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α_{1L}-Adrenoceptors mediate contractions of the isolated mouse prostate

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Abstract

The subtype of α_1-adrenoceptor mediating noradrenaline-induced contractile responses in isolated mouse prostate glands was investigated. Adrenoceptor agonists were able to produce concentration-dependent contractions with the following rank order of potency: adrenaline ≥ noradrenaline ≥ clonidine = phenylephrine > dopamine ≥ isoprenaline. Concentration–response curves to noradrenaline of the prostatic smooth muscle were antagonised by prazosin, *N*-[2-(2-cyclopropylmethoxyphenoxy)ethyl]-5-chloro-α, α-dimethyl-1*H*-indole-3-ethanamine (RS-17053), 2-(2,6-dimethoxyphenoxyethyl)aminomethyl-1,4-benzodioxane (WB 4101), tamsulosin and yohimbine with mean antagonist affinity estimates (pA_2 or apparent pK_B) of 8.12±0.10, 6.56±0.11, 8.38±0.06, 10.14±0.19 and 7.38±1.36 respectively. Propranolol (1 μM) had no antagonist activity ($P=0.994$, $n=6$). Yohimbine (0.01, 0.1, 1 μM) had no antagonist activity in the presence of prazosin (0.1 μM) ($P \geq 0.059$). The results obtained indicate that α_1-adrenoceptors mediate the contractile response in isolated preparations of the mouse prostate. Furthermore, the particular subtype of α_1-adrenoceptor mediating the response to exogenously administered noradrenaline corresponds to the α_{1L}-subtype, the same subtype as that which has been shown to mediate noradrenaline-induced contractile activity in the human prostate.

Keywords: α_{1L}-Adrenoceptor; RS-17053; WB 4101l; Tamsulosin; Prostate; Stroma

1. Introduction

Adrenoceptors can be divided into three families, α_1, α_2 and β, based on their pharmacological and molecular properties along with their structure and signalling mechanisms. Each of these families can be further subdivided to contain at least three subtypes, all of which are coupled to G proteins (Bylund et al., 1998).

Of particular interest in urology are the α_1-adrenoceptors due to the critical role that they play in mediating the dynamic component of benign prostatic hyperplasia (Kyprianou et al., 2000). These α_1-adrenoceptors activate the $G_{q/11}$ signalling pathway to elicit contraction of prostatic smooth muscle through phospholipase C dependent activation of inositol (1,4,5) trisphosphate and diacylglycerol leading to Ca^{2+} influx and activation of protein kinase C (for review, see Minneman, 1988).

Morrow and Creese (1986) were among the first to show evidence of pharmacologically distinct α_1-adrenoceptor subtypes. Since then much work has been carried out in the area of adrenoceptor classification with three subtypes of the α_1-adrenoceptor being identified and fully characterised, the α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors (Bylund et al., 1998; Hieble et al., 1995). However, many studies have suggested that an additional subtype exists which has a low affinity for prazosin (Daniels et al., 1999; Ford et al., 1996, 1997; Hiraoka et al., 1999; Muramatsu et al., 1994; Pennefather et al., 1999). This putative subtype is thought to be a functional phenotype of the α_{1A}-adrenoceptor and has been termed the α_{1L}-adrenoceptor (Ford et al., 1997). While this receptor is yet to be defined in molecular studies, it has been characterised functionally as having not only a low affinity for prazosin but also a low affinity for *N*-[2-(2-cyclopropylmethoxyphenoxy)ethyl]-5-chloro-α, α-dimethyl-1*H*-indole-3-ethanamine (RS-17053; Ford et al., 1996) and 2-(2,6-dimethoxyphenoxyethyl)aminomethyl-1,4-benzodioxane (WB 4101; Muramatsu et al., 1994; Hiraoka et al., 1999) and a high affinity for tamsulosin (Noble et al., 1997; Kava et al., 1998). It is this α_{1L}-adrenoceptor which has been shown to mediate contractions in the prostates of humans (Ford et al., 1996; Muramatsu et al., 1994), guinea pigs (Pennefather et al., 1999) and rats (Hiraoka et al., 1999).

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We have recently shown that nerve mediated contractile responses of the mouse prostate are sympathetically mediated, primarily noradrenergic and mediated by α_1-adrenoceptors (Gray and Ventura, 2005), as is also the case in human, rat and guinea pig prostates (for review, see Pennefather et al., 2000). The particular subtype of α_1-adrenoceptor mediating the contractile response in the mouse prostate has not yet been determined. Thus, the aim of this work was to characterise the α_1-adrenoceptor subtype mediating the noradrenaline-induced contractile response in the mouse prostate in order to determine if it was the same α_{1L} subtype. This would further validate the suitability of the mouse prostate as a model for human prostate function and enable further study into prostate disease to be carried out using the wide variety of gene knockout mice now available.

2. Methods

2.1. Animals and tissues

Adult male Swiss mice (8–16 weeks old) were housed at 22 °C and exposed to a photoperiod of 12 h light/12 h dark. Animals had access to food and water ad libitum. Mice were killed by cervical dislocation before a lower abdominal incision was made exposing the urogenital tract. The penile muscles were cut posteriorly to expose the prostate glands, the whole prostate was carefully dissected out and excess fat and connective tissue was removed. Each mouse provided one preparation. Prior approval for animal experimentation was obtained from the Monash University Standing Committee of Animal Ethics in Animal Experimentation (Ethics Number VCPA/2003/05).

2.2. Isolated organ baths studies

Whole prostate tissues were mounted in 10 ml glass organ baths containing Krebs–Henseleit solution (mM: NaCl 118.0, KCl 4.7, KH_2PO_4 1.18, $NaHCO_3$ 25.0, glucose 11.66, $MgSO_4$ 1.1, $CaCl_2$ 2.5), maintained at 37 °C and bubbled with 5% CO_2 in O_2. One end of the prostate was attached to a Perspex tissue holder incorporating two vertical parallel platinum electrodes and the other end to a Grass FT03C-transducer for recording of isometric contractions of the prostatic smooth muscle. Developed force was recorded via a PowerLab data acquisition system (Chart 3.6) which was run on a Power Macintosh 5500/225 computer. Tissues were equilibrated for 60 min under a resting tension of 0.4–0.7 g. During the equilibration period nerve terminals within the prostatic smooth muscle were electrically stimulated via the electrodes, connected to a Grass S88 stimulator which was used to deliver trains of 0.5 ms duration, 60 V at 0.01 Hz. Nerve terminals were electrically stimulated during the equilibration period to ensure the viability of the tissues.

2.2.1. Inhibitors of uptake and receptor antagonists

Following the initial 60 min equilibration period discrete concentration–response curves to adrenaline were constructed using a dose progression ratio of approximately half a log unit. Discrete concentration–response curves were used rather than cumulative concentration–response curves as the mouse prostate is not able to sustain prolonged contractions as required with cumulative curves. Once the contractile response to each concentration of adrenaline had reached a plateau the tissues were washed out with 4–5 times the bath volume, allowed 10 min to recover and the next concentration applied. If no response was observed after 30 s, the tissues were washed and allowed 10 min to recover. Following this concentration–response curve, a test drug was added to the bath and left in contact with the tissue for 60 min before a second concentration–response curve was constructed using the same protocol as above in the presence of the test drug. During the second curve test drugs were replaced after bath washes. The test drugs used were cocaine (10 μM) and desipramine (10 nM) to block neuronal uptake, β-oestradiol (10 μM) to block extraneuronal uptake, propranolol (1 μM) to block β-adrenoceptors, yohimbine (0.01, 0.1, 1 μM) to block α_2-adrenoceptors and atropine (1 μM) to block muscarinic receptors. An appropriate time control curve was also constructed in which isolated prostates were not exposed to test drugs during the second concentration–response curve.

2.2.2. Effects of adrenoceptor agonists

Following the initial 60 min equilibration period discrete concentration–response curves to various adrenoceptor agonists were constructed using the same protocol as above. Atropine (1 μM) was present in the Krebs–Henseleit solution for the duration of the experiment to block any muscarinic receptors which may have had confounding effects. The agonists used were adrenaline, noradrenaline, phenylephrine, clonidine, dopamine and isoprenaline (1 nM to 0.1 mM). Once an initial dose–response curve had been constructed, prazosin (0.3 μM) was added to the baths. After a 60 min exposure time a second concentration–response curve was constructed. A subset of experiments was also carried out where yohimbine (10 nM) and propranolol (1 μM) were used as antagonists to clonidine and isoprenaline, respectively.

2.2.3. α_1-Adrenoceptor classification

Following the 60 min equilibration period, tissues were exposed to a priming dose of 0.1 mM noradrenaline. Once the contractile response of the tissues had reached a maximum, the tissues were washed with 4–5 times the bath volume and allowed 30 min to recover. Following this, discrete concentration–response curves to noradrenaline (1 nM to 1 mM) were constructed as previously described. Atropine (1 μM) was present in the baths for the duration of the experiment to block any muscarinic effects. Following the initial discrete concentration–response curves the tissues were exposed to an antagonist or vehicle for 60 min before a second concentration response curve was constructed. Vehicles and antagonists were replaced after each bath wash. The antagonists used were prazosin (10, 30, 100 nM), WB 4101 (10, 30, 100 nM), RS-17053 (0.03, 0.1, 0.3, 1, 3 μM), tamsulosin (0.3, 1, 3 nM) or yohimbine (0.01, 0.1, 1 μM). In a subset of experiments, Krebs–Henseleit solution was supplemented with prazosin (0.1 μM) in addition to atropine (1 μM) to test the selectivity of yohimbine (0.01, 0.1, 1 μM).

2.3. Measurement and analysis of data

The peak force (g) of agonist induced contractile responses was measured at each concentration of agonist in the presence and absence of antagonists.

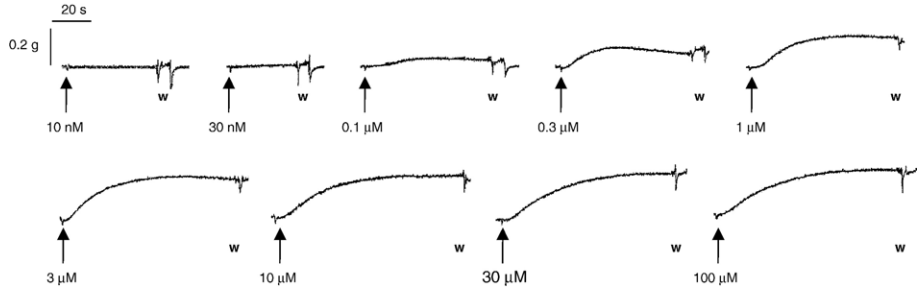

Fig. 1. Representative traces showing the effects of adrenaline (10 nM–100 μM) on preparations of isolated mouse prostate. Traces are representative of 52 experiments. Arrows indicate the administration of each concentration of adrenaline. W = washout.

Mean concentration–response curves in the presence of test drugs were compared with the previously obtained control concentration–response curves (no drug) using a two-way repeated measure analysis of variance (ANOVA; GraphPad Prism v. 4.0). *P*-values used to evaluate statistical significance were the probabilities of a significant interaction between concentration and treatment. Values of $P<0.05$ were considered significant.

The EC_{50} value for each of the agonists was determined using GraphPad Prism (v. 4.0) and the potency ratio for each of the agonists compared to the endogenous agonist noradrenaline was then calculated using the following equation:

$$\text{Potency ratio} = \text{antilog}((-\log EC_{50}\ \text{agonist}) - (-\log EC_{50}\ \text{noradrenaline}))$$

For antagonist studies, raw data was normalised as a percentage of the maximum response obtained in the initial control concentration–response curve. Normalised data was then analysed using nonlinear regression to fit a variable slope sigmoidal dose–response curve using GraphPad Prism (v. 4.0).

Antagonist affinity estimates were expressed as pA_2 or apparent pK_B values and were determined as follows. Schild plots were constructed by comparing the antagonist EC_{50} at each concentration with the EC_{50} of the control concentration–response curve in the presence of vehicle. When the Schild regression indicated that the slope was not significantly different from unity, the slope was constrained to 1 and pA_2 values determined according to the method of Arunlakshana and Schild (1959). Where the Schild regression indicated that the slope was significantly different from unity, mean apparent pK_B values were calculated at the lowest concentration of antagonist to produce a shift using the equation:

$$pK_B = -\log\left[\frac{[B]}{CR-1}\right]$$

where CR is the shift in the concentration–response curve caused by a concentration [B] of antagonist (Furchgott, 1972).

2.4. Drugs

The following drugs were used: (−)arterenol (noradrenaline) bitartrate, atropine sulphate, clonidine hydrochloride, cocaine hydrochloride, desipramine hydrochloride, (−)-epinephrine (adrenaline) bitartrate, 3-hydroxytyramine (dopamine) hydrochloride, (−)-isoproterenol (isoprenaline) hydrochloride, β-oestradiol, L-phenylephrine hydrochloride, prazosin hydrochloride, DL-propranolol hydrochloride and yohimbine hydrochloride (Sigma, St Louis, USA), *N*-[2-(2-cyclopropylmethoxyphenoxy)ethyl]-5-chloro-α, α-dimethyl-1*H*-indole-3-ethanamine hydrochloride (RS-17053; Tocris, Bristol, UK), 2-(2,6-dimethoxyphenoxyethyl)aminomethyl-1,4-benzodioxane hydrochloride (WB 4101; RBI, Natick, USA) and tamsulosin (Yamanouchi Pharm; gift from Assoc. Prof. J.N. Pennefather).

Adrenaline, dopamine, isoprenaline, noradrenaline and phenylephrine were all dissolved and diluted to the required concentrations in catecholamine diluent (mM: NaCl 154.0, NaH_2PO_4 1.2, ascorbic acid 0.2). RS-17053, WB 4101 and β-oestradiol were dissolved in 0.01% dimethylsulphoxide (DMSO), 0.01% and 100% ethanol, respectively and diluted to the required concentration in distilled water. All other drugs were dissolved and diluted to required concentrations in distilled water.

3. Results

3.1. Effects of uptake inhibitors and antagonists on adrenaline-induced contractile responses

Exogenously administered adrenaline elicited concentration dependent contractile responses in isolated preparations of mouse prostates (Fig. 1) with a pD_2 of 6.40 ± 0.27 (Fig. 2). Time control

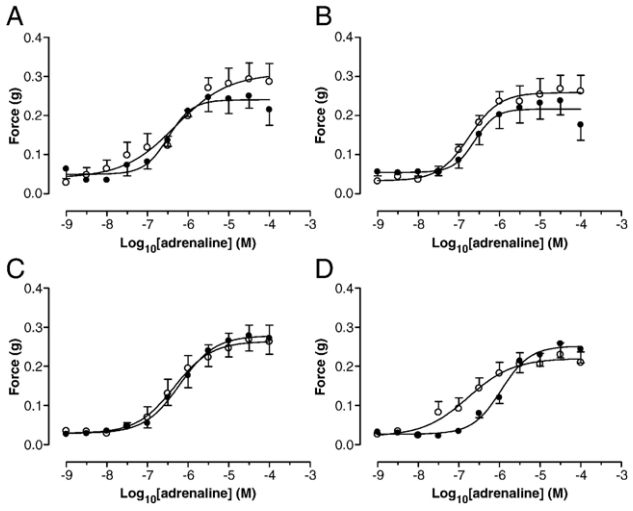

Fig. 2. Log concentration–response curves to adrenaline on isolated preparations of mouse prostate in the absence (open symbols) and presence (filled symbols) of A) 10 μM cocaine, B) 10 μM β-oestradiol, C) 1 μM propranolol and D) 1 μM atropine. Values represent the mean ± S.E.M. $n=5–6$.

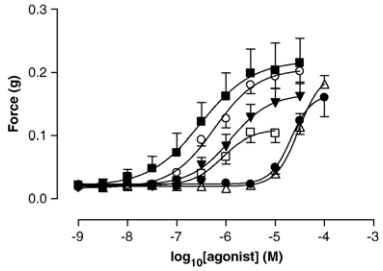

Fig. 3. Log concentration–response curves to: (■) adrenaline, (○) noradrenaline, (▼) phenylephrine, (□) clonidine, (●) dopamine and (△) isoprenaline on isolated preparations of mouse prostate. Values represent the mean±S.E.M. $n=6$.

curves showed that after 1 h, with the addition of no drug, the second concentration–response curve was not different to the first ($P=0.657$, $n=6$). Atropine (1 μM) significantly shifted the mean concentration response curve to adrenaline approximately 7-fold to the right ($P=0.002$, $n=5$; Fig. 2). Cocaine (10 μM), β-oestradiol (10 μM), propranolol (1 μM) and desipramine (10 nM) did not have any significant effects on the mean concentration–response curve to adrenaline ($P\geq 0.184$, $n=5$–6; Fig. 2). None of the test drugs caused a significant change in the maximum response achieved by adrenaline ($P>0.05$, $n=5$–6; Fig. 2).

Yohimbine shifted the concentration–response curve to adrenaline significantly to the right at concentrations of 10 nM and 1.0 μM ($P\leq 0.004$, $n=6$) however not at a concentration of 0.1 μM ($P=0.589$, $n=6$). Yohimbine (10 nM) was also able to attenuate the responses induced by clonidine ($P<0.001$, $n=6$). The log concentration–response curve to noradrenaline was shifted by yohimbine at concentrations of 100 nM and 1 μM ($P<0.001$, $n=6$) however not at a concentration of 10 nM ($P=0.165$, $n=6$). When the Krebs–Henseleit solution was further supplemented with prazosin (0.1 μM), yohimbine (0.01, 0.1, 1 μM) no longer produced shifts in the concentration–response curve to noradrenaline ($P=0.059$, $n=6$).

3.2. Contractile response to adrenoceptor agonists

Subsequent experiments to determine the rank order of adrenoceptor agonist potency were carried out in the presence of atropine (1 μM). Each of the agonists was able to evoke contractile responses in the isolated mouse prostate (Fig. 3). All agonists, with the exception of clonidine, were able to produce maximum responses which were not significantly different from the maximum response obtained by noradrenaline ($P>0.05$, $n=6$; Table 1). The maximum response induced by clonidine was significantly less than that induced by noradrenaline ($P<0.001$, $n=6$; Table 1).

The results shown in Table 1 are the mean negative log EC_{50} (pD_2) values and agonist potency ratios relative to noradrenaline. The rank order of potency for the adrenoceptor agonists was found to be: adrenaline≥noradrenaline≥clonidine=phenylephrine>dopamine≥isoprenaline. Responses evoked by each of the agonists were significantly attenuated by prazosin (0.3 μM, $P<0.001$, $n=6$ for each agonist). Responses to isoprenaline were unaffected by propranolol (1 μM, $P=0.347$, $n=6$).

Table 1
Mean negative log EC_{50} values, mean maximum responses produced and potency ratios at α-adrenoceptors in isolated preparations of the mouse prostate

Agonist	− log EC_{50} (mean±S.E.M.)	Max. response (g; mean±S.E.M.)	Potency ratio[a]
Adrenaline	6.57±0.26	0.22±0.04	2.01
Noradrenaline	6.27±0.10	0.20±0.02	1.00
Clonidine	6.08±0.14	0.10±0.01[b]	0.64
Phenylephrine	6.04±0.14	0.16±0.02	0.59
Dopamine	4.69±0.10	0.16±0.03	0.03
Isoprenaline	4.52±0.07	0.18±0.01	0.02

$n=6$ for each experimental group.

[a] Potency ratio=antilog ((− log EC_{50} value for agonist)−(− log EC_{50} value for noradrenaline)).

[b] Maximum response evoked by clonidine was found to be significantly less than the maximum response induced by noradrenaline ($P<0.001$, $n=6$).

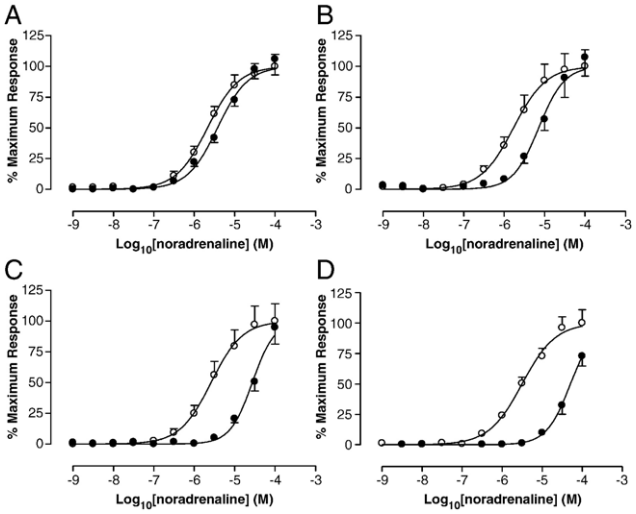

Fig. 4. Log concentration–response curves to noradrenaline on isolated preparations of mouse prostate in the absence (open symbols) and presence (filled symbols) of A) vehicle, B) 10 nM prazosin, C) 30 nM prazosin and D) 100 nM prazosin. Values represent the mean±S.E.M. $n=6$.

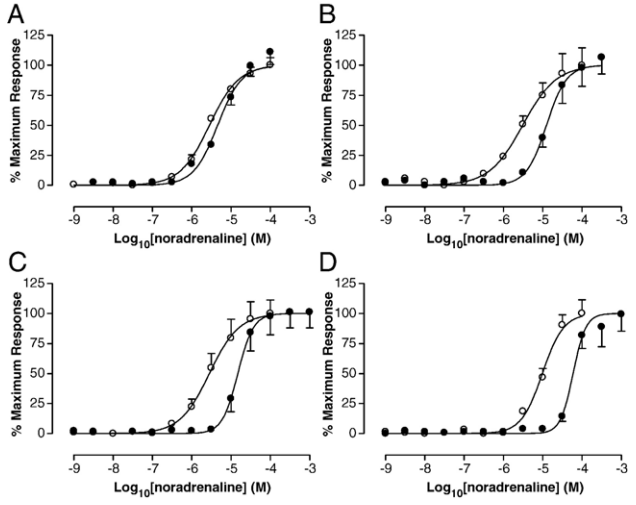

Fig. 5. Log concentration–response curves to noradrenaline on isolated preparations of mouse prostate in the absence (open symbols) and presence (filled symbols) of A) 0.01% DMSO, B) 300 nM RS-17053, C) 1 μM RS-17053 and D) 3 μM RS-17053. Values represent the mean±S.E.M. $n=6$.

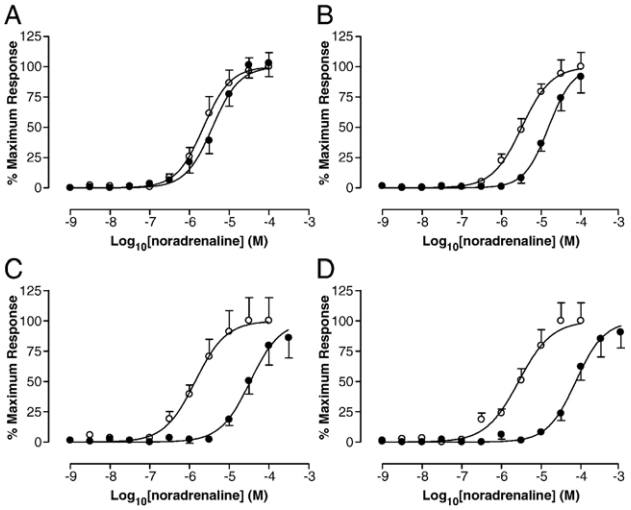

Fig. 6. Log concentration–response curves to noradrenaline on isolated preparations of mouse prostate in the absence (open symbols) and presence (filled symbols) of A) 0.01% ethanol, B) 10 nM WB 4101, C) 30 nM WB 4101 and D) 100 nM WB 4101. Values represent the mean±S.E.M. $n=6$.

3.3. α_1-Adrenoceptor sub-classification using antagonists

Following a priming dose of noradrenaline (0.1 mM), concentration-dependent contractions of isolated mouse prostate glands were produced by noradrenaline with an average pD_2 value of 5.49±0.06 ($n=126$). Prazosin (10, 30, 100 nM; Fig. 4), RS-17053 (0.3, 1, 3 μM; Fig. 5) and WB 4101 (10, 30, 100 nM; Fig. 6) shifted the log concentration–response curve to noradrenaline to the right in a parallel and concentration-dependant fashion ($P\leq 0.007$). Tamsulosin (0.3, 1.0, 3.0 nM; Fig. 7) also produced rightward shifts in the position of the log concentration–response curve however at 3.0 nM the maximum response to noradrenaline was significantly reduced ($P\leq 0.001$, $n=6$). The data in Table 2 shows the affinity estimates for each of the antagonists at α_1-adrenoceptors in isolated preparations of the mouse prostate.

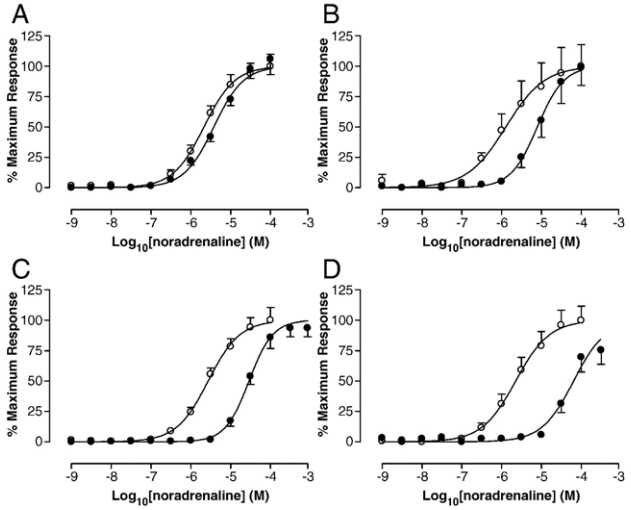

Fig. 7. Log concentration–response curves to noradrenaline on isolated preparations of mouse prostate in the absence (open symbols) and presence (filled symbols) of A) control, B) 0.3 nM tamsulosin, C) 1.0 nM tamsulosin and D) 3.0 nM tamsulosin. Values represent the mean±S.E.M. $n=6$–12.

Table 2
Mean affinity estimates, expressed as pA_2 or pK_B values, for the α_1-adrenoceptor antagonists prazosin, WB 4101, RS-17053, tamsulosin and yohimbine against responses to noradrenaline in the isolated mouse prostate

Antagonist	Slope (mean±S.E.M.)	r	pA_2 or pK_B (mean±S.E.M.)
Prazosin	1.15±0.31	0.965	8.12±0.10
WB 4101	0.79±0.28	0.999	8.38±0.06
RS-17053	0.84±0.32	0.923	6.56±0.11
Tamsulosin			10.14±0.19[a]
Yohimbine			7.38±1.36[b]

$n=6$–12 for each of the antagonists.
[a] Tamsulosin (3.0 nM) caused suppression of maximum response, pK_B value calculated at 0.3 nM tamsulosin.
[b] Yohimbine (10 nM) did not cause any shifts, pK_B value calculated at 100 nM yohimbine.

4. Discussion

To properly assess agonist and antagonist affinities at receptors, all sites of loss and other receptors which confound results should be blocked. We used adrenaline to test for these because it is a good substrate for neuronal uptake (uptake 1) and extraneuronal uptake (uptake 2) and a potent agonist at α- and β-adrenoceptors. As cocaine, desipramine, β-oestradiol and propranolol did not enhance the effects of adrenaline, it can be assumed that neuronal and extraneuronal uptake and postjunctional β-adrenoceptors do not affect the response to exogenously added adrenoceptor agonists to a degree which greatly affects the potency of catecholamines in the mouse prostate. Similar results have also been found in the rat cauda epididymis with propranolol and β-oestradiol (Ventura and Pennefather, 1991) and propranolol was also found to have no effect on noradrenaline-induced contractile responses in prostates and bladder necks from rats and guinea pigs (Cohen and Drey, 1989). Atropine caused a significant shift in the position of the concentration response curve to adrenaline. In a previous study we found atropine to have no effect on electrical field stimulation induced contractile responses of the mouse prostate (Gray and Ventura, 2005) however it has been shown to attenuate responses in the rat and guinea pig prostates (Lau et al., 1998). Although atropine is known to have antagonistic actions at α_1-adrenoceptors, in our hands the dose used is selective for blocking muscarinic receptors. Furthermore, it is well known that cholinergic mechanisms can affect prostatic contractility in a number of other species (for review, see Ventura et al., 2002) and so atropine was added to the bathing solution routinely to prevent interference from muscarinic receptor stimulation.

The rank order of potency of the adrenoceptor agonists (adrenaline ≥ noradrenaline ≥ clonidine = phenylephrine > dopamine ≥ isoprenaline) suggests that the adrenoceptor mediating the contractile response in the mouse prostate is an α-adrenoceptor (Starke, 1981; Wikberg, 1978). Although the high potency of clonidine is suggestive of an α_2-adrenoceptor, the data obtained shows that clonidine has a low intrinsic activity when compared with phenylephrine and the other adrenoceptor agonists. Thus it appears that α_1-adrenoceptors

are mediating the contractile response in the mouse prostate. Further evidence to support this conclusion comes from the effects observed when prazosin, an α_1-adrenoceptor antagonist, was used to antagonise the contractile effects of the adrenoceptor agonists. Isoprenaline, a β-adrenoceptor agonist, was able to produce a contractile response which was unaffected by the β-adrenoceptor antagonist propranolol, however the response was abolished by prazosin suggesting that in the mouse prostate, isoprenaline is acting on α_1-adrenoceptors to mediate contractions.

The observation that yohimbine was able to shift concentration–response curves to noradrenaline, adrenaline and clonidine to the right was unexpected. However, the results obtained from this study indicate that yohimbine is acting at α_1-adrenoceptors rather than α_2-adrenoceptors. This is indicated by the observation that yohimbine's antagonistic actions were not concentration-dependant. Furthermore, the mean pK_B value of 7.38 obtained for yohimbine when antagonising the response to noradrenaline is relatively low. This value is of the order of 10 times less than would be expected at α_2-adrenoceptors (Bylund et al., 1998). While the large error associated with the pK_B value for yohimbine does place this value in the affinity range for yohimbine at α_2-adrenoceptors, further evidence that yohimbine was acting at α_1-adrenoceptors was found when the Krebs–Henseleit solution was supplemented with prazosin and concentration–response curves to noradrenaline were re-constructed. In this subset of experiments three concentrations of yohimbine were unable to cause any shift in the position of the curve to noradrenaline. It is not unexpected that yohimbine could be acting at α_1-adrenoceptors rather than α_2-adrenoceptors given that the potency of yohimbine at α_2-adrenoceptors is only 50 times greater than its potency at α_1-adrenoceptors (Starke, 1981).

Antagonist affinity estimates were calculated from data obtained from concentration–response curves to noradrenaline and compared to data reported in the literature. Noradrenaline was chosen as the agonist rather than the α_1-adrenoceptor specific agonist phenylephrine, as phenylephrine is not potent enough to observe shifts in the position of the concentration–response curve. Furthermore, previous studies in prostates of other species have used noradrenaline as the agonist and we wished to keep this study consistent with those in the literature so that comparisons could be drawn. Estimates of antagonist potency were found to be comparable to those in the literature for their effects on noradrenaline-induced contractions in the human prostate. Muramatsu et al. (1994) reported values of 8.29 for prazosin and 8.39 for WB 4101, Ford et al. (1996) reported slightly higher values of 8.7 for prazosin and 8.9 for WB 4101 as well as values of 7.3 for RS-17053 and 10.41 for tamsulosin. Both of these studies concluded that the α_1-adrenoceptor mediating the noradrenaline-induced contractile response was of the α_{1L} subtype. The same conclusions have also been reached following animal studies of prostates taken from rats (Hiraoka et al., 1999) and guinea pigs (Pennefather et al., 1999) as well as in the rabbit bladder neck (Kava et al., 1998). Each of these studies obtained similar antagonist affinity values for receptors activated by noradrenaline. Though the results from this study are in agreement with those of Ford et al. (1996) it is interesting to note that while Ford was able to antagonise contractions to noradrenaline with 0.03 μM doses of RS-17053, doses of 0.3 μM were required to antagonise the noradrenaline-induced contractile responses in the mouse prostate. The reported antagonist affinity estimates for tamsulosin of 10.41, 9.9 and 10.11 in the human, rat and guinea pig prostates (Ford et al., 1996; Noble et al., 1997; Pennefather et al., 1999) and 10.1 in the rabbit bladder neck (Kava et al., 1998) are in close agreement with our mean apparent pK_B value of 10.14. The previously mentioned studies all noted that at higher concentrations, tamsulosin attenuated the maximum response evoked by noradrenaline. These observations support our findings that at 3.0 nM, tamsulosin reduced the maximum response to noradrenaline in isolated preparations of the mouse prostate.

The involvement of other α-adrenoceptor subtypes can be excluded given the low pA_2 value obtained for prazosin. If the α_1-adrenoceptor mediating the response was of another subtype, prazosin would have yielded a much higher pA_2 value in the range of 9–10.

In conclusion, the results obtained from this study demonstrate that the α_{1L}-adrenoceptor mediates noradrenaline-induced contractile responses in isolated preparations of the mouse prostate. This is the same receptor that has been shown to mediate the contractile response in the human prostate (Ford et al., 1996; Muramatsu et al., 1994) and thus enhances the validity of the mouse prostate as a suitable model for human prostate function.

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