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Noradrenaline contractions of human prostate mediated by α_{1A}-(α_{1c}-) adrenoceptor subtype

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1 The subtype of α_1-adrenoceptor mediating contractions of human prostate to noradrenaline was characterized by use of a range of competitive and non-competitive antagonists.

2 Contractions of the prostate to either noradrenaline (pD_2 5.5), phenylephrine (pD_2 5.1) or methoxamine (pD_2 4.4) were unaltered by the presence of neuronal and extraneuronal uptake blockers. Noradrenaline was about 3 and 10 times more potent than phenylephrine and methoxamine respectively. Phenylephrine and methoxamine were partial agonists.

3 Pretreatment with the alkylating agent, chlorethylclonidine (10^{-4} M) shifted the noradrenaline concentration-contraction curve about 3 fold to the right and depressed the maximum response by 31%. This shift is 100 fold less than that previously shown to be produced by chlorethylclonidine under the same conditions on α_{1B}-adrenoceptor-mediated contractions.

4 Cumulative concentration-contraction curves for noradrenaline were competitively antagonized by WB 4101 (pA_2 9.0), 5-methyl-urapidil (pA_2 8.6), phentolamine (pA_2 7.6), benoxathian (pA_2 8.5), spiperone (pA_2 7.3), indoramin (pA_2 8.2) and BMY 7378 (pA_2 6.6). These values correlated best with published pK_i values for their displacement of [^{3}H]-prazosin binding on membranes expressing cloned α_{1c}-adrenoceptors and poorly with values from cloned α_{1b}- and α_{1d}-adrenoceptors.

5 The good correlation between the functional data on the prostate and the binding data on the expressed α_{1c}-subtype clone for the affinities of the competitive antagonists suggests that they are the same subtype. As the expressed α_{1c}-adrenoceptor clone corresponds to the α_{1A}-adrenoceptor expressed in tissues, contraction of the human prostate to noradrenaline is therefore mediated by an α_{1A}-adrenoceptor.

Keywords: α_1-Adrenoceptor subtypes; human prostate; chlorethylclonidine; WB 4101; 5-methyl-urapidil; phentolamine; benoxathian; spiperone; indoramin; BMY 7378

Introduction

Benign prostatic hyperplasia is frequent in elderly males with a prevalence of 43% in those over 65 displaying some symptoms (Garraway *et al.*, 1991). Bladder outlet obstruction caused by this condition has two components: static, related to cellular mass and dynamic, related to prostatic smooth muscle tone. One pharmacological approach in treatment is to relax prostatic smooth muscle by antagonizing α_1-adrenoceptors.

It has been known for many years that stimulation of the pre-sacral sympathetic nerves in man causes the prostate to contract (Learmonth, 1931). Subsequent work has shown that α-adrenoceptors mediate contraction of the prostate (Caine *et al.*, 1975) and ligand binding experiments revealed both α_1- and α_2-adrenoceptors, the former predominating in the stroma (Chapple *et al.*, 1989; James *et al.*, 1989). Experiments on isolated prostatic tissue showed that it was only the α_1-adrenoceptors which mediated contraction of the tissue (Hieble *et al.*, 1985; Chapple *et al.*, 1989). These studies provided a scientific basis for the use of selective α_1-adrenoceptor antagonists e.g. prazosin, in the treatment of benign prostatic hyperplasia (e.g. Chapple *et al.*, 1990) after initial trials with phenoxybenzamine (Caine *et al.*, 1978). While prazosin may provide symptomatic relief including improved urinary flow rate, there is a therapeutic ceiling to the dose that can be employed due to side effects e.g. hypotension, which also arise from α_1-adrenoceptor antagonism.

Recent research has demonstrated heterogeneity of α_1-adrenoceptors using both pharmacological analysis and receptor cloning. Thus α_{1A}- and α_{1B}-adrenoceptors can be distinguished in functional and ligand binding experiments by their sensitivity to the alkylating agent, chlorethylclonidine and by their affinities for a number of competitive antagonists such as WB 4101 and 5-methyl urapidil (Morrow & Creese, 1986; Gross *et al.*, 1988; Han *et al.*, 1987a,b). The α_{1A} subtype is relatively insensitive to chlorethylclonidine and has a high affinity for WB 4101 and 5-methyl urapidil while the opposite is true for the α_{1B} subtype. On the basis of these selectivities the α_1-adrenoceptor mediating contraction of smooth muscle in several tissues has been characterized. For example, in the rat epididymal vas deferens, contractions are mediated via α_{1A}-adrenoceptors while in the spleen they are mediated via α_{1B}-adrenoceptors (Aboud *et al.*, 1993; Burt *et al.*, 1995).

Molecular cloning studies have identified three subtypes of the α_1-adrenoceptor, α_{1b}, α_{1c} and α_{1d} (upper case letters refer to pharmacologically defined subtypes and lower case letters to those defined by molecular biology; Bylund *et al.*, 1994). All three subtypes have been cloned from both rat and human cDNA libraries (Lomasney *et al.*, 1991; Bruno *et al.*, 1991; Ramarao *et al.*, 1992; Laz *et al.*, 1993; Hirasawa *et al.*, 1993) and are expressed tissue-dependently in both species (Rokosh *et al.*, 1994; Price *et al.*, 1994). The α_{1b} clone when expressed in cell lines that have been transfected with the cDNA for this subtype and the tissue α_{1B} adrenoceptor have very similar pharmacological profiles (Lomasney *et al.*, 1991). The α_{1d} subtype clone when expressed in cells was originally thought to correspond to the classical α_{1A} subtype and was therefore called the α_{1a} clone (Lomasney *et al.*, 1991). However, a near identical clone was isolated which had a different pharmacology from the α_{1A} or α_{1B} subtypes and was therefore called the α_{1d} clone (Perez *et al.*, 1991). Schwinn & Lomasney (1992) then agreed that their clone was the same subtype as that cloned by

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Perez *et al.* (1991), and also had a different pharmacology from the α_{1A} subtype. There is currently little evidence for functional α_{1D}-adrenoceptors although they may be present in the rat vasculature (Saussy *et al.*, 1994). The α_{1c} clone is now considered to represent the classical α_{1A} subtype found in tissues (Laz *et al.*, 1993; Perez *et al.*, 1994; Burt *et al.*, 1995). The α_{1c} clone was originally isolated from a bovine brain cDNA library and although it had a very similar pharmacology to the α_{1A}-adrenoceptor, it was thought to represent a new subtype as it was also chlorethylclonidine-sensitive (Schwinn *et al.*, 1990). However, the degree to which it is sensitive to chlorethylclonidine has been questioned recently and it may only be partially sensitive, at least in the rat (Forray *et al.*, 1994a).

All three α_1-adrenoceptor clones have been found to be expressed in the human prostate by RNAse protection assay and quantitative solution hybridization assays showed that the predominant subtype expressed was the α_{1c}-adrenoceptor. The mRNA for this subtype was also found to be predominantly expressed in the stromal (fibromuscular) compartment by *in situ* hybridization (Price *et al.*, 1993).

These findings raise the possibility that the α_1-adrenoceptor subtype in the prostate might differ from that in the vasculature. Therefore the aim of the present experiments was to use drugs with known subtype selectivity to characterize pharmacologically the α_1-adrenoceptor in the prostate as a step in the development of prostate-selective α_1-adrenoceptor antagonists for treatment of benign prostatic hyperplasia. A preliminary account of some of these results has been published (Marshall *et al.*, 1992).

Methods

Prostatic chips taken from patients undergoing transurethral resection for benign prostatic hyperplasia (age 60–85 years, $n=12$) were collected in Tyrode solution and stored overnight at 4°C for experimental use the next day. Prostatic chips (about 20 mm × 4 mm × 2 mm) were selected which contained the most smooth muscle. They were suspended in Tyrode solution (composition mM: Na^+ 149, Cl^- 141, HCO_3^- 12, D-glucose 5.6, HPO_4^{2-} 0.3, K^+ 2.7, Mg^{2+} 0.5 and Ca^{2+} 1.8) at 37°C in 5 ml tissue baths and bubbled with 95%O_2/5%CO_2. The strips were placed under 1 g resting tension, and equilibrated for 1 h. Changes in isometric tension were measured with Grass FT.03 transducers and recorded by Biopac Systems Inc. MP100WS for Windows.

Cumulative additions of noradrenaline were added to each tissue to produce concentration-response curves as the response to noradrenaline was maintained and the maximum response was not much different to a single dose of noradrenaline producing a maximal response. After 1 h the curve was then either repeated, or repeated in the presence of cocaine and β-oestradiol (both 10^{-5} M), or in the presence of an antagonist (equilibrated with the tissue for 30 min). In some tissues a concentration-effect curve to another agonist was measured. The alkylating agent chlorethylclonidine was incubated with the tissue for 30 min and then washed out for 30 min. The effect of the highest concentration of dimethylsulphoxide DMSO (0.01%) resulting in the tissue bath due to the stock solution of some compounds being dissolved in it, was also measured on the noradrenaline repeat curve.

Data analysis

All the responses were calculated as percentage maximum response to noradrenaline in the initial curve and plotted as the mean ± s.e.mean of 3 or 4 separate experiments. For the competitive antagonists, WB 4101, 5-methyl urapidil, phentolamine, benoxathian, spiperone, indoramin and BMY 7378, Schild plots were constructed from the dose-ratios obtained to calculate their pA_2 values (Arunlakshana & Schild, 1959). Curve fitting for the calculation of EC_{50} values by non linear regression and linear regression for the calculation of pA_2 values was performed using InPlot (GraphPAD Software, San Diego, Calif., U.S.A.). Dose-ratios were calculated using the second concentration-response curve in the absence and presence of the antagonists.

Drugs and solutions

WB 4101 (2(2,6-dimethoxyphenoxyethyl)amino-methyl-1,4-benzodioxane hydrochloride) and chlorethylclonidine were donated by Pfizer Central Research, Kent. Noradrenaline bitartrate, phenylephrine hydrochloride, methoxamine hydrochloride, cocaine hydrochloride, β-oestradiol and phentolamine were obtained from Sigma and 5-methyl-urapidil, benoxathian hydrochloride, spiperone hydrochloride and BMY

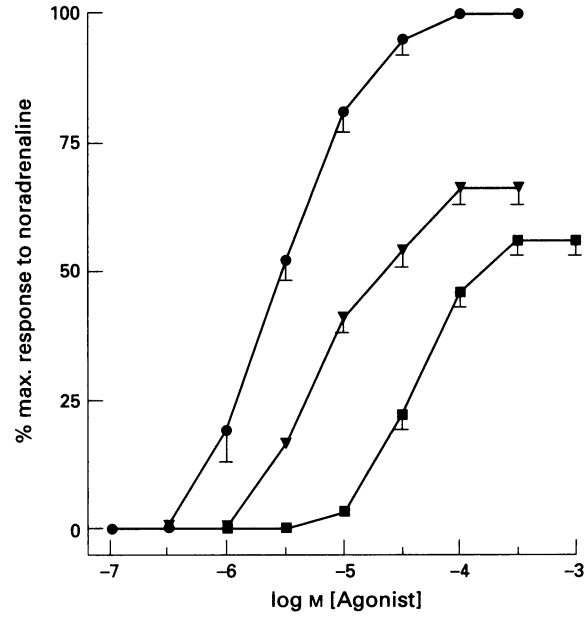

Figure 1 Cumulative concentration-effect curves for noradrenaline (●), phenylephrine (▼), and methoxamine (■), in human prostate. Each plot represents the mean with s.e.mean of at least 4 separate experiments.

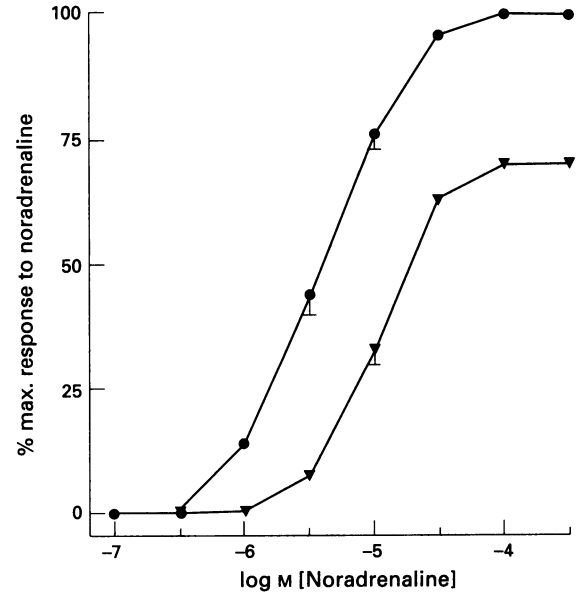

Figure 2 The effect of chlorethylclonidine on contractions to noradrenaline in human prostate. Control (●); plus chlorethylclonidine 10^{-4} M (▼). Each plot represents the mean with s.e.mean of at least 4 separate experiments.

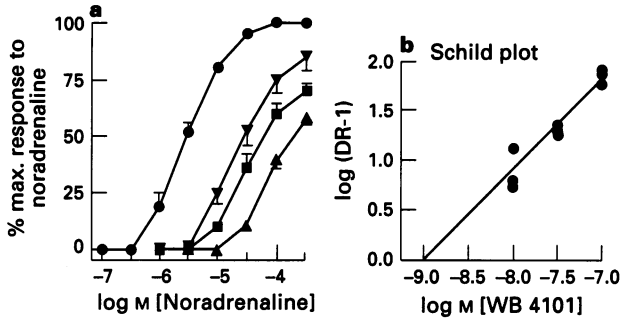

Figure 3 Antagonism of contractions to noradrenaline in human prostate by WB 4101. (a) Control (●); plus WB 4101 1×10^{-8} M (▼), 3×10^{-8} M (■), 1×10^{-7} M (▲). Each plot represents the mean with s.e.mean of at least 4 separate experiments. (b) Schild plot using dose ratios from (a).

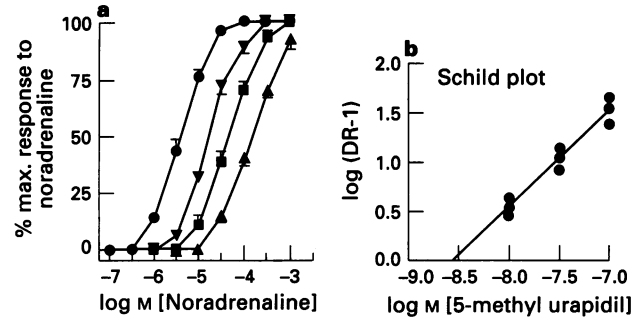

Figure 4 Antagonism of contractions to noradrenaline in human prostate by 5-methyl urapidil. (a) Control (●); plus 5-methyl urapidil 1×10^{-8} M (▼), 3×10^{-8} M (■), 1×10^{-7} M (▲). Each plot represents the mean with s.e.mean of at least 3 separate experiments. (b) Schild plot using dose ratios from (a).

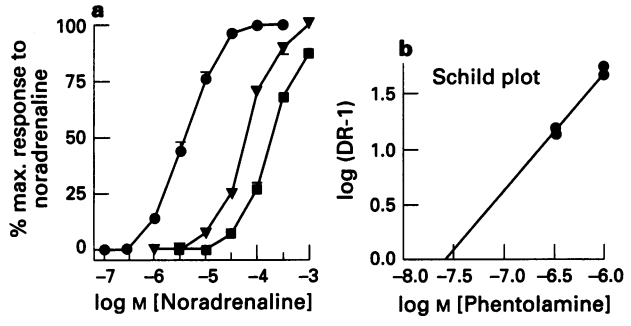

Figure 5 Antagonism of contractions to noradrenaline in human prostate by phentolamine. (a) Control (●); plus phentolamine 3×10^{-7} M (▼), 1×10^{-6} M (■). Each plot represents the mean with s.e.mean of at least 3 separate experiments. (b) Schild plot using dose ratios from (a).

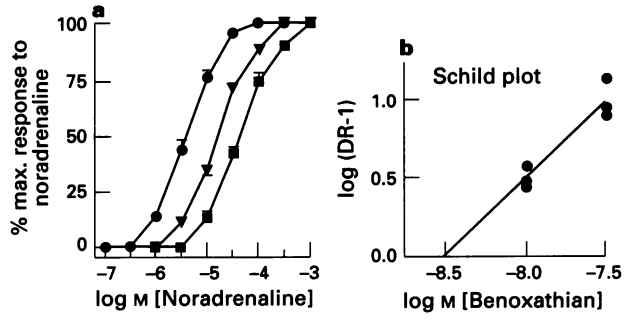

Figure 6 Antagonism of contractions to noradrenaline in human prostate by benoxathian. (a) Control (●); plus benoxathian 1×10^{-8} M (▼), 3×10^{-8} M (■). Each plot represents the mean with s.e.mean of at least 3 separate experiments. (b) Schild plot using dose ratios from (a).

7378 dihydrochloride (8[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspiro[4,5]decane-7,9-dione dihydrochloride) were obtained from RBI. All stock solutions were made in distilled water and diluted to working concentrations in Krebs solution except for spiperone and β-oestradiol which were dissolved in DMSO first, then diluted in Krebs solution. Stock solutions of antagonists were stored frozen while agonists were prepared fresh each day.

Results

Noradrenaline produced a dose-dependent contraction of the human prostate and the repeat concentration-effect curve was not significantly different from the initial curve (pD_2 5.5 ± 0.1, maximum response 0.66 ± 0.07 g, Figure 1). The responses to noradrenaline were not affected by the highest concentration

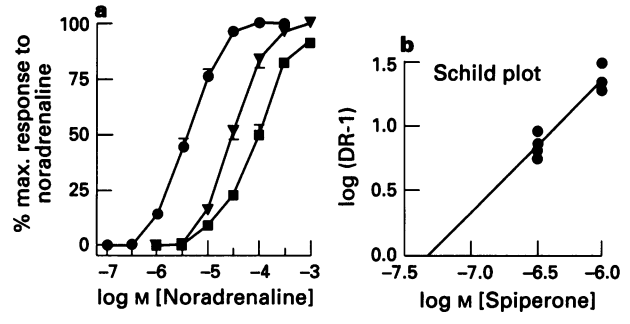

Figure 7 Antagonism of contractions to noradrenaline in human prostate by spiperone. (a) Control (●); plus spiperone 3×10^{-7} M (▼), 1×10^{-6} M (■). Each plot represents the mean with s.e.mean of at least 3 separate experiments. (b) Schild plot using dose ratios from (a).

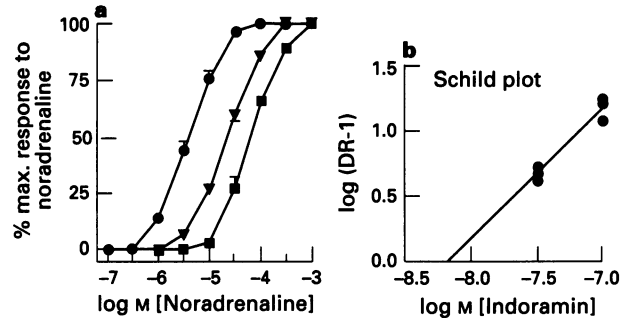

Figure 8 Antagonism of contractions to noradrenaline in human prostate by indoramin. (a) Control (●); plus indoramin 3×10^{-8} M (▼), 1×10^{-7} M (■). Each plot represents the mean with s.e.mean of at least 3 separate experiments. (b) Schild plot using dose ratios from (a).

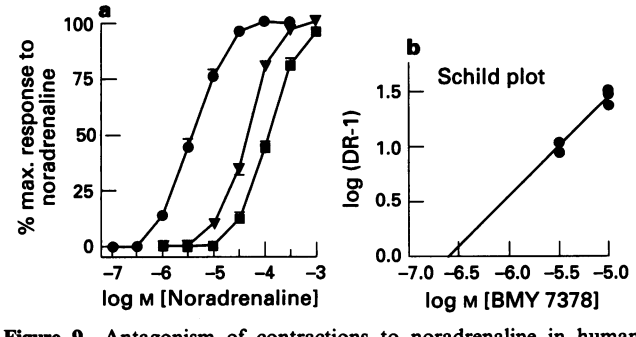

Figure 9 Antagonism of contractions to noradrenaline in human prostate by BMY 7378. (a) Control (●); plus BMY 7378, 3×10^{-6} M (▼), 1×10^{-5} M (■). Each plot represents the mean with s.e.mean of at least 3 separate experiments. (b) Schild plot using dose ratios from (a).

Table 1 Comparison of pA_2 values for the antagonists with their published pK_i on cloned subtypes

Antagonist	pK_i on cloned α_1-adrenoceptors expressed in cells* α_{1b}	α_{1c}	α_{1d}	pA_2 human prostate
Prazosin	9.6±0.2	9.2±0.2	9.4±0.2	8.5[1]
WB4101	8.2±0.1	9.5±0.3	9.2±0.1	9.0
5-methyl urapidil	6.8±0.3	8.8±0.1	7.3±0.3	8.6
Phentolamine	7.3±0.2	8.1±0.3	7.6±0.2	7.6
Benoxathian	7.8	9.0	8.7	8.5
Spiperone	8.3±0.2	7.9±0.3	7.9±0.2	7.3
Indoramin	7.3±0.1	8.2±0.3	6.8±0.2	8.2
BMY 7378	7.2	6.6	9.4	6.6

*Data are mean±s.e.mean for values from Faure *et al.*, 1994; Forray *et al.*, 1994b; Kenny *et al.*, 1994a,b; Testa *et al.*, 1994; Goetz *et al.*, 1995 (no s.e.mean for compounds with only one or two values). In each study the hamster α_{1b}, bovine α_{1c} and rat α_{1d} clones were used except for Goetz *et al.* (1995) and Forray *et al.* (1994b) where the three human α_1-subtype clones were used.
[1]Data from Marshall *et al.* (1992).

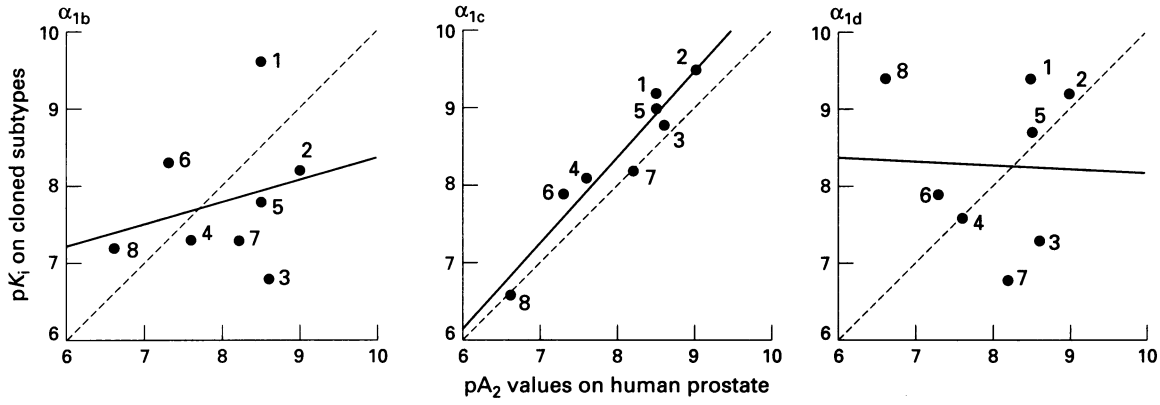

Figure 10 Correlation of average pK_i values for the displacement of [^{3}H]-prazosin on cloned α_1-adrenoceptor subtypes (Table 1) from Faure *et al.*, 1994; Forray *et al.*, 1994b; Kenny *et al.*, 1994a,b; Testa *et al.*, 1994; Goetz *et al.*, 1995, with pA_2 values for the antagonists prazosin (1), WB 4101 (2), 5-methyl urapidil (3), phentolamine (4), benoxathian (5), spiperone (6), indoramin (7) and BMY 7378 (8) against human prostate noradrenaline contractions. The solid line is a linear regression fit through all the points and the dashed line has a slope equal to unity, passing through the origin.

Table 2 Correlation values and slopes of the correlations for the pA_2 values with their pK_i values shown in Table 1

α_1-Subtype	Correlation (r)	Slope
α_{1b}	0.26	0.29±0.44
α_{1c}	0.96	1.11±0.13
α_{1d}	−0.04	−0.05±0.52

of DMSO (0.01%) in the tissue bath. When neuronal and extraneuronal uptake was blocked by cocaine and β-oestradiol (both 10^{-5} M) the concentration-effect curve to noradrenaline was not altered. Phenylephrine and methoxamine also dose-dependently contracted the prostate (pD_2 5.1±0.1 and 4.4±0.1 respectively, Figure 1) but appeared to be partial agonists in this tissue (maximum response compared to noradrenaline 66±1% for phenylephrine and 56±1% for methoxamine). The responses to phenylephrine and methoxamine were not altered in the presence of cocaine and β-oestradiol (both 10^{-5} M).

Chlorethylclonidine (1×10^{-4} M, 30 min), produced about a 3 fold rightward shift in the concentration-effect curve and a 31±1% decrease in the maximum (Figure 2). WB 4101 was a competitive antagonist producing dose-dependent rightward shifts in the concentration-effect curves (pA_2 9.0, slope 0.91±0.11, Figure 3). The same was also true for 5-methyl urapidil (pA_2 8.6, slope 0.99±0.09, Figure 4), phentolamine (pA_2 7.6, slope 1.06±0.06, Figure 5), benoxathian (pA_2 8.5, slope 0.99±0.16, Figure 6), spiperone (pA_2 7.3, slope 1.04±0.12, Figure 7), indoramin (pA_2 8.2, slope 1.01±0.12, Figure 8) and BMY 7378, (pA_2 6.6, slope 0.91±0.11, Figure 9).

Discussion

The human prostate was shown to contract to noradrenaline, with its potency and maximal response being unaffected by neuronal and extraneuronal uptake blockade by cocaine and β-oestradiol, which were therefore not included in further experiments. The α_1-adrenoceptor agonists, phenylephrine and methoxamine, also contracted the prostate, indicating that α_1-adrenoceptors mediate at least part of the response to noradrenaline. The most potent of the three agonists was noradrenaline with phenylephrine and methoxamine being about 3 and 10 fold less potent respectively. Phenylephrine and methoxamine also appeared to be partial agonists with respect to the maximum response to noradrenaline. Although they are usually considered to be full agonists, it may be that they have a slightly lower efficacy compared to noradrenaline and this is not noticeable in other tissues where there is a larger receptor reserve.

Another possible reason for the maximum response to noradrenaline being greater than that of the other agonists in this tissue is that it may also be mediated by α_2-adrenoceptors. However the full α_2-adrenoceptor agonist, UK-14,304, did not have any contractile effect in preliminary experiments, in agreement with Chapple *et al.* (1989) and prazosin has a pA_2 against the noradrenaline contraction consistent for an α_1-

adrenoceptor (Marshall *et al.*, 1992). Therefore the response to noradrenaline is mediated by α_1-adrenoceptors, in agreement with Chapple *et al.* (1989) and was therefore a suitable agonist to study the α_1-adrenoceptor subtype(s) in this tissue. Human hyperplastic prostatic tissue shows no relaxation to isoprenaline in *in vitro* function studies (Caine *et al.*, 1975; Kitada, 1983). Therefore it was considered unnecessary to include a β-adrenoceptor antagonist in these experiments.

Chlorethylclonidine selectively alkylates tissue α_{1B}-adrenoceptors (e.g. in rat spleen, Burt *et al.*, 1995) and the expressed α_{1b}-adrenoceptor clone (Perez *et al.*, 1991) rather than tissue α_{1A}-adrenoceptors (e.g. lack of effect in rat vas deferens, Burt *et al.*, 1995) or the expressed α_{1c}- and α_{1d}-adrenoceptor clones (Forray *et al.*, 1994a; Perez *et al.*, 1991). The degree of sensitivity to chlorethylclonidine of the α_{1c} clone may however be species-dependent to some extent (Forray *et al.*, 1994a). The response to noradrenaline in the prostate was antagonized by chlorethylclonidine under the same conditions that were used for the rat spleen and vas (Burt *et al.*, 1995). However, its effect was not as great as that observed on the rat spleen where it caused about a 300 fold shift of the phenylephrine curve compared to about a 3 fold shift of the noradrenaline curve in the prostate. Hence, contraction of the prostate is unlikely to be mediated solely by α_{1B}-adrenoceptors but could be mediated by α_{1A}- or α_{1D}-adrenoceptors, as the corresponding expressed clones for these two subtypes (α_{1c} and α_{1d}), have both been shown to be partially chlorethylclonidine-sensitive.

However, chlorethylclonidine did have a greater effect in the prostate than in the rat vas deferens where it had no effect. One problem with the interpretation of the effects of chlorethylclonidine is that the degree to which it affects a functional response depends to some extent on the receptor reserve of the tissue. If a tissue has a large receptor reserve then a reduction in receptor density may result in a rightward shift in the concentration-response curve without a reduction in the maximum response. On the other hand, if a tissue has a small receptor reserve then an equivalent reduction in receptor density may result in a rightward shift of the concentration-response curve and also a decrease in the maximum response. The fact that a decrease in maximum response was observed in the prostate after chlorethylclonidine treatment with a relatively small rightward shift is consistent with a small receptor reserve in this tissue. The rat vas deferens does have a large α_1-adrenoceptor reserve (Diaz-Toledo & Marti, 1988) so a small shift in the noradrenaline curve in this tissue would probably not be accompanied by a reduction in maximum response. The reduced maximum response in the prostate would then only represent a difference in receptor reserve between the prostate and the vas deferens. Therefore it could be argued that the 3 fold shift for the noradrenaline curve in the prostate shows relatively little difference in the effects of chlorethylclonidine between the two tissues. The classical α_{1A}-subtype such as that found in the rat vas deferens corresponds to the cloned α_{1c}-adrenoceptor (Laz *et al.*, 1993; Perez *et al.*, 1994; Burt *et al.*, 1995) and this clone also shows some species differences in chlorethylclonidine-sensitivity. Therefore the subtypes in the rat vas deferens and the human prostate could both be the α_{1A}-subtype and the difference in chlorethylclonidine sensitivity may reflect a species difference. Alternatively the subtype in the prostate could be an α_{1D}-adrenoceptor. However, there are currently no functional data for chlorethylclonidine on a known α_{1D}-mediated response with which to compare its effect in the prostate. In comparison the α_1-adrenoceptors in the rat spleen were much more sensitive to chlorethylclonidine than those in the rat vas deferens (Burt *et al.*, 1995) and human prostate, as a 300 fold shift in the concentration-response curve could not be explained away in terms of receptor reserve and experimental variability.

Due to the problems of interpreting the effects of chlorethylclonidine in some cases (particularly in distinguishing between the α_{1c}- and α_{1d}-subtypes), affinities of subtype-selective competitive antagonists may give more reliable information. The affinity of a range of competitive antagonists has now been measured on membranes from cells transfected with the cDNA for each of the three cloned α_1 subtypes in several studies. While prazosin has been found to be non-selective, others have shown some degree of selectivity between the subtypes (Faure *et al.*, 1994; Forray *et al.*, 1994b; Kenny *et al.*, 1994a,b; Testa *et al.*, 1994; Goetz *et al.*, 1995). The affinity of the same antagonists has been measured here in functional studies for the α_1 subtype mediating contraction of the prostate by calculation of pA_2 values. Table 1 compares the pA_2 values obtained for these antagonists with their average published pK_i values on the expressed cloned subtypes (Faure *et al.*, 1994; Forray *et al.*, 1994b; Kenny *et al.*, 1994a,b; Testa *et al.*, 1994; Goetz *et al.*, 1995). The pA_2 values have been plotted against their average pK_i values for each of the cloned subtypes in order to see with which one the functional α_1-adrenoceptor mediating contraction in the human prostate most closely correlates (Figure 10). The correlation values (r) and slopes of the correlations are shown in Table 2. They show that the subtype in the prostate is unlike either the α_{1b} or α_{1d}-subtypes but correlates very well with the α_{1c}-subtype ($r = 0.96$).

In conclusion, the α_1-adrenoceptor mediating contractions to noradrenaline in the human prostate was only partially sensitive to chlorethylclonidine and the affinities of subtype-selective antagonists for this functional receptor correlated very well with the expressed α_{1c}-subtype clone. On this evidence the α_1-adrenoceptor mediating the contraction is the same as the expressed α_{1c} subtype clone, which corresponds well with this subtype having the highest expression in the prostatic stroma (Price *et al.*, 1993). As the expressed α_{1c} subtype clone corresponds to the tissue α_{1A}-adrenoceptor (Laz *et al.*, 1993; Perez *et al.*, 1994; Burt *et al.*, 1995), the subtype mediating contraction of the human prostate is the α_{1A}-adrenoceptor. This conclusion is therefore consistent with the findings that α_1-adrenoceptors in human prostate were similar to tissue α_{1A}-adrenoceptors in binding studies (Testa *et al.*, 1993) and similar to the expressed bovine α_{1c} clone in functional studies (Lepor *et al.*, 1993). An antagonist selective for the α_{1A}-subtype may therefore be of benefit in the treatment of benign prostatic hyperplasia.

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