of K^+ channels and inhibition of Ca^{2+} channels, but whether each mode is linked to a particular receptor subtype is unclear.

2.1.4. Effects of ageing on prejunctional α_2-adrenoceptor function

A decreased sensitivity of prejunctional α_2-adrenoceptors has been reported in most studies of ageing, and should result in an increased release of neurotransmitter, and this coupled with a reported decline in the re-uptake of norepinephrine (see Docherty, 1990a) with age should serve to maintain neurotransmission even if postjunctional responsiveness declines with age. There is an age-related decline in both prejunctional α_2- and 5-HT_1-receptor responsiveness in rat vas deferens, and pithed rat (see Docherty, 1990a), suggesting that the decline in response occurs at a postreceptor level, either at the level of the G-protein or beyond. In man, one of the most consistently reported changes during ageing is an increased plasma level of noradrenaline (Zeigler et al., 1976) due to an increased rate of appearance of noradrenaline in the plasma (MacGilchrist et al., 1989). A decreased function of the disposition mechanisms for norepinephrine, particularly the re-uptake process, linked to decrease function of prejunctional α_2-adrenoceptors, is a likely explanation of the increased plasma levels.

2.2. Prejunctional α_1-adrenoceptors

2.2.1. α_1-Adrenoceptor mediated inhibition

Following the subclassification of α-adrenoceptors into α_1- and α_2- subtypes, it was generally assumed that prejunctional α-adrenoceptors were exclusively of the α_2-subtype. However, Kobinger and Pichler (1980) demonstrated that the α_1-adrenoceptor selective agonist methoxamine inhibited the tachycardia to electrical stimulation in the pithed rat and this inhibition was antagonised by the α_1-adrenoceptor antagonist prazosin (see also Docherty, 1984). In addition, there are studies of postjunctional responses in vitro which support the contention that inhibitory prejunctional α_1-adrenoceptors exist in rat ventricle, rat vas deferens, rat kidney, dog heart, rat atria, rat tail artery, guinea-pig atria and on the cholinergic nerves of rat gastric fundus (for references, see Docherty, 1989). Admittedly, Rump and Majewski (1987) reported that inhibition of cyclooxygenase with indomethacin prevented the prejunctional inhibitory effects of methoxamine suggesting a role for prostaglandins, and Shinozuka et al. (1995) found that the inhibitory effect of methoxamine on noradrenaline release was blocked by adenosine deaminase and potentiated by the adenosine uptake inhibitor, dipyrisamole, suggesting that the effect involves adenyl purines. These latter studies may suggest transsynaptic inhibition by substances produced postjunctionally by α_1-adrenoceptor stimulation.

There are problems in interpreting the evidence in terms of inhibitory prejunctional α_1-adrenoceptors: different studies may be examining different phenomena, so that some studies may be of transsynaptic control, some of truly prejunctional α_1-inhibitory adrenoceptors; some of α_2-adrenoceptor subtypes which have high affinity for prazosin.

2.2.2. α_1-Adrenoceptor mediated facilitation

α_1-Adrenoceptor agonists have been reported to facilitate release of acetylcholine in rat heart (Bognar et al., 1990), parasympathetic ganglia of cat urinary bladder (Keast et al., 1990) and rat bladder (Yoshimura and de Groat, 1992). These α_1-adrenoceptors may be on the soma of bladder parasympathetic neurones and mediate a slow postsynaptic depolarisation (de Groat and Booth, 1980; Yoshimura and de Groat, 1992). The α_1-adrenoceptor

agonists methoxamine and phenylephrine are also reported to facilitate release of acetylcholine, in cholinergic nerve terminals of rat bladder (Somogyi et al., 1995). In rat cortical synaptosomes, phenylephrine increased the basal release of noradrenaline and this action was blocked by prazosin (Pastor et al., 1996). Phenylephrine also increased the basal release of noradrenaline in rat urinary bladder, and this action was blocked by the noradrenaline uptake blocker desipramine (Somogyi et al., 1995). The α_1-adrenoceptor mediated facilitation occurs in the same nerves as α_2-adrenoceptor mediated inhibition (Keast et al., 1990), and by analogy with muscarinic facilitation, may involve protein kinase C (Somogyi et al., 1996). Facilitation of rat spinal motoneuron activity is reported to be mediated by α_{1A}-adrenoceptors (Wada et al., 1997).

3. Postjunctional α-adrenoceptors

3.1. Postjunctional α_1-adrenoceptors

3.1.1. α_1-Adrenoceptor subtypes

α_1-Adrenoceptors were initially subdivided into α_{1A} and α_{1B}-subtypes in ligand binding studies, based on the affinities of a series of ligands, especially WB 4101 and prazosin (Morrow and Creese, 1986), and based on the ability of the alkylating agent chloroethylclonidine to inactivate the α_{1B} but not the α_{1A} subtype (Han et al., 1987). Under this classification, functional receptors mediating contractions of rat vas deferens are α_{1A}, and those of rat spleen (excluding α_2-adrenoceptors) are α_{1B} (Han et al., 1987).

Molecular cloning techniques revealed initially four subtypes of α_1-adrenoceptor (see Bylund et al., 1994). The α_{1b}-adrenoceptor subtype (the lower case subscript being used for recombinant receptors, and upper case subscript for pharmacologically defined receptor subtypes) was the first to be cloned, from the hamster (Cotecchia et al., 1988), and this clone expressed a protein with the radioligand binding properties of the α_{1B}-adrenoceptor. Other clones were the rat α_{1a} (Lomasney et al., 1991), the bovine α_{1c} (Schwinn et al., 1990) and rat α_{1d} (Perez et al., 1991). However, the α_{1a} and α_{1d} clones showed 99.8% homogeneity and appeared to represent the same subtype. It is now clear that the α_{1a}/α_{1d} clone represents a novel subtype of α_1-adrenoceptor (α_{1D}), whereas the α_{1c} is now identified with the α_{1A}-ligand binding site. These clones have now been renamed to match the functional receptors: α_{1A} (formerly α_{1c}), α_{1B} (formerly α_{1b}), and α_{1D} (formerly α_{1a}/α_{1d}) (see Table 1).

A major stimulus towards the development of new α_1-adrenoceptor drugs has been to treat the condition of benign prostatic hypertrophy, which affects a large proportion of elderly men, causing problems with micturition due to outflow obstruction. The outflow obstruction consists of a static component due to compression of the urethra by the enlarged prostate, and a dynamic component due to sympathetic contraction of the smooth muscle of the bladder neck, prostate and urethra, mediated by α_1-adrenoceptors. The dynamic component may contribute nearly 50% of the total urethral obstruction (as judged by the effects of spinal anaesthesia; Furuya et al., 1982), leading to the use of initially non-selective α-adrenoceptor antagonists (Caine, 1986). New α_1-adrenoceptor antagonists were developed for effects in the lower urinary tract (e.g., alfuzosin; Lefevre-Borg et al., 1993), and the receptors involved were identified as α_{1A}-adrenoceptors. However, some antagonists which were selective for α_{1A}-adrenoceptors in ligand binding studies had low potencies in functional studies of the lower urinary tract, e.g., RS 17053 (*N*-[2-(2-cyclopropylmethoxyphenoxy)ethyl]-5-chloro-α, α-dimethyl-1*H*-indole-3-ethanamine hydrochloride; Ford et al., 1996; Kenny et al., 1996), SB 216469 (*N*-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]-3-methyl-4-oxo-2-phenyl-4*H*-1-benzopropyran-8-carboxamide monoymethanesulphonate; Chess-Williams et al., 1996). These studies brought the study of α_{1A}-adrenoceptors into contact with parallel studies on α_{1L}-adrenoceptors.

3.1.2. α_{1L}-Adrenoceptors

One of the earliest functional subclassifications of α_1-adrenoceptors was into α_{1H} and α_{1L}, with high and low affinity for prazosin (see Flavahan and Vanhoutte, 1986), although it has been pointed out that prazosin has a wide range of affinities for α_1-adrenoceptors in functional studies (Drew, 1985; Docherty, 1989). This was further developed by Muramatsu et al. α_1-Adrenoceptors in blood vessels were subdivided into three subtypes, α_{1H}, α_{1N} and α_{1L}, based on their affinities for prazosin, WB 4101 and HV 723 (Muramatsu et al., 1990). α_{1H}-Adrenoceptors have high affinity for prazosin, and appear to match the α_{1A}, α_{1B}, α_{1D} classes (Muramatsu et al., 1995), whereas α_{1L} and α_{1N} have low affinity for prazosin and do not seem to match current molecular cloning based classifications. Under this classification, and often based on the low potency of prazosin, rabbit aorta, mesenteric and carotid arteries (Muramatsu et al., 1990), guinea-pig aorta, human prostate (Muramatsu et al., 1995), rat anococcygeus muscle (Ford et al., 1993), rabbit bladder neck (Kava et al., 1998), rabbit cutaneous resistance arteries (predominant adrenoceptor is α_{1B}: Smith et al., 1997), and rat small mesenteric artery (Van der Graaf et al., 1996) are reported to contain α_{1L}-adrenoceptors. Rat vas deferens is reported to contain α_{1L} in addition to α_{1A}, mediating contraction to both exogenous and endogenous noradrenaline (Ohmura et al., 1992).

We have studied contractile responses of epididymal portions of rat vas deferens to noradrenaline and to electrical stimulation. The contraction to noradrenaline is predominantly α_{1A}-adrenoceptor mediated as demonstrated by the very significant correlation with α_{1A}-adrenoceptor ligand binding sites (Docherty, 1998; see Fig. 4). In con-

Table 1
Summary of α_1-adrenoceptor subtype characteristics

Receptor subtype	1A	1B	1D	1L
Functional responses	Rat vas deferens contraction; control of blood pressure	Rat spleen contraction; control of blood pressure; role in rat tail artery contraction	Role in rat aorta contraction;	Human prostate contraction; rat vas deferens contraction
Ligand binding assay (other than transfected)	Rat submandibular gland	Rat spleen		
Selective agonists	Oxymetazoline; A61603			
Selective antagonists	RS 17053, SB216469		BMY 7378	low potency of RS17053; low potency of SB216469
Sensitivity to other agents		Very sensitive to CEC		
Second messenger systems	$G_{q/11}$, PI turnover	$G_{q/11}$, PI turnover	$G_{q/11}$, PI turnover	
Notes		Also α_2-component to spleen contraction; CEC also affects other subtypes		No gene identified; similarities to α_{1A}

Abbreviations (other than those explained in the main text): A 61603 (*N*-[5-(4,5-dihydro-1*H*-imidazol-2yl)-2-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-methanesulfonamide); BMY 7378: (8-[2-(4-(2-methoxyphenyl) piperazin-1-yl)ethyl]-8-azaspiro[4,5]decane-7,9-dione); CEC (chloroethylclonidine); PI: phosphoinositol.

Table 2
Summary of α_2-adrenoceptor subtype characteristics

Receptor subtype	2A/2D	2B	2C
Functional responses	Prejunctional inhibition in most adrenergic nerves; pressor responses in pithed rat; central hypotensive action	Pressor responses in anaesthetised mouse	Contraction of human saphenous vein; prejunctional inhibition in human and rat atria
Ligand binding assay (other than transfected)	Human platelet (2A); rat submandibular gland (2D)	Rat kidney	Opossum kidney (OK) cell line
Selective agonists	Oxymetazoline		
Selective antagonists	BRL 44408	ARC239, prazosin	ARC239, prazosin
Second messenger systems	G_i/G_o: decrease cAMP, inhibit Ca^{2+} channel (prej.), open K^+ channels (prej.)	G_i/G_o: decrease cAMP	G_i/G_o: decrease cAMP, inhibit Ca^{2+} channel (prej.), open K^+ channels (prej.)
notes	2A in man/rabbit; 2D in rat/mouse		

prej: Prejunctional.

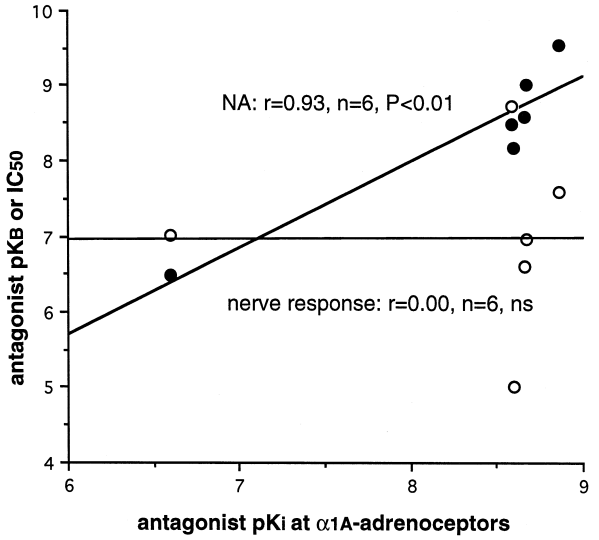

Fig. 4. Correlation between antagonist affinity for α_{1A}-ligand binding sites (data from Goetz et al., 1995; Marshall et al., 1995) and antagonist postjunctional potency in functional studies of rat vas deferens (antagonists employed: prazosin, WB 4101, 5-methylurapidil, benoxathian, BMY 7378, RS 17053; Docherty, 1998). There was significant correlation between affinity (pK_i) for α_{1A}-adrenoceptors and antagonist potency (pK_B) against contractions to exogenous noradrenaline (filled symbols; $r = 0.93$, $n = 6$, $P < 0.01$). There was no correlation between antagonist affinity for α_{1A}-adrenoceptors and antagonist potency (IC_{50}) at inhibiting nerve-evoked contractions (open symbols; $r = 0.00$, $n = 6$, ns), so that this response is not α_{1A}-adrenoceptor mediated and may be α_{1L}-like.

trast antagonist potency (IC_{50}) for inhibition of the contractile response to electrical stimulation in epididymal portions (in the presence of nifedipine 10 μM) did not correlate with any α_1-adrenoceptor ligand binding site (see Fig. 4).

Genetic polymorphism of α_{1A}-adrenoceptors does not explain α_{1L}-adrenoceptors, since all variants have been found to have similar pharmacological characteristics (Shibata et al., 1996). The α_{1A}-adrenoceptor, expressed in the Chinese hamster ovary CHO-K1 cell line, displayed binding properties of the α_{1A}-adrenoceptor but functionally, in terms of inositol phosphate accumulation, the receptor displayed properties of the α_{1L}-adrenoceptor (Ford et al., 1997). Hence, presumably due to factors determined by the methodology employed, and perhaps due to environmental differences around the receptor, the same receptor can show characteristics of both α_{1A}- and α_{1L}-adrenoceptors: hence α_{1A} and α_{1L} may be different affinity/conformational states of the α_{1A}-adrenoceptor. This is not simply a difference between lipophilic and non-lipophilic ligands in comparisons between membrane preparations and intact cells, since highly lipophilic ligands differed in their ability to discriminate between α_{1A}- and α_{1L}-adrenoceptors (Ford et al., 1997). However, α_{1A}- and α_{1L}-adrenoceptors can be demonstrated under virtually identical conditions in functional contractile studies (cf. results from rat vas deferens in Fig. 4).

3.1.3. Responses mediated by α_{1A}-adrenoceptors

Contractions are reported to be mediated at least partly by α_{1A}-adrenoceptors in a number of tissues including rat vas deferens (Burt et al., 1995; Noble et al., 1997; Burt et al., 1998), rat renal artery (also α_{1D}, Villalobos-Molina et al., 1997), rat tail artery (Villalobos-Molina and Ibarra, 1996; Lachnitt et al., 1997, including a second subtype), rat right atrium (positive inotropic actions, also α_{1B}; Yu and Han, 1994), rabbit ear artery (also second subtype, Fagura et al., 1997), human vas deferens (Furukawa et al., 1995; Moriyama et al., 1997), and human prostate (Marshall et al., 1995; also α_{1B}, Teng et al., 1994; but see above). In rat vas deferens α_{1A}-adrenoceptors mediate two types of response: phasic due to release of Ca^{2+} from ryanodine sensitive stores, and tonic via protein kinase C by diacylglycerol and influx of Ca^{2+} via nifedipine sensitive stores (Burt et al., 1998).

A61603 is an α_{1A}-adrenoceptor selective agonist, reported to be 200 times more potent than noradrenaline at causing contractions of rat vas deferens (Knepper et al., 1995).

3.1.4. Responses mediated by α_{1B}-adrenoceptors

Contractions are reported to be mediated at least partly by α_{1B}-adrenoceptors in a number of tissues including rat spleen (Burt et al., 1995; Noble et al., 1997), mouse spleen (Eltze, 1996a), rat right atrium (positive inotropic, also α_{1A}: Yu and Han, 1994), rabbit corpus cavernosum (Noble et al., 1997), rabbit cutaneous resistance arteries (also α_{1L}, Smith et al., 1997), human prostate (also α_{1A}, Teng et al., 1994).

Risperidone was suggested to be an α_{1B}-adrenoceptor selective antagonist in ligand binding studies (Sleight et al., 1993); however, this selectivity has been questioned in functional studies (Eltze, 1996b).

3.1.5. Responses mediated by α_{1D}-adrenoceptors

Contractions are reported to be mediated at least partly by α_{1D}-adrenoceptors in a number of tissues including rat aorta, mesenteric artery and pulmonary artery (predominantly α_{1D}, but receptor heterogeneity, Hussain and Marshall, 1997), rat renal artery (also α_{1A}; Villalobos-Molina et al., 1997), rat carotid artery, mesenteric artery, aorta (Villalobos-Molina and Ibarra, 1996), rabbit aorta (also possibly α_{1A}: Fagura et al., 1997), and rabbit ventricle (also other subtypes, Yang and Endoh, 1997). In contrast, α_{1D} are reported to be involved in contractions of rat aorta, and iliac artery, but not in caudal, mesenteric or renal arteries (Piascik et al., 1995). BMY 7378 is a selective antagonist at α_{1D}-adrenoceptors (Goetz et al., 1995).

Clearly, contractions in a number of tissues are mediated by more than one subtype of α_1-adrenoceptor (e.g., rat aorta, see Aboud and Docherty, 1993; Van der Graaf et al., 1996; Hussain and Marshall, 1997), and currently available subtype selective antagonists are often not selective enough to tease out clearly which receptors are pre-

sent. Receptor knock-out studies in mice may help. For instance, contractions in rat tail artery develop more slowly in α_{1B}-adrenoceptor knock-out mice (Daly et al., 1998), so that subtle differences can be revealed following receptor knock-out.

3.1.6. Chloroethylclonidine and α_1-adrenoceptors

Chloroethylclonidine has been used to identify subtypes of α_1-adrenoceptor, due to its actions to alkylate α_{1B}-adrenoceptors, but chloroethylclonidine interacts with all subtypes of α_1-adrenoceptor (Michel et al., 1993), and with α_2-adrenoceptors (Michel et al., 1993; O'Rourke et al., 1997). Chloroethylclonidine has two actions on rat aorta: reduction of the contraction to low concentrations of noradrenaline by α_1-adrenoceptor antagonism, and irreversible partial agonism in combination with high concentrations of noradrenaline (O'Rourke et al., 1995, 1997). In the absence of chloroethylclonidine, exposure to phenoxybenzamine virtually abolished contractions to subsequent noradrenaline. However, when tissues were exposed to chloroethylclonidine prior to exposure to phenoxybenzamine, a large contraction was produced by subsequent noradrenaline (O'Rourke et al., 1997). Receptor protection with the α_2-adrenoceptor antagonists yohimbine or methoxyidazoxan, but not the α_1-adrenoceptor antagonist prazosin, significantly reduced the ability of chloroethylclonidine to prevent the actions of phenoxybenzamine against noradrenaline. These results suggest that chloroethylclonidine interacts as a silent irreversible agonist with α_2-adrenoceptors in rat aorta to make contractions to subsequent noradrenaline resistant to α-adrenoceptor blockade.

3.1.7. Postjunctional α_1-adrenoceptor second messenger systems

α_1-Adrenoceptors are coupled to a wide variety of second messenger systems via G-proteins, predominantly to pertussis toxin insensitive G-proteins of the $G_{q/11}$ family to phospholipase C (Minneman, 1988; Wu et al., 1992), but is also linked through pertussis sensitive G-proteins of the G_i or G_o family to phospholipase A2 (Exton, 1996). Activation of all α_1-adrenoceptor subtypes results via phospholipase C in formation of inositol triphosphate and diacylglycerol. Diacylglycerol stimulates protein kinase C and inositol triphosphate acts on the inositol triphosphate receptor in endoplasmic reticulum to release stored calcium: the net result is increased entry of extracellular Ca^{2+} and/or release from Ca^{2+} stores (Minneman, 1988; Wu et al., 1992). α_1-Adrenoceptor activation causes phospholipase A_2 stimulation and arachidonic acid release in the mammalian COS cell line (Perez et al., 1993), causes arachidonic acid release by phospholipase D activation in rat tail artery (Gu et al., 1992) and rat fibroblasts (Ruan et al., 1998), and can lead to cAMP production (Perez et al., 1993; Ruan et al., 1998). Other reported α_1-adrenoceptor actions involve stimulation of the Na^+–K^+–Cl^- cotransport and a chloride pump to increase $[Cl]_i$ and shift E_{Cl} to potentiate depolarisation caused by noradrenaline in rat femoral artery (Davis et al., 1997); arachidonic acid release and reactive oxygen species generation causing smooth muscle proliferation (Nishio and Watanabe, 1997); regulation of gene expression (Mark et al., 1990).

3.2. Postjunctional α_2-adrenoceptors

3.2.1. Postjunctional α_2-adrenoceptors in vivo

α_2-Adrenoceptors occur on vascular smooth muscle and mediate vasoconstrictor responses in the pithed rat preparation (Drew and Whiting, 1979; Docherty et al., 1979; Docherty and McGrath, 1980). More recently, the subtypes of α_2-adrenoceptor involved in these pressor responses have been investigated. The correlation between the functional postjunctional α_2-adrenoceptor in the pithed rat was closest with the α_{2D}-adrenoceptor ligand binding site of submandibular gland ($r = 0.91$) than with the rat kidney α_{2B}-adrenoceptor ($r = 0.77$), and the correlation with the α_{2C}-adrenoceptor subtype was relatively poor ($r = 0.71$, unpublished) (Gavin and Docherty, 1996). This suggests that the predominant receptor mediating pressor responses in the pithed rat is the α_{2D}-adrenoceptor, although other subtypes, especially the α_{2B}-adrenoceptor, may also be involved.

Studies of α_2-adrenoceptors in knock-out mice do not necessarily disagree with these findings. In conscious mice lacking the $\alpha_{2A/D}$-adrenoceptor, central hypotensive actions of α_2-adrenoceptor agonists were absent (MacMillan et al., 1996), but in mice lacking the α_{2B}-adrenoceptor peripheral hypertensive actions of α_2-adrenoceptor agonists were absent (Link et al., 1996). However, it may be that $\alpha_{2A/D}$ adrenoceptors mediate both central hypotension and peripheral hypertension, but the central actions dominate in conscious animals. Our results do not rule out the involvement of α_{2B}-adrenoceptors in pressor responses in pithed rats, but suggest that $\alpha_{2A/D}$ are predominant.

3.2.2. Postjunctional α_2-adrenoceptors in isolated tissues

In terms of postjunctional α_2-adrenoceptors in isolated tissues, there is relatively little evidence available as to subtypes mediating vascular contractions, given the relatively few preparations in which these receptors can be demonstrated in isolation. The human saphenous vein is a preparation in which postjunctional α_2-adrenoceptors are the dominant adrenoceptors mediating contraction. In our studies of side branches of the human saphenous vein, the postjunctional α-adrenoceptors appear to be a homogeneous population of α_2-adrenoceptors with no evidence for α_1-adrenoceptors: yohimbine was approximately 10 times more potent than prazosin; both yohimbine and prazosin produce parallel shifts in the noradrenaline concentration–response curve (see Smith et al., 1992b); potent α_1-adrenoceptor antagonists such as HV 723 (see Muramatsu et al., 1990) have relatively low potency; the α_1-

adrenoceptor selective agonist phenylephrine had low potency; prazosin antagonised contractions to phenylephrine and noradrenaline to the same extent; the α_2-adrenoceptor selective agonist oxymetazoline had relatively high potency (see Gavin et al., 1997). Other authors have investigated the postjunctional α-adrenoceptors of human saphenous vein and found that contractions are mediated predominantly by α_2-adrenoceptors (Muller-Schweinitzer, 1984; Steen et al., 1984), or by a combination of α_1- and α_2-adrenoceptors (Eskinder et al., 1988; Roberts et al., 1992). Differences between studies may be due to differences in source of veins: varicose vein surgery of predominantly female patients (present results and Muller-Schweinitzer, 1984; Steen et al., 1984); coronary artery bypass surgery of (presumably) predominantly male patients (Eskinder et al., 1988; Roberts et al., 1992), side branches of varicose veins from predominantly female patients (author's studies).

We have previously investigated the postjunctional α_2-adrenoceptor mediating contraction of the human saphenous vein and found that it does not resemble the α_{2A}-adrenoceptor of human platelet (Smith et al., 1992b), and now find that it closely resembles the α_{2C}-adrenoceptor (Gavin et al., 1997). In the porcine palmer lateral vein and common digital artery a low potency of prazosin suggests the presence of an $\alpha_{2A/D}$-adrenoceptor (Blaylock and Wilson, 1995), and an $\alpha_{2A/D}$-adrenoceptor has also been reported in dog saphenous vein (Hicks et al., 1991; MacLennan et al., 1997). In a number of tissues, α_2-adrenoceptors contribute to a predominantly α_1-adrenoceptor mediated response. In rat cremaster arterioles and venules, part of the contractile response is α_2-adrenoceptor mediated, and based on the potency of BRL 44408, responses seem to be mediated by α_{2D}-adrenoceptors (Leech and Faber, 1996). Studies of α_2-adrenoceptors in the rat tail artery (Xiao and Rand, 1989), tail vasculature (Redfern et al., 1995) and rabbit corpus cavernosum smooth muscle (Gupta et al., 1998; see also Andersson and Wagner, 1995) did not investigate the subtype involved. α_2-Adrenoceptors are also reported to enhance the effects of α_1-adrenoceptor agonists in guinea-pig cauda epididymis (Haynes and Hill, 1996), and in mouse vas deferens (Bultmann et al., 1991). $\alpha_{2A/D}$-Adrenoceptors are present postjunctionally in rat pancreatic islets where they mediate inhibition of insulin secretion (Niddam et al., 1990).

3.2.3. Postjunctional α_2-adrenoceptor second messenger systems

It has long been known that α_2-adrenoceptors negatively couple to adenylate cyclase via a G_i protein susceptible to pertussis toxin, but whether this action is the main mode of action in producing vascular contractions is debatable. Certainly, α_2-adrenoceptor agonists enhance contractions to α_1-adrenoceptor agonists in guinea-pig cauda epididymis, an effect that is not by enhancement of inositol phosphate accumulation, but may be by inhibition of forskolin-stimulated cAMP accumulation (Haynes and Hill, 1996). A component of the α-adrenoceptor mediated contraction of rabbit corpus cavernosum smooth muscle is α_2-adrenoceptor mediated, and α_2-adrenoceptor agonists inhibit forskolin stimulated cAMP accumulation in these cells (Gupta et al., 1998). In the guinea-pig uterus, α_2-adrenoceptor agonism enhances contractions to α_1-adrenoceptor agonists, and inhibits forskolin stimulation cAMP accumulation (Haynes et al., 1993). α_2-Adrenoceptor mediated pressor responses are sensitive to pertussis toxin (Boyer et al., 1983; Docherty, 1990b), suggesting the involvement of a G_i or G_o protein. Admittedly, pressor responses to α_2-adrenoceptor agonists in the pithed rat are strongly dependent on angiotensin II, as shown by the actions of captopril (Docherty, 1988b). However, in porcine palmer lateral vein, Wright et al. (1995) found that α_2-adrenoceptor contractions are not mediated by reduction in cAMP per se, but when cAMP levels are elevated by agents which stimulate adenylate cyclase, α_2-adrenoceptors can act to inhibit cAMP production. In human subcutaneous resistance vessels, α_2-adrenoceptor contractions involve an influx of Ca^{2+}, probably through voltage operated Ca^{2+} channels, involving a pertussis toxin sensitive G-protein (Parkinson and Hughes, 1995). Unlike α_1-adrenoceptors, α_2-adrenoceptors are not coupled to phospholipase C, but may be linked to phospholipase A_2 in some cell types, although this does not seem to be the mode of action in resistance vessels (Parkinson and Hughes, 1995).

3.2.4. α_2-Adrenoceptor subtype selective drugs

SKF 104078 (6-chloro-9-[(3-methyl-2-butenyl)oxyl]-3-methyl-1*H*-2,3,4,5-tetrahydro-3-benzazepine) was suggested to be a postjunctionally selective antagonist, blocking postjunctional α_2-adrenoceptors, leaving prejunctional α_2-adrenoceptors functioning (Ruffolo et al., 1987), but SKF 104078 is reported to have prejunctional antagonist actions in rat vas deferens, human saphenous vein, pithed rat heart and guinea-pig atrium in the same concentration-range as it blocked postjunctional α_2-adrenoceptors (Connaughton and Docherty, 1988, 1990; Oriowo et al., 1991; Akers et al., 1991; Molderings and Gothert, 1995). Ligand binding studies do not support the contention that SK 104078 is selective, as it binds with relatively high affinity to $\alpha_{2A/D}$-adrenoceptors as well as α_{2B} and α_{2C} (Svensson et al., 1996).

BRL 44408 is a potent selective antagonist at $\alpha_{2A/D}$-adrenoceptors, both in ligand binding and functional studies (Young et al., 1989; Gavin et al., 1997). A number of antagonists show low potency at $\alpha_{2A/D}$-adrenoceptors, including prazosin and ARC239 (see Ho et al., 1998).

A selective α_{2D}-adrenoceptor agonist may have benefits over non-selective agonists by acting centrally to lower blood pressure with diminished peripheral pressor effects (see Link et al., 1996; MacMillan et al., 1996). In terms of antagonists, an α_{2B}-adrenoceptor antagonist may have ad-

vantages in blocking postjunctional α_{2B} without affecting prejunctional α_{2D}, although α_{2D} may also be of importance in blood pressure control.

4. Postjunctional α-adrenoceptors and ageing

Responsiveness of vascular α_1-adrenoceptors has been widely studied in relation to ageing; however, most studies have failed to find any change with age in contractile responses of isolated blood vessels or in pressor responses to agonists. Contractile responses to α_1-adrenoceptor agonists may be influenced by altered function of the vascular endothelium so that an increased responsiveness to α_1-adrenoceptor agonists of rat tail artery with age can be explained by diminished vasodilator function of the vascular endothelium (Tabernero and Vila, 1995).

The pressor potency of the α_2-adrenoceptor agonist xylazine is reduced by ageing in the rat (Docherty, 1988b). However, this age-related difference in the pressor potency of xylazine is abolished by the angiotensin converting enzyme inhibitor captopril, suggesting that an age-related decline in angiotensin levels (or responsiveness) causes the change in α_2-responsiveness. In human saphenous veins obtained from varicose vein surgery of predominantly female patients, a significant age-related negative correlation between noradrenaline potency and age has been reported (Docherty, 1993), suggesting that the ability of these veins to respond to sympathetic stimulation is decreased by age and that this may contribute to postural hypotension in the elderly. However, the ability of α_2-adrenoceptor agonists to potentiate α_1-adrenoceptor mediated contractions is unchanged by age in rat tail artery (Tsai et al., 1993). Age may differentially affect α_1- and α_2-adrenoceptor subtypes.

5. Physiological responses mediated by α-adrenoceptors

5.1. Physiological responses mediated by α_1-adrenoceptors

Piascik et al. (1990) reported that the α_{1A}-subtype played a role in the tonic maintenance of blood pressure in the conscious rat, whereas the α_{1B}-subtype participates in the response to exogenous agonists. In knock-out mice lacking the α_{1B}-adrenoceptor subtype, there was no effect on basal blood pressure, but the pressor response to phenylephrine were significantly blunted (Cavalli et al., 1997). These results may suggest that both α_{1A}- and α_{1B}-adrenoceptors are involved in blood pressure control, and further studies may lead to more selective α_1-adrenoceptor antagonists as antihypertensives, avoiding side effects such as postural hypotension?

5.2. Physiological responses mediated by α_2-adrenoceptors

As has been elegantly shown using knock-out mice, α_{2A}-adrenoceptors are involved in the central hypotensive actions of α_2-adrenoceptor agonists whereas α_{2B}-adrenoceptors are involved in the peripheral pressor responses (MacMillan et al., 1996; Link et al., 1996). There were no haemodynamic effects produced by disruption of the α_{2C}-adrenoceptor (Link et al., 1996). These effects are systemic cardiovascular effects and do not allow for subtle effects on different vascular beds, nor do they prove categorically that the $\alpha_{2A/D}$-subtype has purely central actions or that the α_{2B}-subtype is the only mediator of pressor responses. Clearly, there is a need for more detailed studies of knock-out mice to answer these questions.

In wild type mice, the α_2-adrenoceptor agonist dexmedetomidine produces antinociceptive (Stone et al., 1997), sedative and hypothermic actions, which were absent in α_{2A} mutant mice, but effects of dexmedetomidine were relatively unaffected in α_{2B} or α_{2C} knockout mice (Hunter et al., 1997). The α_{2A}-mutant mice had diminished morphine analgesic potency (Stone et al., 1997). However, other knock-out studies suggest that the α_{2C}-adrenoceptor is also involved in the hypothermic actions of α_2-agonists (Sallinen et al., 1997). The antinociceptive actions of α_2-agonists involve G_i and particularly G_{i3} (Raffa et al., 1996).

6. Conclusion

The characteristics of α_1- and α_2-adrenoceptor subtypes are summarised in Tables 1 and 2. Although a great deal is known about the function of α-adrenoceptor subtypes, a number of major questions remain to be answered: the identity of the α_{1L}-response; the second messengers involved in a significant number of responses; therapeutic potential of the development of receptor subtype selective agonists and antagonists. Mutant mice, in which receptor genes have been manipulated preventing expression, or causing overexpression, of a receptor protein, will be powerful tools in future studies of the physiological function of α-adrenoceptor subtypes.

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References

Aboud, R.W., Shafii, M., Docherty, J.R., 1993. Investigations of the subtypes of α_1-adrenoceptor mediating contractions of rat aorta, vas deferens and spleen. Br. J. Pharmacol. 109, 80–87.

Ahlquist, R.P., 1948. A study of the adrenotropic receptors. Am. J. Physiol. 153, 586–600.

Akers, I., Coates, J., Drew, G.M., Sullivan, A.T., 1991. α_2-Adrenoceptor blocking profile of SK and F 104078: further evidence for receptor subtypes. Br. J. Pharmacol. 102, 943–949.

Allgaier, C., Feuerstein, T.J., Hertting, G., 1986. *N*-ethyl-maleimide (NEM) diminishes α_2-adrenoceptor mediated effects on noradrenaline release. Naunyn-Schmiedeberg's Arch. Pharmacol. 333, 104–109.

Andersson, K.-E., Wagner, G., 1995. Physiology of penile erection. Physiol. Rev. 75, 192–236.

Bacq, Z.M., Frederico, H., 1934. Action adrenolytique d'un derive de dioxane (933F). Comptes Rendues Societe Belge de Biologie 117, 806–808.

Berthelsen, S., Pettinger, W.A., 1977. A functional basis for classification of a-adrenergic receptors. Life Sci. 21, 595–606.

Blaylock, N.A., Wilson, V.G., 1995. Pharmacological characterization of noradrenaline-induced contractions of the porcine isolated palmer lateral vein and palmer common digital artery. Br. J. Pharmacol. 114, 694–702.

Bognar, T.I., Baretti, R., Fischer, S., Veldet, C., Fuder, H., 1990. Alpha-adrenoceptor mediated facilitation of acetylcholine release in rat perfused heart. J. Pharmacol. Exp. Ther. 254, 702–710.

Bohmann, C., Schollmeyer, P., Rump, L.C., 1993. α_2-Autoreceptor subclassification in rat isolated kidney by use of short trains of electrical stimulation. Br. J. Pharmacol. 108, 262–268.

Borton, M., Docherty, J.R., 1990. The effects of ageing on prejunctional 5-hydroxytryptamine receptors in the rat vas deferens. Naunyn-Schmiedeberg's Arch. Pharmacol. 342, 130–135.

Boyer, J.L., Cardenas, C., Posadas, C., Garcia-Sainz, J.A., 1983. Pertussis toxin induces tachycardia and impairs the increase in blood pressure produced by alpha2-adrenergic agonists. Life Sci. 33, 2627–2633.

Brown, G.L., Gillespie, J.S., 1957. The output of sympathetic transmitter from the spleen of the cat. J. Physiol. 138, 81–102.

Browne, I., Thomas, G., Gavin, K., Docherty, J.R., 1994. Prejunctional actions of *N*-ethyl-maleimide and phenoxybenzamine in rat vas deferens. Eur. J. Pharmacol. 265, 125–132.

Bultmann, R., von Kugelgen, I., Starke, K., 1991. Contraction-mediating α_2-adrenoceptors in the mouse vas deferens. Naunyn-Schmiedeberg's Arch. Pharmacol. 343, 623–632.

Burt, R.P., Chapple, C.R., Marshall, I., 1995. Evidence for a functional α_{1A}- (α_{1C}-) adrenoceptor mediating contraction of rat epididymal vas deferens and an α_{1B}-adrenoceptor mediating contraction of the rat spleen. Br. J. Pharmacol. 115, 467–475.

Burt, R.P., Chapple, C.R., Marshall, I., 1998. α_{1A}-Adrenoceptor mediated contraction of rat prostatic vas deferens and the involvement of ryanodine stores and Ca^{2+} influx stimulated by diacylglycerol and PKC. Br. J. Pharmacol. 123, 317–325.

Bylund, D.B., 1985. Heterogeneity of alpha-2 adrenergic receptors. Pharmacol. Biochem. Behav. 22, 835–843.

Bylund, D.B., 1988. Subtypes of α_2-adrenoceptors: pharmacological and molecular biological evidence converge. Trends Pharmacol. Sci. 9, 356–361.

Bylund, D.B., 1992. Subtypes of α_1- and α_2-adrenergic receptors. FASEB J. 6, 832–839.

Bylund, D.B., Eikenberg, D.C., Heible, J.P., Langer, S.Z., Lefkowitz, R.J., Minneman, K.P., Molinoff, P.B., Ruffolo, R.R., Trendelenburg, U., 1994. IV. International union of pharmacology nomenclature of adrenoceptors. Pharmacol. Rev. 46, 121–136.

Caine, M., 1986. The present role of α-adrenergic blockers in the treatment of benign prostatic hypertrophy. J. Urol. 136, 1–4.

Cavalli, A., Lattion, A., Hummler, E., Nenninger, M., Pedrazzini, T., 1997. Decreased blood pressure response in mice deficient of the alpha 1b-adrenergic receptor. Proc. Natl. Acad. Sci. USA 94, 11589–11595.

Chess-Williams, R., Chapple, C.R., Verfurth, F., Noble, A.J., Couldwell, C.J., Michel, M.C., 1996. The effects of SB 216469, an antagonist which discriminates between the α_{1A}-adrenoceptor and the human prostatic α_1-adrenoceptor. Br. J. Pharmacol. 119, 1093–1100.

Connaughton, S., Docherty, J.R., 1988. Evidence that SK and F 104078 does not differentiate between pre- and postjunctional alpha-2 adrenoceptors. Naunyn-Schmiedeberg's Arch. Pharmacol. 338, 379–382.

Connaughton, S., Docherty, J.R., 1990. Functional evidence for heterogeneity of peripheral prejunctional α_2-adrenoceptors. Br. J. Pharmacol. 101, 285–290.

Cotecchia, S., Schwinn, D.A., Randall, R.R., Lefkowitz, R.J., Caron, M.G., Kobilka, B.K., 1988. Molecular cloning and expression of the cDNA for the hamster α_1-adrenergic receptor. Proc. Natl. Acad. Sci USA 85, 7159–7163.

Daly, C.J., Cotecchia, S., McGrath, J.C., 1998. Low frequency electrical field stimulation elicits responses in segments of mouse tail artery which are slower in alpha1B-knockout mice than in control mice. Naunyn-Schmiedeberg's Arch. Pharmacol. 358, R600.

Daniel, E.E., Gaspar, V., Berezin, I., Kwan, C.Y., 1995. Characterization of alpha2 adrenoceptors and other adrenoceptors in membranes isolated from dog mesenteric nerve axons. J. Pharmacol. Exp. Ther. 275, 978–986.

Davis, J.P.L., Harper, A.A., Chipperfield, A.R., 1997. Stimulation of intracellular chloride accumulation by noradrenaline and hence potentiation of its depolarization of rat arterial smooth muscle in vitro. Br. J. Pharmacol. 122, 639–642.

de Groat, W.C., Booth, A.M., 1980. Inhibition and facilitation in parasympathetic ganglia. Fed. Proc. 39, 2990–2996.

Delmas, P., Brown, D.A., Dayrell, M., Abogadie, F.C., Caulfield, M.P., Buckley, N.J., 1998. On the role of endogenous G-protein bg subunits in N-type Ca^{2+} current inhibition by neurotransmitters in rat sympathetic neurones. J. Physiol. 506, 319–329.

Docherty, J.R., 1984. An investigation of presynaptic alpha-adrenoceptor subtypes in the pithed rat heart and in the rat isolated vas deferens. Br. J. Pharmacol. 82, 15–23.

Docherty, J.R., 1988a. Pertussis toxin and prejunctional α_2-adrenoceptors in rat heart and vas deferens. J. Auton. Pharmacol. 8, 197–201.

Docherty, J.R., 1988b. The effects of ageing on vascular alpha-adrenoceptors in pithed rat and rat aorta. Eur. J. Pharmacol. 146, 1–5.

Docherty, J.R., 1989. The pharmacology of α_1- and α_2-adrenoceptors: evidence for and against a further subdivision. Pharmacol. Ther. 44, 241.

Docherty, J.R., 1990a. Cardiovascular responses in ageing: a review. Pharmacol. Rev. 42, 103–125.

Docherty, J.R., 1990b. No effect of pertussis toxin on peripheral prejunctional alpha-2 adrenoceptor mediated responses and on endothelium-dependent relaxations in the rat. Br. J. Pharmacol. 100, 348–352.

Docherty, J.R., 1993. Effects of ageing on the vasoconstrictor responses to noradrenaline and 5-hydroxytryptamine in the human saphenous vein. Cardiol. Elderly 1, 327–330.

Docherty, J.R., 1994. Alpha-adrenoceptors: from theoretical concept to molecular visualisation. Ir. J. Med. Sci. 163, 4–8.

Docherty, J.R., 1998. Investigations of the subtype of α_1-adrenoceptor in rat vas deferens. Naunyn-Schmiedeberg's Arch. Pharmacol. 358, R612.

Docherty, J.R., Brady, G., 1995. Prejunctional actions of K^+ channel blockers in rat vas deferens. Eur. J. Pharmacol. 287, 287–293.

Docherty, J.R., Hyland, L., 1985. Vascular α_2-adrenoceptors can mediate nerve stimulation-evoked contractions. Clin. Sci. 68 (Suppl. 10), 117s–120s.

Docherty, J.R., McGrath, J.C., 1980. A comparison of pre- and postjunctional potencies of several alpha-adrenoceptor agonists in the cardio-

vascular system and anococcygeus muscle of the rat: evidence for two types of postjunctional alpha-adrenoceptor. Naunyn-Schmiedeberg's Arch. Pharmacol. 312, 107–116.

Docherty, J.R., MacDonald, A., McGrath, J.C., 1979. Further subclassification of alpha-adrenoceptors in the cardiovascular system, vas deferens and anococcygeus muscle of the rat. Br. J. Pharmacol. 67, 421P.

Drew, G.M., 1985. What do antagonists tell us about α-adrenoceptors?. Clin. Sci. 68, 15s–19s, Suppl. 10.

Drew, G.M., Whiting, S.B., 1979. Evidence for two distinct types of postsynaptic α-adrenoceptor in vascular smooth muscle in vivo. Br. J. Pharmacol. 67, 207–215.

Eltze, M., 1996a. Functional evidence for an alpha 1B-adrenoceptor mediating contraction of the mouse spleen. Eur. J. Pharmacol. 311, 187–198.

Eltze, M., 1996b. In functional experiments, risperidone is selective, not for the B, but for the A subtype of alpha-1 adrenoceptor. Eur. J. Pharmacol. 295, 69–73.

Eskinder, H., Hillard, C.J., Olinger, G.N., Christensen, C.W., Baker, J.E., Warltier, D.C., Gross, G.J., 1988. Alpha adrenoceptor subtypes and receptor reserve in human versus canine saphenous vein: sensitivity to blockade by nitroglycerin. J. Pharmacol. Exp. Ther. 247, 941–948.

Exton, J.H., 1996. Regulation of phosphoinositide phospholipases by hormones, neurotransmitters, and other agonists linked to G proteins. Annu. Rev. Pharmacol. Toxicol. 36, 481–509.

Fagura, M.S., Lyfdford, S.J., Douggall, I.G., 1997. Pharmacological classification of α_1-adrenoceptors mediating contractions of rabbit isolated ear artery: comparison with rat isolated thoracic aorta. Br. J. Pharmacol. 120, 247–258.

Feuvrier, E., Aubert, M., Mausset, A.L., Alonso, G., Gaillet, S., Malaval, F., Szafarczyk, A., 1998. Glucocorticoids provoke a shift from alpha2- to alpha1-adrenoceptor activities in cultured hypothalamic slices leading to opposite noradrenaline effect on corticotropin-releasing hormone release. J. Neurochem. 70, 1199–1209.

Flavahan, N.A., Vanhoutte, P.A., 1986. α_1-Adrenoceptor subclassification in vascular smooth muscle. Trends Pharmacol. Sci. 7, 347–349.

Ford, A.P.D.W., Berge, N.V., Clarke, D.E., 1993. Characterisation of α_1-adrenoceptors in isolated anococcygeus muscle of rat. Br. J. Pharmacol. 109, 112P.

Ford, A.P.D.W., Arredondo, N.F., Blue, D.R., Bonhaus, D.W., Jasper, J., Kava, M.S., Lesnick, J., Pister, J.R., Shieh, I.M., Vimont, R.L., Williams, T.J., McNea, J.E., Stamey, T.A., Clarke, D.E., 1996. RS-17053,a selective α_{1A}-adrenoceptor antagonist, displays low affinity for functional α_1-adrenoceptors in human prostate: implications for adrenoceptor classification. Mol. Pharmacol. 49, 209–215.

Ford, A.P.D.W., Daniels, D.V., Chang, D.J., Gever, J.R., Jasper, J.R., Lesnick, J.D., Clarke, D.E., 1997. Pharmacological pleiotropism of the human recombinant α_{1A}-adrenoceptor: implications for α_1-adrenoceptor classification. Br. J. Pharmacol. 121, 137–1135.

Furukawa, K., Rosario, D.J., Smith, D.J., Chapple, C.R., Uchiyama, T., Chess-Williams, R., 1995. α_{1A}-Adrenoceptor-mediated contractile responses of the human vas deferens. Br. J. Pharmacol. 116, 1605–1610.

Furuya, S., Kumamoto, Y., Yokoyama, E., Tsukamoto, T., Izumi, T., Abiko, Y., 1982. Alpha-adrenergic activity and urethral pressure in prostatic zone in benign prostatic hypertrophy. J. Urol. 128, 836–839.

Gavin, K., Docherty, J.R., 1996. Investigation of the subtype of α_2-adrenoceptor mediating pressor responses in the pithed rat. Eur. J. Pharmacol. 318, 81–87.

Gavin, K.T., Colgan, M.-P., Moore, D., Shanik, G., Docherty, J.R., 1997. α_{2C}-Adrenoceptors mediate contractile responses to noradrenaline in the human saphenous vein. Naunyn-Schmiedeberg's Arch. Pharmacol. 355, 406–411.

Goetz, A.S., King, H.K., Ward, S.D.C., True, T.A., Rimele, T.J., Saussy, D.L., 1995. BMY 7378 is a selective antagonist of the D subtype of α_1-adrenoceptors. Eur. J. Pharmacol. 272, R5–R6.

Gu, H., Trajkovic, S., LaBelle, E.F., 1992. Norepinephrine-induced phosphatidylcholine hydrolysis by phospolipases D and C in rat tail artery. Am. J. Physiol. 262, C1376–C1383.

Gupta, S., Moreland, R.B., Yang, S., Gallant, C.M., Goldstein, I., Traish, A., 1998. The expression of functional postsynaptic a2-adrenoceptors in the corpus cavernosum smooth muscle. Br. J. Pharmacol. 123, 1237–1245.

Han, C., Abel, P.W., Minneman, K.P., 1987. α_1-Adrenoceptor subtypes linked to different mechanisms for increasing intracellular Ca^{2+} in smooth muscle. Nature 329, 333–335.

Harrison, J.K., Pearson, W.R., Lynch, K.R., 1991. Molecular characterization of α_1- and α_2-adrenoceptors. Trends Pharmacol. Sci. 12, 62–67.

Haynes, J.M., Hill, S.J., 1996. α-Adrenoceptor mediated responses of the cauda epididymis of the guinea-pig. Br. J. Pharmacol. 119, 1203–1210.

Haynes, J.M., Adams, G.D., Pennefather, J.N., 1993. α_2-Adrenoceptors in the guinea-pig uterus: heterogeneity in the circular and longitudinal smooth muscle layers. Eur. J. Pharmacol. 250, 231–237.

Hein, L., Kobilka, B.K., 1998. Clinical and molecular pharmacology of adrenergic receptors. Naunyn-Schmiedeberg's Arch. Pharmacol. 358, R575.

Heise, A., Kroneberg, G., Schlossman, K., 1971. α-Sympathicomimetische eigenschaften als ursache der blutdrucksteigernden und blutdruckenkenden wirkung von BAY 1470. Naunyn-Schmiedeberg's Arch. Pharmacol. 268, 348–360.

Hicks, P.E., Barras, M., Herman, G., Mauduit, P., Armstrong, J.M., Rossignol, B., 1991. α-Adrenoceptor subtypes in dog saphenous vein that mediate contraction and inositol phosphate production. Br. J. Pharmacol. 102, 151–161.

Hieble, J.P., Bylund, D.B., Clarke, D.E., Eikenburg, D.C., Langer, S.Z., Lefkowitz, R.J., Minneman, K.P., Ruffolo, R.R., 1995. International Union of Pharmacology: X. Recommendation for nomenclature of α_1-adrenoceptors: consensus update. Pharmacol. Rev. 47, 267–270.

Ho, S.L., Honner, V., Docherty, J.R., 1998. Investigation of the subtypes of α_2-adrenoceptor mediating prejunctional inhibition in rat atrium and cerebral cortex. Naunyn-Schmeidberg's Arch. Pharmacol. 357, 634–639.

Hunter, J.C., Fontana, D.J., Hedley, L.R., Japser, J.R., Lewis, R., Link, R.E., Secchi, R., Sutton, J., Eglen, R.M., 1997. Assessment of the role of alpha2-adrenoceptor subtypes in the antinociceptive, sedative and hypothermic action of dexmedetomidine in transgenic mice. Br. J. Pharmacol. 122, 1339–1344.

Hussain, M., Marshall, I., 1997. Characterization of α_1-adrenoceptor subtypes mediating contractions to phenylephrine in rat thoracic aorta, mesenteric artery and pulmonary artery. Br. J. Pharmacol. 122, 849–858.

Kaschube, M., Brasch, H., 1990. Pre- and postjunctional effects of *N*-ethylmaleimide in the isolated mouse vas deferens. Eur. J. Pharmacol. 178, 151–159.

Kava, M.S., Blue, D.R., Vimont, R.L., Clarke, D.E., Ford, A.P.D.W., 1998. α_{1L}-Adrenoceptor mediation of smooth muscle contraction in rabbit bladder neck: a model for lower urinary tract tissues of man. Br. J. Pharmacol. 123, 1359–1366.

Keast, J.R., Kawatani, M., de Groat, W.C., 1990. Sympathetic modulation of cholinergic transmission in cat vesical ganglia is mediated by α_1- and α_2-adrenoceptors. Am. J. Physiol. 258, R44–R50.

Kenny, B.A., Miller, A.M., Williamson, I.J.R., O'Connell, J., Chalmers, D.H., Naylor, A.M., 1996. Evaluation of the pharmacological selectivity profile of α_1-adrenoceptor antagonists at prostatic α_1-adrenoceptors: binding, functional and in vivo studies. Br. J. Pharmacol. 118, 871–878.

Kitamura, Y., Nomura, Y., 1987. Uncoupling of rat cerebral cortical α_2-adrenoceptors from GTP-binding proteins by *N*-ethylmaleimide. J. Neurochem. 49, 1894–1901.

Knepper, S.M., Buckner, S.A., Brune, M.E., DeBernardis, J.F., Meyer, M.D., Hancock, A.A., 1995. A-61603, a potent α_1-adrenergic receptor agonist, selective for the α_{1A} receptor subtype. J. Pharmacol. Exp. Ther. 274, 97–103.

Kobinger, W., Pichler, L., 1980. Investigations into different types of post

and presynaptic α-adrenoceptors at cardiovascular sites in rats. Eur. J. Pharmacol. 65, 393–402.

Lachnitt, W.G., Tran, A.M., Clarke, D.E., Ford, A.P.D.W., 1997. Pharmacological characterization of an α_{1A}-adrenoceptor mediating contractile responses to noradrenaline in isolated caudal artery of rat. Br. J. Pharmacol. 120, 819–826.

Langer, S.Z., 1974. Presynaptic regulation of catecholamine release. Biochem. Pharmacol. 23, 1793–1800.

Langer, S.Z., 1997. 25 years since the discovery of presynaptic receptors: present knowledge and future perspectives. Trends Pharmacol. Sci. 18, 95–99.

Langer, S.Z., Massingham, R., Shepperson, N.B., 1981. Presence of postsynaptic α_2-adrenoceptors of predominantly extrasynaptic location in the vascular smooth muscle of the dog hind limb. Clin. Sci. 59, 225s–228s, Suppl. 6.

Lanier, S.M., Downing, S., Duzie, E., Homey, C.J., 1991. Isolation of rat genomic clones encoding subtypes of the α_2-adrenergic receptor. J. Biol. Chem. 266, 10470–10478.

Leech, C.J., Faber, J.E., 1996. Different α-adrenoceptor subtypes mediate constriction of arterioles and venules. Am. J. Physiol. 270, H710–H722.

Lefevre-Borg, F., O'Connor, S.E., Shoemaker, H., Hicks, P.E., Lechaire, J., Gautier, E., Pierre, F., Pimoule, C., Manoury, P., Langer, S.Z., 1993. Alfuzosin, a selective α_1-adrenoceptor antagonists in the lower urinary tract. Br. J. Pharmacol. 109, 1282–1289.

Limberger, N., Trendelenburg, A.-U., Starke, K., 1992. Pharmacological characterisation of presynaptic α_2-autoreceptors in rat submaxillary gland and heart atrium. Br. J. Pharmacol. 107, 246–255.

Link, R.E., Desai, K., Hein, L., Stevens, M.E., Chruscinski, A., Bernstein, D., Barsh, G.S., Kobilka, B.K., 1996. Cardiovascular regulation in mice lacking alpha sub 2-adrenergic receptor subtypes b and c. Science 273, 803–806.

Lomasney, J.W., Cotecchia, S., Lorenz, W., Leung, W.-Y., Schwinn, D.A., Yang-Feng, T.L., Brownstein, M., Lefkowitz, R.J., Caron, M., 1991. Molecular cloning and expression of the cDNA for the α_{1A}-adrenergic receptor. J. Biol. Chem. 266, 6365–6369.

Lorenz, W., Lomasney, J.W., Collins, S., Regan, J.W., Caron, M.G., Lefkowitz, R.J., 1990. Expression of three α_2-adrenergic receptor subtypes in rat tissues: implications for α_2-receptor classification. Mol. Pharmacol. 38, 599–603.

MacGilchrist, A.J., Hawksby, C., Howes, L.G., Reid, J.L., 1989. Rise in plasma noradrenaline with age results from an increase in spillover rate. Gerontology 35, 7–13.

MacLennan, S.J., Luong, L.A., Jasper, J.R., To, Z.P., Eglen, R.M., 1997. Characterization of α_2-adrenoceptors mediating contraction of dog saphenous vein: identity with human 2A subtype. Br. J. Pharmacol. 121, 1721–1729.

MacMillan, L.B., Hein, L., Smith, M.S., Piascik, M.T., Limbird, L.E., 1996. Central hypotensive effects of the alpha sub 2a-adrenergic subtype. Science 273, 801–803.

Mark, W.M., Mat, J.A.P.D., Stephen, M.S., 1990. α_1-Adrenergic stimulation of platelet-derived growth factor signal transduction. Science 270, 296–299.

Marshall, I., Burt, R.P., Chapple, C.R., 1995. Noradrenaline contractions of human prostate mediated by α_{1A}- (α_{1c}-) adrenoceptor subtype. Br. J. Pharmacol. 115, 781–786.

Michel, M.C., Kerker, J., Branchek, T.A., Forray, C., 1993. Selective irreversible binding of chloroethylclonidine at α_1- and α_2-adrenoceptor subtypes. Mol. Pharmacol. 44, 1165–1170.

Miller, R.J., 1998. Presynaptic receptors. Annu. Rev. Pharmacol. Toxicol. 38, 201–207.

Minneman, K.P., 1988. Alpha1-adrenergic receptor subtypes, inositol phosphates and sources of cell Ca^{2+}. Pharmacol. Rev. 40, 87–119.

Molderings, G.J., Gothert, M., 1995. Subtype determination of presynaptic α_2-adrenoceptors in the rabbit pulmonary artery and human saphenous vein. Naunyn-Schmiedeberg's Arch. Pharmacol. 352, 483–490.

Moriyama, N., Nasu, K., Takeuchi, T., Akiyama, K., Murata, S., Mishimatsu, H., Yano, J., Tsujimoto, G., Kawabe, K., 1997. Quantification and distribution of α_1-adrenoceptor subtype mRNAs in human vas deferens: comparison with those of epididymal and pelvic portions. Br. J. Pharmacol. 122, 1009–1014.

Morrow, A.L., Creese, I., 1986. Characterization of α_1-adrenergic receptor subtypes in rat brain: a re-evaluation of [^{3}H]WB4101 and [^{3}H]prazosin binding. Mol. Pharmacol. 29, 321–330.

Muller-Schweinitzer, E., 1984. Alpha-adrenoceptors, 5-hydroxytryptamine receptors and the action of dihydroergotamine in human venous preparations obtained during saphenectomy procedures for varicose veins. Naunyn-Schmiedeberg's Arch. Pharmacol. 327, 299–303.

Muramatsu, I., Ohmura, T., Kigoshi, S., Hashimoto, S., Oshita, M., 1990. Pharmacological subclassification of α_1-adrenoceptors in vascular smooth muscle. Br. J. Pharmacol. 99, 197–201.

Muramatsu, I., Oshita, M., Ohmura, T., Kigoshi, S., Akino, H., Gobara, M., Okada, K., 1995. Pharmacological characterization of α_1-adrenoceptor subtypes in the human prostate: functional and binding studies. Br. J. Urol. 74, 572–578.

Murphy, T.V., Foucart, S., Majewski, H., 1992. Prejunctional α_2-adrenoceptors in mouse atria function through G-proteins which are sensitive to *N*-ethylmaleimide, but not pertussis toxin. Br. J. Pharmacol. 106, 871–876.

Musgrave, I., Marley, P., Majewski, H., 1987. Pertussis toxin does not attenuate α_2-adrenoceptor mediated inhibition of noradrenaline release in mouse atria. Naunyn-Schmiedeberg's Arch. Pharmacol. 336, 280–286.

Niddam, R., Angel, I., Bidet, S., Langer, S.Z., 1990. Pharmacological characterization of α_2-adrenergic receptor subtype involved in the release of insulin from rat isolated pancreatic islets. J. Pharmacol. Exp. Ther. 254, 883–887.

Nishio, E., Watanabe, Y., 1997. The involvement of reactive oxygen species and arachidonic acid in α_1-adrenoceptor-induced smooth muscle cell proliferation and migration. Br. J. Pharmacol. 121, 665–670.

Noble, A.J., Chess-Williams, R., Couldwell, C., Furukawa, K., Uchyiuma, T., Korstanje, C., Chapple, C.R., 1997. The effects of tamsulosin, a high affinity antagonist at functional α_{1A}- and α_{1D}-adrenoceptor subtypes. Br. J. Pharmacol. 120, 231–238.

Ohmura, T., Oshita, M., Kigoshi, S., Muramatsu, I., 1992. Identification of α_1-adrenoceptor subtypes in the rat vas deferens: binding and functional studies. Br. J. Pharmacol. 107, 698–704.

Oriowo, M.A., Hieble, J.P., Ruffolo, R.R., 1991. Evidence for heterogeneity of prejunctional α_2-adrenoceptors. Pharmacology 43, 1–13.

O'Rourke, M., Kearns, S., Docherty, J.R., 1995. Investigations of the actions of chloroethylclonidine in rat aorta. Br. J. Pharmacol. 115, 1399–1406.

O'Rourke, M., Gavin, K., Docherty, J.R., 1997. Further investigation of the α-adrenoceptor mediated actions of chloroethylclonidine in rat aorta. Eur. J. Pharmacol. 336, 37–42.

Parkinson, N.A., Hughes, A.D., 1995. The mechanism of action of α_2-adrenoceptors in human isolated subcutaneous resistance arteries. Br. J. Pharmacol. 115, 1463–1468.

Pastor, C., Badia, A., Sabria, J., 1996. Possible involvement of alpha-1 adrenoceptors in the modulation of [^{3}H]noradrenaline release in rat brain cortical and hippocampal synaptosomes. Neurosci. Lett. 216, 187–190.

Perez, D.M., Piascik, M.T., Graham, R.M., 1991. Solution-phase library screening for the identification of rare clones: isolation of an α_{1D}-adrenergic receptor cDNA. Mol. Pharmacol. 40, 876–883.

Perez, D.M., DeYoung, M.P., Graham, R.M., 1993. Coupling of expressed α_{1B}- and α_{1D}-adrenergic receptors to multiple signaling

pathways is both G-protein and cell type specific. Mol. Pharmacol. 44, 784–795.

Piascik, M.T., Kusiak, J.W., Barron, K.W., 1990. α_1-Adrenoceptor subtypes and the regulation of peripheral hemodynamics in the conscious rat. Eur. J. Pharmacol. 186, 273–278.

Piascik, M.T., Guarino, R.D., Smith, M.S., Soltis, E.E., Saussy, D.L., Perez, D.M., 1995. The specific contribution of the novel alpha-1D adrenoceptor to the contraction of vascular smooth muscle. J. Pharmacol. Exp. Ther. 275, 1583–1589.

Raffa, R.B., Connelly, C.D., Chambers, J.R., Stone, D.J., 1996. Alpha-subunit G-protein antisense oligonucleotide effects on supraspinal (i.c.v.) alpha2-adrenoceptor antinociception in mice. Life Sci. 58, 77–80.

Raiteri, M., Bonanno, G., Maura, G., Pende, M., Andrioli, G.C., Ruelle, A., 1992. Subclassification of release-regulating α_2-autoreceptors in human brain cortex. Br. J. Pharmacol. 107, 1146–1151.

Redfern, W.S., MacLean, M.R., Clague, R.U., McGrath, J.C., 1995. The role of α_2-adrenoceptors in the vasculature of the rat tail. Br. J. Pharmacol. 114, 1724–1730.

Roberts, S.P., Kelly, J., Cawthorne, M.A., Sennitt, M.V., 1992. SK and F 104078, a postjunctionally selective α_2-adrenoceptor antagonist in the human saphenous vein in vitro. Naunyn-Schmiedeberg's Arch. Pharmacol. 345, 327–332.

Ruan, Y., Kan, H., Parmentier, J.-H., Fatima, S., Allen, L.F., Malik, K.U., 1998. Alpha-1A adrenergic receptor stimulation with phenylephrine promotes arachidonic acid release by activation of phospholipase D in rat-1 fibroblasts: inhibition by protein kinase A. J. Pharmacol. Exp. Ther. 284, 575–585.

Ruffolo, R.R., Sulpizio, A.C., Nichols, A.J., DeMarinis, R.M., Heible, J.P., 1987. Pharmacologic differentiation between pre- and postjunctional α_2-adrenoceptors by SF and F 104078. Naunyn-Schmiedeberg's Arch. Pharmacol. 336, 415–418.

Rump, L.C., Majewski, H., 1987. Modulation of noradrenaline release through α_1- and α_2-adrenoceptors in rat isolated kidney. J. Cardiovasc. Pharmacol. 9, 500–507.

Rump, L.C., Volk, V., Ruff, G., Schollmeyer, P., 1992. Activation of α_1- and α_2-adrenoceptors inhibits noradrenaline release in rabbit renal arteries: effects of pertussis toxin and *N*-ethylmaleimide. J. Auton. Pharmacol. 12, 97–108.

Rump, L.C., Bohmann, C., Schaible, U., Schollhor, J., Limberger, N., 1995. α_{2C}-Adrenoceptor-modulated release of noradrenaline in human right atrium. Br. J. Pharmacol. 116, 2617–2624.

Sallinen, J., Link, R.E., Haapalinna, A., Viitamaa, T., Kulatunga, M., Sjoholm, B., MacDonald, E., Pelto-Huikko, M., Leino, T., Barsh, G.S., Kobilka, B.K., Scheinin, M., 1997. Genetic alteration of alpha 2C-adrenoceptor expression in mice: influence on locomotor, hypothermic, and neurochemical effects of dexmedetomidine, a subtype-nonselective alpha2-adrenoceptor agonist. Mol. Pharmacol. 51, 36–46.

Schwartz, D.D., 1997. Activation of alpha-2 adrenergic receptors inhibits norepinephrine release by a pertussis toxin-insensitive pathway independent of changes in cytosolic calcium in cultured rat sympathetic neurones. J. Pharmacol. Exp. Ther. 282, 248–255.

Schwinn, D.A., Lomasney, J.W., Lorenz, W., Szklut, P.J., Fremeau, R.T., Yang-Feng, T.L., Caron, M.G., Lefkowitz, R.J., Cotecchia, S., 1990. Molecular cloning and expression of the cDNA for a novel α_1-adrenergic receptor subtype. J. Biol. Chem. 265, 8183–8189.

Shibata, K., Hirasawa, A., Moriyama, N., Kawabe, K., Ogawa, S., Tsujimoto, G., 1996. α_{1a}-Adrenoceptor polymorphism: pharmacological characterization and association with benign prostatic hypertrophy. Br. J. Pharmacol. 118, 1403–1408.

Shinozuka, K., Kunitomo, M., Bjur, R.A., Westfall, D.P., Hattori, K., 1995. Effect of methoxamine on noradrenaline release in the caudal artery of hypertensive rats. Clin. Exp. Pharmacol. Physiol. 22 (Suppl. 1), S88–S90.

Sleight, A.J., Koek, W., Bigg, D.C., 1993. Binding of antipsychotic drugs at alpha 1A- and alpha 1B-adrenoceptors: risperidone is selective for the alpha 1B-adrenoceptors. Eur. J. Pharmacol. 238, 407–410.

Smith, K., Docherty, J.R., 1992. Are the prejunctional α_2-adrenoceptors of the rat vas deferens and submandibular gland of the α_{2A}- or α_{2D}-subtype?. Eur. J. Pharmacol. 219, 203–210.

Smith, K., Connaughton, S., Docherty, J.R., 1992a. Investigations of prejunctional α_2-adrenoceptors in rat atrium, vas deferens and submandibular gland. Eur. J. Pharmacol. 211, 251–256.

Smith, K., Connaughton, S., Docherty, J.R., 1992b. Investigations of the subtype of α_2-adrenoceptor mediating contraction of the human saphenous vein. Br. J. Pharmacol. 106, 447–451.

Smith, K., Gavin, K., Docherty, J.R., 1995. Investigation of the subtype of α_2-adrenoceptor mediating prejunctional inhibition of cardio-acceleration in the pithed rat heart. Br. J. Pharmacol. 115, 316–320.

Smith, K.M., Macmillan, J.B., McGrath, J.C., 1997. Investigation of α_1-adrenoceptor subtypes mediating vasoconstriction in rabbit cutaneous resistance arteries. Br. J. Pharmacol. 122, 825–832.

Somogyi, G.T., Tanowitz, M., de Groat, W.C., 1995. Prejunctional facilitatory alpha-1 adrenoceptors in the rat urinary bladder. Br. J. Pharmacol. 114, 1710–1716.

Somogyi, G.T., Tanowitz, M., Zernova, G., de Groat, W.C., 1996. M_1 muscarinic receptor-induced facilitation of ACh and noradrenaline release in the rat bladder is mediated by protein kinase C. J. Physiol. 496, 245–254.

Starke, K., 1977. Regulation of noradrenaline release by presynaptic receptor systems. Rev. Physiol. Biochem. Pharmacol. 77, 1–124.

Starke, K., 1987. Presynaptic-autoreceptors. Rev. Physiol. Biochem. Pharmacol. 107, 73–146.

Starke, K., Langer, S.Z., 1979. A note on the terminology for presynaptic receptors. In: Langer, S.Z., Starke, K., Dubocovich, M.L. (Eds.), Presynaptic Receptors. Pergamon, Oxford, pp. 1–3.

Starke, K., Montel, H., Schumann, J.J., 1971. Influence of cocaine and phenoxybenamine on noradrenaline uptake and release. Naunyn-Schmiedeberg's Arch. Pharmacol. 274, 18–45.

Starke, K., Wagner, J., Schumann, J.J., 1972. Adrenergic neurone blockade with clonidine: comparison with guanethidine and local anaesthetics. Influence of cocaine and phenoxybenamine on noradrenaline uptake and release. Arch. Int. Pharmacodyn. Ther. 195, 291–308.

Steen, S., Sjoberg, T., Skarby, T., Norgren, L., Andersson, K.-E., 1984. The postjunctional α-adrenoceptors of the human saphenous vein. Acta Pharmacol. Toxicol. 55, 351–357.

Stone, L.S., MacMillan, L.B., Kitto, K.E., Limbird, L.E., Wilcox, G.L., 1997. The alpha2a adrenergic receptor subtype mediates spinal analgesia evoked by alpha-2 agonists and is necessary for spinal adrenergic-opioid synergic. J. Neurosci. 17, 7157–7165.

Svensson, S.P., Bailey, T.J., Porter, A.C., Richman, J.G., Regan, J.W., 1996. Heterologous expression of the cloned guinea pig alpha 2A, alpha 2B, and alpha 2C adrenoceptor subtypes. Radioligand binding and functional coupling to a cAMP-responsive reporter gene. Biochem. Pharmacol. 51, 291–300.

Tabernero, A., Vila, E., 1995. Effect of age on noradrenaline response in tail artery and aorta: role of endothelium. J. Auton. Pharmacol. 15, 327–333.

Teng, C.-M., Guh, J.-H., Ko, F.-N., 1994. Functional identification of α_1-adrenoceptor subtypes in human prostate: comparison with those in rat vas deferens and spleen. Eur. J. Pharmacol. 265, 61–66.

Thoenen, H., Hurlimann, A., Haefely, W., 1964. Wirkungen von phenoxybenzamin, phentolamine und azapetin auf adrenergische synapsen der katzenmilz. Helv. Physiol. Pharmacol. Acta 22, 148–161.

Trendelenberg, A.-U., Limberger, N., Starke, K., 1993. Presynaptic α_2-autoreceptors in brain cortex: α_{2D} in the rat and α_{2A} in the rabbit. Naunyn-Schmiedeberg's Arch. Pharmacol. 348, 35–45.

Trendelenberg, A.-U., Limberger, N., Rump, L.C., 1994. α_2-Adrenergic receptors of the α_{2C}-subtype mediate inhibition of norepinephrine release in human kidney cortex. Mol. Pharmacol. 45, 1168–1176.

Trendelenburg, A.-U., Sutej, I., Wahl, A.C., Molderings, G.J., Rump, L.C., Starke, K., 1997. A re-investigation of questionable subclassifications of presynaptic α_2-autoreceptors: rat vena cava, rat atria, human kidney and guinea-pig urethra. Naunyn-Schmiedeberg's Arch. Pharmacol. 356, 721–737.

Tsai, H., Buchholz, J., Duckles, S.P., 1993. Postjunctional α_2-adrenoceptors in blood vessels: effects of age. Eur. J. Pharmacol. 237, 311–316.

Uhlen, S., Xia, Y., Chhajlani, V., Felder, C.C., Wikberg, J.E.S., 1992. [^{3}H]MK 912 binding delineates two α_2-adrenoceptor subtypes in rat CNS, one of which is identical with the cloned pA2d α_2-adrenoceptor. Br. J. Pharmacol. 106, 986–995.

Van der Graaf, P.H., Shankley, N.P., Black, J.W., 1996. Analysis of the effects of α_1-adrenoceptor antagonists on noradrenaline-mediate contraction of rat small mesenteric artery. Br. J. Pharmacol. 118, 1308–1316.

Villalobos-Molina, R., Ibarra, M., 1996. Alpha 1-adrenoceptors mediating contraction in arteries of normotensive and spontaneously hypertensive rats are of the alpha1D or alpha 1A subtypes. Eur. J. Pharmacol. 298, 257–263.

Villalobos-Molina, R., Lopez-Guerrero, J.J., Ibarra, M., 1997. Alpha 1D- and alpha-1A-adrenoceptors mediate contraction in rat renal artery. Eur. J. Pharmacol. 322, 225–227.

Wada, T., Hasegawa, Y., Ono, H., 1997. Characterization of alpha1-adrenoceptor subtypes in facilitation of rat spinal motoneuron activity. Eur. J. Pharmacol. 340, 45–52.

Wahl, C.A., Trendelenburg, A.U., Starke, K., 1996. Presynaptic alpha-2 autoreceptors in mouse heart atria: evidence for the alpha 2D subtype. Naunyn-Schmiedeberg's Arch. Pharmacol. 354, 253–261.

Weber, H.D., 1989. Presynaptic α_2-adrenoceptors at the terminals of perivascular sympathetic nerves are coupled to an *N*-ethylmaleimide-sensitive G-protein. Naunyn-Schmiedeberg's Arch. Pharmacol. 339, R35.

Westfall, T.C., 1977. Local regulation of adrenergic neurotransmission. Physiol. Rev. 57, 659–728.

Wright, I.K., Harling, R., Kendall, D.A., Wilson, V.G., 1995. Examination of the role of inhibition of cyclic AMP in a2-adrenoceptor mediated contractions of the porcine isolated palmer lateral vein. Br. J. Pharmacol. 114, 157–165.

Wu, D., Katz, A., Lee, C., Simon, M.I., 1992. Activation of phospholipase C by α_1-adrenergic receptors in mediated by the alpha subunits of Gq family. J. Biol. Chem. 267, 25798–25802.

Xiao, X.H., Rand, M.J., 1989. α_2-Adrenoceptor agonists enhance vasoconstrictor responses to α_1-adrenoceptor agonists in rat tail artery by increasing the influx of Ca^{2+}. Br. J. Pharmacol. 98, 1032–1038.

Yang, H.-T., Endoh, M., 1997. Pharmacological evidence for α_{1D}-adrenoceptors in the rabbit ventricular myocardium: analysis with BMY 7378. Br. J. Pharmacol. 122, 1541–1550.

Yoshimura, N., de Groat, W.C., 1992. Patch clamp analysis of afferent and efferent neurons that innervate the urinary bladder of the rat. Soc. Neurosci. Abstr. 18, 126.

Young, P., Berge, J., Chapman, H., Cawthorne, M.A., 1989. Novel α_2-adrenoceptor antagonists show selectivity for α_{2A}- and α_{2B}-adrenoceptor subtypes. Eur. J. Pharmacol. 168, 381–386.

Yu, G.-S., Han, C., 1994. Role of α_{1A}- and α_{1B}-adrenoceptors in phenylephrine induced positive inotropic response in isolated rat left atrium. J. Cardiovasc. Pharmacol. 24, 745–752.

Zeigler, M.G., Lake, C.R., Kopin, I., 1976. Plasma noradrenaline increases with age. Nature 261, 333–335.