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ABT-866, a novel α_{1A}-adrenoceptor agonist with antagonist properties at the α_{1B}- and α_{1D}-adrenoceptor subtypes

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Abstract

N-[3-(1*H*-Imidazol-4-ylmethyl)phenyl]ethanesulfonamide, maleate (ABT-866) is a novel α_1-adrenoceptor agent with mixed pharmacological properties in vitro. Compared to phenylephrine, ABT-866 demonstrates intrinsic activity at the α_{1A}-adrenoceptor subtype present in the rabbit urethra ($pD_2 = 6.22$, with 80% of the phenylephrine response), reduced intrinsic activity at the α_{1B}-adrenoceptor subtype in the rat spleen ($pD_2 = 6.16$, with 11% of the phenylephrine response), and no intrinsic activity at the rat aorta α_{1D}-adrenoceptor subtype. ABT-866 also demonstrated antagonism at the rat spleen α_{1B}-adrenoceptor ($pA_2 = 5.39 \pm 0.08$, slope $= 1.20 \pm 0.12$), and the rat aorta α_{1D}-adrenoceptor ($pA_2 = 6.18 \pm 0.09$, slope $= 0.96 \pm 0.13$). This is in contrast to the weak non-selective activity seen with the α_1-adrenoceptor agonist, phenylpropanolamine (2-amino-1-phenyl-1-propanol hydrochloride), and the $\alpha_{1A/D}$-adrenoceptor selective agonist 1-(2′,5′-dimethoxyphenyl)-2-aminoethanol hydrochloride (ST-1059), the active metabolite of midodrine, that has been used clinically for the treatment of stress urinary incontinence. This study identifies a unique agent that may prove to be a valuable in vivo tool in testing the hypothesis that the α_{1A}-adrenoceptor can be stimulated to contract the smooth muscle present in the urethra without evoking blood pressure elevations presumably caused by α_{1B}- and α_{1D}-adrenoceptor subtype involvements in the vasculature.

Keywords: Adrenoceptor; α_{1A}-Adrenoceptor agonist; $\alpha_{1B/D}$-Adrenoceptor antagonist; Urethra; ABT-866; Phenylpropanolamine; Midodrine; ST-1059

1. Introduction

Adrenergic nerves have been identified in human urethral smooth muscle tissue (Ek et al., 1977a; Brading et al., 1999). It has also been demonstrated that α_1-adrenoceptor antagonists inhibit while agonists increase urethral tone (Ek et al., 1977b; Donker et al., 1972; Fossberg et al., 1983; Ahlstrom et al., 1990). A rational basis for the treatment of stress urinary incontinence with α_1-adrenoceptor agonists has been demonstrated clinically using phenylpropanolamine (Collste and Lindskog, 1987) and midodrine (Jonas, 1977; Weil et al., 1998; Andersson et al., 1983). However, both agents have met with limited success in the pharmacological treatment of stress urinary incontinence, due in part to the undesirable cardiovascular effects of non-selective α_1-adrenoceptor stimulation.

The recent introduction of the selective α_{1A}-adrenoceptor antagonist tamsulosin for the treatment of benign prostatic hyperplasia has shown that α_{1A}-adrenoceptors are the major α_1-adrenoceptor subtype responsible for lower urinary tract function (De Mey, 1998). With regards to the role of other adrenoceptors, results from mice deficient in α_{1B}-adrenoceptor show a reduced blood pressure response to exogenous stimulation indicating an important role for the α_{1B}-adrenoceptor subtype in the control of hemodynamic events (Cavalli et al., 1997). Recently, a potential role for the α_{1D}-adrenoceptor subtype in modulating bladder filling symptoms associated with detrusor instability was suggested (Schwinn and Michelotti, 2000). It was also reported that the α_{1D}-adrenoceptor subtype was up regulated in response to bladder outlet obstruction in rats, a laboratory model of urge urinary incontinence (Hampel et al., 2000).

We report here on the novel in vitro effects of ABT-866 (Fig. 1) a compound that selectively stimulates the α_{1A}-adrenoceptor subtype present in the lower urinary tract

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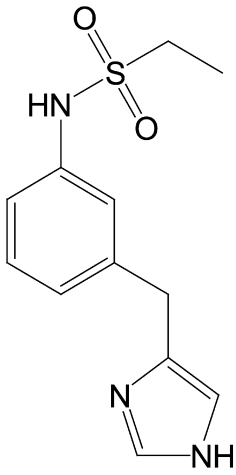

Fig. 1. Chemical structure of ABT-866, *N*-[3-(1*H*-imidazol-4-ylmethyl)-phenyl]ethanesulfonamide.

(Morita et al., 1993; Testa et al., 1993; Schwinn and Michelotti, 2000) and blocks the α_{1B}- and α_{1D}-adrenoceptor subtypes.

2. Materials and methods

This manuscript adheres to the nomenclature for adrenergic receptors as suggested by Bylund et al. (1994) and Hieble et al. (1995). All studies were carried out in accordance with guidelines outlined by the Animal Welfare Act, the Association for Assessment and Accreditation of Laboratory Animals and the Institutional Animal Care and Use Committee of Abbott Laboratories.

2.1. Radioligand binding assays

Radioligand binding at the adrenergic receptor sites was performed according to Knepper et al. (1995). Briefly, the cDNA encoding bovine α_{1A}, rat α_{1D} (Lomasney et al., 1991) and hamster α_{1B} (Cotecchia et al., 1988) receptors were obtained from Triangle Universities Licensing Consortium (Research Triangle Park, NC), expressed in mouse fibroblast cells (LTK^-) and membranes prepared and frozen at −70 °C until time of assay. Receptor binding assays were performed using the method of Greengrass and Bremner (1979). This protocol employed 1 ml final volumes in 50 mM Tris–HCl using 0.8 mg wet weight of cloned receptor membranes with 0.2 nM [^{3}H]prazosin in the presence and absence of various competing compounds. Non-specific binding was defined in the presence of 10 μM phentolamine. Subtype selective α_{2A}-adrenoceptor radioligand binding was performed according to the method of Uhlen and Wikberg (1991).

Animals were euthanized by means of an intraperitoneal injection of pentobarbital solution, at a lethal dose of 200 mg/kg Fatal-Plus® (Vortech Pharmaceuticals, Dearborn, MI). Tissues were immediately excised and placed in Krebs–Henseleit solution. The solution contained in mM: 120 NaCl, 18.0 $NaHCO_3$, 11.0 dextrose, 4.7 KCl, 2.5 $CaCl_2$, 1.5 $MgSO_4$, 1.2 KH_2PO_4 and equilibrated with 5% CO_2:95% O_2. The pH was adjusted to 7.4 at 37 °C by titration with a saturated solution of $NaHCO_3$. Propranolol (4 μM) was included in all assays to block β-adrenoceptors.

2.2. Rabbit urethra α_{1A}-adrenoceptor protocol

The urethra was removed from Female New Zealand white rabbits (1.75–3.75 kg) along with the urinary bladder attached and immediately placed into oxygenated Krebs–Henseleit bicarbonate solution. The urethra was separated from the bladder and the proximal end cut into 4 tissue rings approximately 2–3 mm wide. The urethra ring was attached to a stationary glass rod and a Grass FT03 transducer at a basal preload of 1.0 g. Data were recorded on a Grass model-7 polygraph. Tissues were rinsed every 10 min for a total of 75 min. The urethra was exposed to 80 mM potassium chloride, rinsed to basal tension and again with 10 μM phenylephrine. These two preliminary exposures made subsequent exposure to the test agents more reproducible. After an additional 60-min equilibration period, a reference concentration response curve was generated for each tissue using phenylephrine as the reference agonist. A cumulative concentration response (10 nM–3 mM) protocol was employed. Following a 75-min washout period, a second response curve was then generated in the same fashion using the test agent. Each tissue was used for only one test agonist.

2.3. Rat spleen α_{1B}-adrenoceptor protocol

The entire spleen was removed from male Sprague–Dawley rats (150–200 g), split longitudinally into two preparations per rat and mounted as described above (Han et al., 1987; Burt et al., 1992). A phenylephrine concentration response curve was generated in a cumulative fashion, the tissues rinsed for 90 min and a second concentration response curve (10 nM–1 mM) generated for the test agent. For determining the antagonist potency of ABT-866, the test agent was allowed a 45-min exposure time before a second phenylephrine response curve was generated in the presence of the antagonist. The individual tissues were exposed to only one concentration of test antagonist.

2.4. Rat aorta α_{1D}-adrenoceptor protocol

The method used was as described by Buckner et al., 1996. Briefly, the thoracic aorta was removed from male Sprague–Dawley rats (350–450 g), cleaned of extraneous tissue, and the endothelium removed by passing a 100-mm length of polyethylene-160 tubing through the lumen. The aorta was cut into 3- to 4-mm rings and mounted in 10-ml isolated tissue baths as described above. Absence of functional endothelium was confirmed by loss of the 10 μM

acetylcholine-induced relaxations of 10 μM phenylephrine-induced contractions. A phenylephrine concentration response curve (1 nM–1 mM) was generated in a cumulative fashion, the tissues rinsed for 90 min and a second concentration response curve generated for the test agent. Antagonist potency was determined as described above.

2.5. Rat vas deferens α_{2A}-adrenoceptor protocol

The entire vas deferens was removed from male Sprague–Dawley rats (350–450 g) and the epididymal portion discarded (Connaughton and Docherty, 1990). The prostatic portion was cut in a helical fashion and mounted between two platinum electrodes. One end was fixed to the stationary end of the electrode and the other to a Grass Instruments FT03 transducer at a basal preload of 0.5 g and placed in a 10-ml isolated tissue bath at 37 °C. The tissues were stimulated with a Grass Instruments S88 stimulator combined with a voltage–current stabilizing amplifier (Mayo Clinic). The stimulating parameters were: 0.1 Hz frequency, 25 V (supramaximal) with duration of 1.0 ms. Current was limited to 140 mA. This stimulation produced a rapid, biphasic contractile twitch that became reproducible and monophasic after approximately 15 min. The stimulus was applied for the duration of the agonist response curve. Cumulative concentrations of clonidine were used as a reference agonist producing a concentration-dependent reduction in the stimulated twitch response that resulted in complete cessation of the contractions. When the contractions were reduced to zero, the stimulus was stopped and the tissues thoroughly rinsed for 90 min at 10-ml intervals. The concentration response curve (10 pM–300 μM) was then repeated using the test agonist. Experimental protocol and data analysis performed as described above.

2.6. Drugs and chemicals

N-[3-(1*H*-imidazol-4-ylmethyl)phenyl]ethanesulfonamide, maleate (ABT-866); 1-(2′,5′-dimethoxyphenyl)-2-aminoethanol hydrochloride (ST-1059); and phenylpropanolamine HCl, 2-amino-1-phenyl-1-propanol hydrochloride; were synthesized at Abbott Laboratories (Abbott Park, IL). L-Phenylephrine, (±)-propranolol HCl, prazosin HCl, and clonidine HCl were purchased from Sigma (St. Louis, MO).

2.7. Data analysis

Concentration response curves were analyzed using a four-parameter curve fitting routine, described previously (Zielinski and Buckner, 1998). The maximum peak amplitude response was used for analysis. Results were expressed as g of tension and as a percentage of maximum response. Potencies were expressed as pD_2, the negative log10 (EC_{50} or IC_{50}). Differences in (EC_{50} or IC_{50}) values were calculated by analysis of variance (ANOVA), followed by Fisher's probabilistic least significance difference (PLSD) test for significance. Schild analysis was used to determine the antagonist potency and is expressed as pA_2 (Schild, 1947).

3. Results

3.1. Radioligand binding

ABT-866 exhibited nanomolar affinity for the α_{1A}-adrenoceptor expressed in the bovine clonal cell line (pK_i = 6.79; Table 1) and similar affinities for the rat clonal α_{1D}, pK_i = 6.55, and the human clonal α_{2A}-adrenoceptor subtypes, pK_i = 6.76. ABT-866 showed weaker affinity ($P < 0.0001$) for the hamster clonal α_{1B}, pK_i = 6.06.

Phenylpropanolamine was 55-fold weaker than ABT-866 at the α_{1A}-adrenoceptor subtype ($P < 0.05$), as indicated by a pK_i = 5.05. Phenylpropanolamine showed no α_{1A}-adrenoceptor subtype selectivity with binding affinities, α_{1B}–pK_i = 5.02, and α_{1D}–pK_i = 5.07. Phenylpropanolamine exhibited 32-fold greater affinity for the α_{2A}-adrenoceptor, pK_i = 6.56 versus the α_{1A}-adrenoceptor subtype ($P < 0.005$).

Compared to ABT-866, the radioligand binding affinity of ST-1059 was significantly weaker for the α_{1A}-adrenoceptor subtype, pK_i = 5.89, $P < 0.0001$. ST-1059, however, showed weaker affinity for the α_{1B}-adrenoceptor subtype, pK_i = 5.16 ($P < 0.001$), than seen at the α_{1A}-adrenoceptor subtype. Compared to its affinity at the α_{1A}-adrenoceptor, ST-1059 was non-selective in its affinity for the α_{1D}- and

Table 1
Radioligand binding affinities of the adrenergic agents expressed as pK_i

Radioligand binding	ABT-866 (pK_i)	Phenylpropanolamine (pK_i)	ST-1059 (pK_i)	Phenylephrine (pK_i)
Bovine clonal α_{1A}	6.79 ± 0.04	5.05 ± 0.24[a]	5.89 ± 0.07[b]	6.03 ± 0.26
Hamster clonal α_{1B}	6.06 ± 0.07[c]	5.02 ± 0.26	5.16 ± 0.03	5.90 ± 0.09
Rat clonal α_{1D}	6.55 ± 0.06	5.07 ± 0.21	5.78 ± 0.06	6.79 ± 0.05
Human clonal α_{2A}	6.76 ± 0.11	6.56 ± 0.14	5.83 ± 0.16	ND[d]

Data represents the mean ± S.E.M, $n = 4–8$.

[a] $P < 0.05$ where ABT-866 shows greater affinity than phenylpropanolamine for the bovine clonal α_{1A} adrenoceptor.

[b] $P < 0.0001$ where ABT-866 shows greater affinity than ST-1059 for the bovine clonal α_{1A} adrenoceptor.

[c] $P < 0.0001$ where ABT-866 shows greater affinity for the bovine clonal α_{1A} adrenoceptor than for the hamster clonal α_{1B} adrenoceptor.

[d] Not determined.

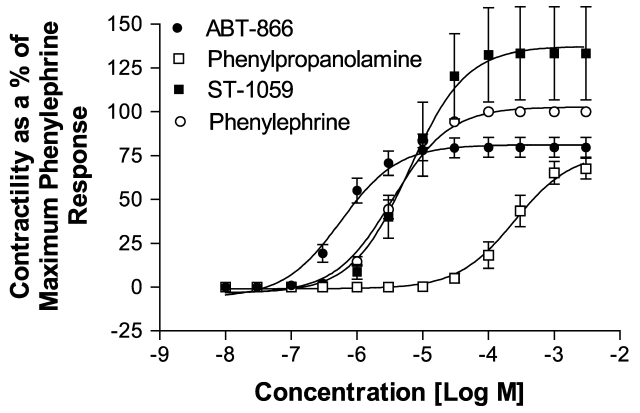

Fig. 2. Contractile response curves in the rabbit urethra (α_{1A}-adrenoceptor) to ABT-866, phenylpropanolamine, ST-1059, and phenylephrine. Data are presented as percentage of the maximum response evoked by phenylephrine (mean ± S.E.M., $n = 4–8$).

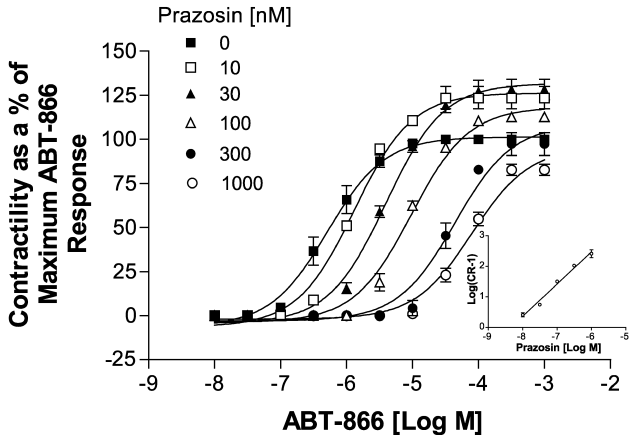

Fig. 3. Prazosin blockade of ABT-866 evoked contractions of the rabbit urethra (α_{1A}-adrenoceptor) with Schild plot inset. Prazosin $pA_2 = 8.34 \pm 0.14$, slope = 1.06 ± 0.04, $n = 15$.

α_{2A}-adrenoceptor with pK_i values of 5.78 and 5.83, respectively. Data for the reference standard phenylephrine were included in Table 1 for comparative purposes and indicate that phenylephrine is preferentially an α_{1D}-adrenoceptor subtype agonist.

3.2. Isolated tissue bath assays

Phenylephrine was employed as a reference agent for the α_1-adrenoceptor assays. The maximum contractions evoked by phenylephrine were 5.65 ± 0.61, 0.37 ± 0.002, and 1.12 ± 0.07 g for the rabbit urethra α_{1A}, rat spleen α_{1B} and rat aorta α_{1D}-adrenoceptor subtypes, respectively. Clonidine, an α_{2A}-adrenoceptor agonist, was used as a reference compound for the field-stimulated vas deferens and inhibited the field-stimulated twitch from 0.71 ± 0.14 g to complete inhibition of contractions.

3.3. Rabbit urethra α_{1A}

The adrenoceptor subtype responsible for contractions of the lower urinary tract is currently recognized as the α_{1A} (Schwinn and Michelotti, 2000). ABT-866 contracted the rabbit urethra with a potency $pD_2 = 6.22 \pm 0.05$ and intrinsic activity 80% of the tension evoked by phenylephrine (Fig. 2, Table 2). The contractions evoked by ABT-866 were blocked by prazosin in a competitive fashion ($pA_2 = 8.34 \pm 0.14$, $n = 12$), with parallel shifts of the concentration response curve, no reduction in maximum response and a Schild slope (1.06 ± 0.04) not different from unity (Fig. 3).

3.4. Rat spleen α_{1B}

In contrast to the robust intrinsic activity produced by ABT-866 in the rabbit urethra, ABT-866 showed only 11% intrinsic activity ($P < 0.001$) relative to phenylephrine at the α_{1B}-adrenoceptor subtype expressed in the rat spleen (Fig. 4A, Table 2). Due to the minimal activity of ABT-866 in this assay it was retested as an antagonist. ABT-866 antagonized the contractions evoked by phenylephrine in the rat spleen with a pA_2 value of 5.39 ± 0.08, slope = 1.20 ± 0.12, $n = 18$ (Fig. 5). In this assay, phenylpropanolamine and ST-1059 exhibited 34% and 68% intrinsic activity relative to phenylephrine, respectively.

Table 2
Data are expressed as potency pD_2, (mean ± S.E.M., $n = 4–8$)

Agonist potency	ABT-866 (pD_2)	Phenylpropanol-amine (pD_2)	ST-1059 (pD_2)	Reference agonist (pD_2)
Rabbit urethra α_{1A}	6.22 ± 0.05 (80 ± 5.6%)	3.63 ± 0.01[a] (68 ± 5.8%)[b]	5.15 ± 0.07[a] (133 ± 26.6%)	5.44 ± 0.06 (100%)
Rat spleen α_{1B}	6.16 ± 0.38 (11 ± 2.5%)[c]	3.55 ± 0.14 (34 ± 4.9%)	4.07 ± 0.07 (68 ± 11.2%)	5.15 ± 0.05 (100%)
Rat aorta α_{1D}	0	4.24 ± 0.11 (91 ± 2.1%)	5.73 ± 0.14 (106 ± 6.7%)	6.60 ± 0.09 (100%)
Rat vas deferens α_{2A}	5.45 ± 0.19[d] (34 ± 6.7%)[e]	5.1 ± 0.04 (96 ± 1.0%)	8.23 ± 0.05 (20 ± 2.5%)	8.0 ± 0.06 (100)

Number in parenthesis represents intrinsic activity relative to the reference agent phenylephrine for all assays except the α_{2A}-adrenoceptor where clonidine was used.

[a] $P < 0.0001$ where ABT-866 is more potent at the rabbit urethra α_{1A} adrenoceptor than phenylpropanolamine and ST-1059.
[b] $P < 0.05$ where ABT-866 shows greater intrinsic activity at the rabbit urethra α_{1A} adrenoceptor than phenylpropanolamine.
[c] $P < 0.001$ where ABT-866 shows greater intrinsic activity at the rabbit urethra α_{1A} adrenoceptor than at the rat spleen α_{1B} adrenoceptor.
[d] $P < 0.05$ where ABT-866 is more potent at the rabbit urethra α_{1A} adrenoceptor than the rat vas deferens α_{2A} adrenoceptor.
[e] $P < 0.0001$ where ABT-866 shows greater intrinsic activity at the rabbit urethra α_{1A} adrenoceptor than at the rat vas deferens α_{2A} adrenoceptor.

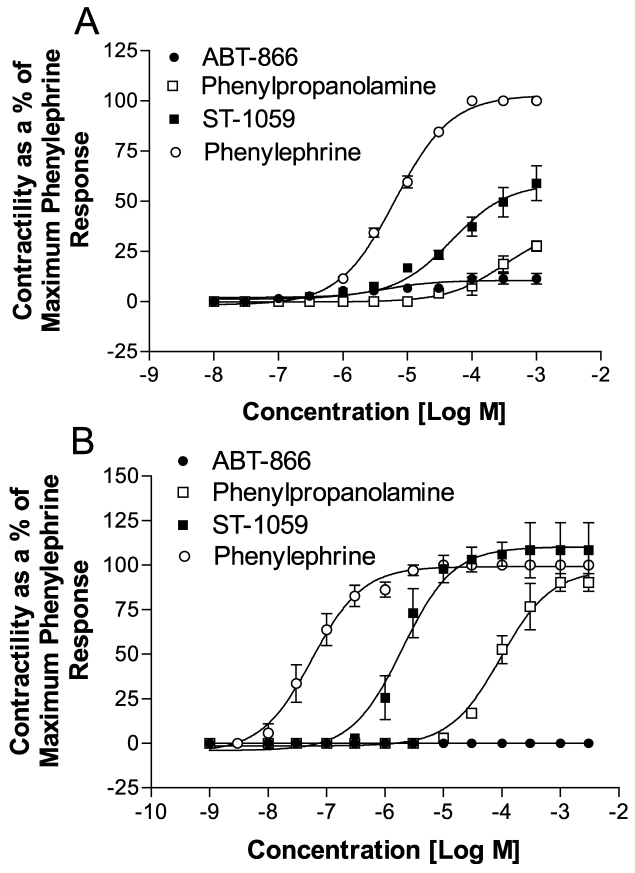

Fig. 4. (A) Contractile response curves in the rat spleen (α_{1B}-adrenoceptor) to ABT-866, phenylpropanolamine, ST-1059, and phenylephrine. Data are presented as percentage of the maximum response evoked by phenylephrine (mean ± S.E.M., $n = 4–8$). (B) Contractile response curves in the rat aorta (α_{1D}-adrenoceptor) to ABT-866, phenylpropanolamine, ST-1059, and phenylephrine. Data are presented as percentage of the maximum response evoked by phenylephrine (mean ± S.E.M., $n = 4–8$).

3.5. Rat aorta α_{1D}

ABT-866 was devoid of agonistic activity at the α_{1D}-adrenoceptor subtype expressed in the rat aorta, up to a maximum concentration of 1 mM (Fig. 4B, Table 2). In view of the absence of α_{1D} stimulation, ABT-866 was evaluated as an antagonist. ABT-866 antagonized the contractions evoked by phenylephrine in the rat aorta with a pA_2 value of 6.18 ± 0.09, slope = 0.96 ± 0.13, $n = 16$ (Fig. 6).

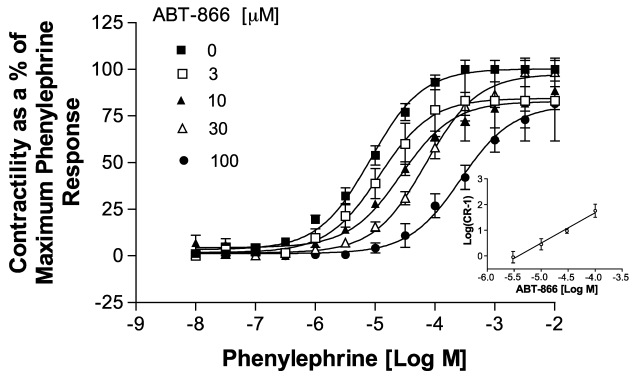

Fig. 5. ABT-866 blockade of phenylephrine-evoked contractions of the rat spleen (α_{1B}-adrenoceptor). Data are presented as shifts in the phenylephrine response curves, Schild plot inset ($pA_2 = 5.39 \pm 0.08$, slope = 1.20 ± 0.12, $n = 18$).

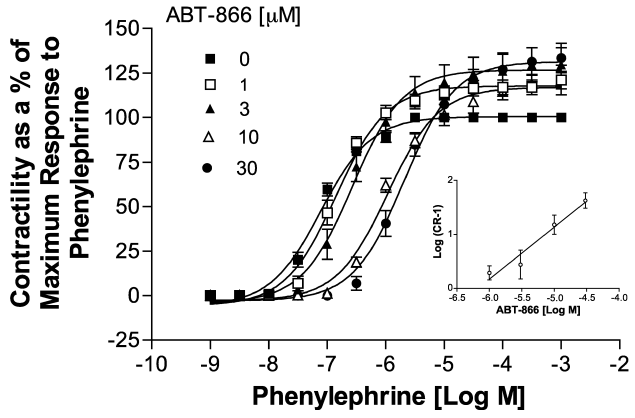

Fig. 6. ABT-866 blockade of phenylephrine-evoked contractions of the rat aorta (α_{1D}-adrenoceptor). Data are presented as shifts in the phenylephrine response curves, Schild plot inset ($pA_2 = 6.18 \pm 0.09$, slope = 0.96 ± 0.13, $n = 16$).

3.6. Rat vas deferens α_{2A}

At the presynaptic α_{2A}-adrenoceptor subtype, ABT-866 showed activity in inhibiting the electrically stimulated rat vas deferens, $pD_2 = 5.45$ with 34% intrinsic activity relative to the control agent clonidine (Fig. 7, Table 2). Phenylpropanolamine showed similar potency to ABT-866 but greater intrinsic activity (96% of the response to clonidine, $P < 0.0001$). ST-1059 was a potent agonist, $pD_2 = 8.23$, but with limited intrinsic activity (20% of the clonidine response).

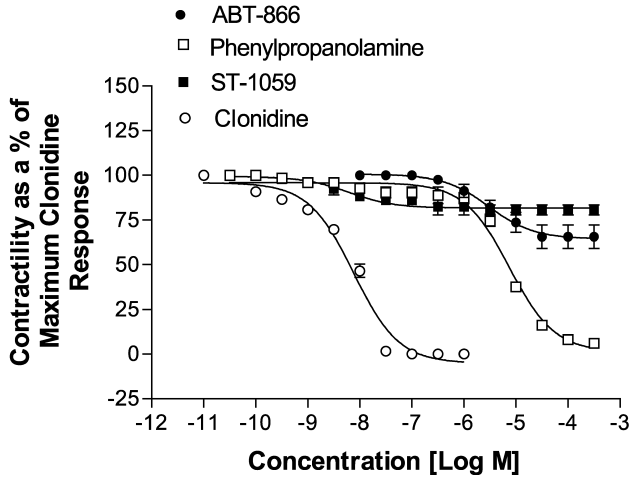

Fig. 7. Reductions in the field-stimulated twitch response of the rat vas deferens (α_{2A}-adrenoceptor) to ABT-866, phenylpropanolamine, ST-1059, and clonidine. Data are presented as percentage of the maximum response evoked by clonidine (mean ± S.E.M., $n = 4–8$).

4. Discussion

In the current study, the relative affinities at the α_{1A}-adrenoceptor subtype were ABT-866 > ST-1059>phenylpropanolamine, $P < 0.0001$ and $P < 0.05$, respectively. ABT-866 exhibited 55-fold greater affinity for the α_{1A}-adrenoceptor subtype than phenylpropanolamine. ABT-866 also showed 5-fold radioligand binding selectivity for the α_{1A}-adrenoceptor subtype over the α_{1B}-adrenoceptor subtype ($P < 0.0001$); however, no differences were seen in the affinities at the α_{1A}-, α_{1D}-, or α_{2A}-adrenoceptor subtypes. Phenylpropanolamine exhibited 32-fold greater affinity for the α_{2A}-adrenoceptor subtype than seen for the α_{1A}-adrenoceptor ($P < 0.005$) and no α_1-adrenoceptor subtype selectivity. ST-1059 exhibited 5-fold weaker affinity at the α_{1B}-adrenoceptor subtype compared to its affinity at the α_{1A}-adrenoceptor subtype ($P < 0.05$). ST-1059 was non-selective in its affinity for the α_{1A}-, α_{1D}- and α_{2A}-adrenoceptor subtypes. Phenylephrine exhibited selectivity for the α_{1D}-adrenoceptor subtypes with relative affinities ($\alpha_{1D} > (\alpha_{1A} = \alpha_{1B})$) $P < 0.05$.

It has been suggested that the resting urethral tone in the rabbit and human are in part maintained by stimulation of the α_{1A}-adrenoceptor subtype (Morita et al., 1993; Testa et al., 1993). This concept has been supported clinically by the success of phenylpropanolamine (Ahlstrom et al., 1990; Collste and Lindskog, 1987) and ST-1059 in alleviating the symptoms of stress urinary incontinence. These agents however have met with limited success due to the negative cardiovascular side effects.

The radioligand binding affinity for ABT-866 at the α_{1A}-adrenoceptor subtype was expressed functionally in the rabbit urethra α_{1A} as a potent agonist with intrinsic activity slightly weaker than phenylephrine $P < 0.050$. The prazosin shift of the ABT-866 concentration response curve would suggest that ABT-866 is a competitive agonist. The affinities for the α_{1B}- and α_{1D}-adrenoceptor subtypes were expressed functionally as agonism/antagonism at the rat spleen α_{1B} and as antagonism at the rat aorta α_{1D}-adrenoceptor subtype. This was in contrast to the functional agonism expressed by phenylpropanolamine and ST-1059 at all three α_1-adrenoceptor subtypes. All three agents were agonists at the α_{2A} rat vas deferens and inhibited the field stimulated twitch response. ABT-866 showed weak intrinsic activity with 34% of the response seen with clonidine. Phenylpropanolamine showed similar potency to ABT-866, but with greater intrinsic activity, whereas ST-1059 was a potent agonist with limited intrinsic activity (20% of the response to phenylephrine).

Non-selective α_1-adrenoceptor agonists have demonstrated limited clinical utility due to adverse cardiovascular effects (Jonas, 1977; Fossberg et al., 1983; Collste and Lindskog, 1987; Weil et al., 1998). An improved pharmacological profile for an agent designed to increase lower urinary tract resistance may be realized with agonists that possess greater α_{1A}-adrenoceptor subtype selectivity over the $\alpha_{1B/D}$-adrenoceptor subtypes, like A-61603, or an agent with mixed pharmacology showing α_{1A}-adrenoceptor agonism and functional antagonism at the $\alpha_{1B/D}$-adrenoceptor subtypes, like ABT-866. Currently, highly selective α_{1A}-adrenoceptor agonists such as A-61603 do not have sufficient therapeutic index to eliminate subtype specific cardiovascular effects as demonstrated with in vivo models in the dog (Knepper et al., 1995). Therefore, as α_{1B}- and α_{1D}-adrenoceptor antagonists exhibit antihypertensive effects, a combination of α_{1A}-adrenoceptor agonism and $\alpha_{1B/D}$-adrenoceptor antagonism may prove beneficial in treating lower urinary tract leakage. The pharmacological profile of ABT-866 offers a means of testing such a hypothesis.

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