British Journal of Pharmacology (1998) 124, 593–599 © 1998 Stockton Press All rights reserved 0007–1188/98 $12.00
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Species differences in the distribution of β-adrenoceptor subtypes in bladder smooth muscle

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1 The β-adrenoceptor (β-AR) subtypes mediating relaxation of the rabbit, rat and canine detrusors were subjected to functional investigation using selective β-AR agonists and antagonists.

2 In all three species, isoprenaline, noradrenaline and adrenaline each produced a concentration-dependent relaxation of the detrusor. The rank order for their relaxing potency was isoprenaline > adrenaline > noradrenaline in rabbits and rats, but isoprenaline > noradrenaline > adrenaline in dogs.

3 Dobutamine did not produce relaxation of the detrusors at concentrations that are selective for β_1-AR. The selective β_2-AR agonist, procaterol, had a more potent relaxing effect on rabbit and rat detrusors than on the canine detrusor. CGP-12177A, a selective β_3-AR agonist, was more effective in the rabbit than in the other two species. On the other hand, the relaxing effect of another β_3-AR agonist, CL316243, was more pronounced in dogs and rats than in rabbits.

4 CGP-20712A (10^{-9} to 10^{-7} M), a selective β_1-AR antagonist, caused a slight rightward shift of the concentration-relaxation response curve for isoprenaline in the canine detrusor (pA_2 9.41), but not in the rabbit and rat detrusors. ICI-118,551, a selective β_2-AR antagonist, antagonized the isoprenaline-induced relaxation in rabbits (pA_2 9.45) and rats (pA_2 9.05), but not in dogs. Bupranolol, a non-selective β-AR antagonist, caused a rightward shift of the concentration-relaxation curve for isoprenaline in the rabbit (pA_2 9.32) and rat (pA_2 8.98). However, higher concentrations (3×10^{-8} to 10^{-5} M) were needed to induce a rightward shift of the curve for isoprenaline in the dog (pA_2 8.19) than in the other two species.

5. We have confirmed that the distribution of β-AR subtypes in the detrusor muscle varies significantly from species to species and we provide here the first evidence of the presence of β_3-AR in the detrusor. It is suggested that the relaxation induced by adrenoceptor agonists in urinary bladder smooth muscle may be mediated mainly via β_2-AR in rabbits, via both β_2- and β_3-AR in rats, but mainly via β_3-AR in dogs.

Keywords: Rabbit detrusor; rat detrusor; canine detrusor; β-adrenoceptor; β_3-adrenoceptor; selective agonists; selective antagonists

Introduction

The urinary bladder is innervated by both sympathetic and parasympathetic fibres via the hypogastric and pelvic nerves (Kuru, 1965). The detrusor muscle responds to adrenergic stimulation by relaxation, and to cholinergic stimulation by contraction. The relaxation of the bladder caused by increased hypogastric nerve activity, and mediated via β-adrenoceptor (β-AR) activation (Levin *et al*., 1980), is of greatest importance during the collecting phase of bladder filling.

The distribution of the various β-AR subtypes is not homogeneous among the detrusors of different mammalian species. For example, the relaxation responses seen in the detrusors of the cat (Nergårdh *et al*., 1977) and guinea-pig (Li *et al*., 1992) are mediated mainly via β_1-AR, whereas in the rat (Elmér, 1974) and rabbit (Anderson & Marks, 1984; Levin *et al*., 1988) the detrusor responses are said to be mediated via β_2-AR. Further, Morita *et al*. (1993) suggested that both β_1- and β_2-ARs are present in the canine detrusor. With regard to the human detrusor, there have been conflicting reports concerning the distribution of the various β-AR subtypes. Thus, while Levin *et al*. (1988) demonstrated a predominance of β_2-AR in a radioligand binding study, Nergårdh *et al*. (1977); Larsen (1979) and Kullendorff *et al*. (1987) all suggested the presence of a β-AR subtype other than β_1 and β_2.

Recently, a β_3-AR has been identified in a variety of mammalian tissues, including human tissues (Emorine *et al*., 1989; Krief *et al*., 1993; Berkowitz *et al*., 1995). Stimulation of β_3-AR produces lipolysis in white adipose tissue, thermogenesis in brown adipose tissue and relaxation of the alimentary tract. However, it is unclear whether β_3-ARs are present in the mammalian urinary bladder and, if so, what function they perform. The aim of the present study was to clarify which β-AR subtypes are present in the detrusor of three mammalian species (rabbit, rat and dog), with special attention being paid to the presence or absence of the β_3-AR subtype. We also undertook a functional analysis of the relaxation induced by β-AR agonists, including catecholamines, in the various detrusors. In addition, we examined the interaction between selective β-AR antagonists and the isoprenaline-induced relaxation in these same detrusors.

Methods

Animals

This study was conducted according to guidelines approved by the Laboratory Animal Committee of Kissei Pharmaceutical Co. Ltd. Male Japanese White rabbits (2.0–3.5 kg, from SLC, Hamamatsu, Japan), male Sprague-Dawley rats (200–380 g, from SLC) and mongrel dogs of either sex (7–14 kg, from

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Nagoya Labo Service, Nagoya, Japan) were used. They were maintained in a 12 h light-dark cycle with free access to water and standard laboratory food until the day of the experiment.

Tissue preparation and experimental protocol

Rabbits, rats and dogs were anaesthetized with urethane (0.8 g kg^{-1}, intravenously), with diethyl ether or with sodium pentobarbitone (30 mg kg^{-1}, intravenously), respectively. The animals were killed by rapid exsanguination and the urinary bladder removed. After removal of the fat and mucosa, a detrusor strip approximately 10×2 mm was taken and suspended in a 10 ml organ bath containing Krebs solution. This bath solution was maintained at 37°C and continuously gassed with a mixture of 95% oxygen and 5% carbon dioxide. The preparations were equilibrated for 60 min after the establishment of an initial resting tension of 5 mN for rabbits and rats, and 7 mN for dogs. One end of each strip was connected to a force-displacement transducer (SB-IT, Nihon-Kohden, Tokyo, Japan) and changes in muscle tension were measured and recorded on a pen-writing oscillograph (Rectigraph 8S, Sanei, Tokyo, Japan). Concentration-response curves for catecholamines and for β-adrenoceptor agonists were obtained by the cumulative addition of each substance to the bathing fluid. In experiments examining the effects of β-adrenoceptor antagonists, tissues were exposed to the appropriate antagonist for 30 min before we began to collect data for the isoprenaline concentration-response curve. Only one agonist concentration-response curve was generated per tissue. All experiments were conducted in the presence of 10^{-6} M phentolamine, an α-adrenoceptor antagonist.

Analysis of data

The results are expressed as mean ± s.e.mean or with 95% confidence intervals in parentheses. The relaxing effect of each agonist was expressed in terms of the percentage of resting tension seen with each of a range of doses of the agonist. The 0 percent of the tonus level was expressed as a maximal relaxation induced by 10^{-5} M forskolin. The pD_2 value, which is the negative logarithm of the EC_{50} value, was calculated for each agonist from its concentration-relaxation curve. The pA_2 values for antagonists, as defined by Arunlakshana & Schild (1959), were obtained from linear regression analysis of plots of values for $\log(CR-1)$ vs the negative log of the antagonist concentration. Statistical analysis was performed using Student's two-tailed t test. A probability level of less than 0.05 was accepted as significant.

Drugs

The following drugs were used: (−)-isoprenaline (+)-bitartrate, procaterol hydrochloride (Sigma Chemical, St. Louis, MO, U.S.A.), forskolin (Wako Pure Chemical, Osaka, Japan), (±)-dobutamine hydrochloride, (±)-CGP-12177A hydrochloride ((±)-4-(3-t-butylamino-2-hydroxypropoxy) benzimidazol-2-one hydrochloride), ICI-118,551 hydrochloride (erythro-(±)-1-(7-methylindan-4-yloxy)-3-isopropylamino-butan-2-ol hydrochloride) (Funakoshi, Tokyo, Japan), (±)-noradrenaline (Sankyo, Tokyo, Japan), (−)-adrenaline (Daiichi, Tokyo, Japan), phentolamine mesylate (Ciba-Geigy, Basel, Switzerland) and dimethyl sulphoxide (DMSO) (Nacalai tesque, Kyoto, Japan). Bupranolol hydrochloride was extracted from Looser (Kaken, Urayasu, Japan). CL316243 ((**R,R**)-5-[2-[[2-(3-chlorophenyl)-2-hydroxyethylamino]propyl]-1,3-benzodioxole-2,2-dicarboxylate) and CGP-20712A (2-hydroxy-5(2-((2-hydroxy-3-(4-((1-methyl-4-trifluoromethyl) 1H-imidazole-2-yl)-phenoxy)propyl)amino)ethoxy)-benzamide monomethane sulphonate) were synthesized in our laboratories (Kissei, Hotaka, Japan). Forskolin was dissolved in 100% DMSO; the other drugs in distilled water. The solutions were prepared on the day of the experiment and kept in dark vessels to minimize light-induced degradation. Subsequent dilutions of the drugs were prepared in distilled water. The concentrations presented are the calculated final concentrations in the bath solution. The Krebs solution was of the following composition (mM): NaCl 118.1, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, $NaHCO_3$ 25.0, KH_2PO_4 1.2 and glucose 11.1 (pH 7.4).

Results

Isoprenaline-, noradrenaline- and adrenaline-induced relaxation of the rabbit, rat and canine detrusors

An apparent relaxation of the detrusor from each of the three species was produced by forskolin (10^{-5} M). In the detrusors isolated from rabbits, rats and dogs, the tension decreased to 42 ± 2, 43 ± 1 and 54 ± 1% of the resting tension respectively.

The relaxing potencies of isoprenaline, noradrenaline and adrenaline were studied in the three detrusors, and the results are shown in Table 1, Figures 1 and 2. All three catecholamines produced concentration-dependent relaxation of the detrusor in each species. The maximal relaxation for a given agent did not differ significantly between the three species. In the rabbit detrusor, isoprenaline exhibited a potency that was roughly 5 times and 177 times higher than those of adrenaline and noradrenaline, respectively. The pD_2 values were 9.05 (8.81–9.30), 8.34 (7.98–8.70) and 6.80 (6.53–7.07) for isoprenaline, adrenaline and noradrenaline, respectively. The rat detrusor was also relaxed by these catecholamines, the corresponding pD_2 values being 8.28 (7.96–8.60), 6.93 (6.65–7.22) and 6.42 (6.04–6.81). On the other hand, in the canine detrusor the rank order for their relaxing activity was isoprenaline > noradrenaline > adrenaline, the pD_2 values being 6.97 (6.56–7.37), 6.07 (5.49–6.65) and 5.59 (4.90–6.28), respectively.

Table 1 The pD_2 values for β-adrenoceptor agonists in rabbit, rat and canine detrusors

	Rabbit detrusor	*Rat detrusor*	*Canine detrusor*
Isoprenaline	9.05 (8.81–9.30)	8.28 (7.96–8.60)	6.97 (6.56–7.37)
Adrenaline	8.34 (7.98–8.70)	6.93 (6.65–7.22)	5.59 (4.90–6.28)
Noradrenaline	6.80 (6.53–7.07)	6.42 (6.04–6.81)	6.07 (5.49–6.65)
Dobutamine	6.64 (6.20–7.07)	4.97 (4.74–5.20)	5.84 (5.50–6.19)
Procaterol	9.46 (9.14–9.77)	7.95 (7.46–8.44)	5.77 (5.57–5.97)
CGP-12177A	8.19 (7.86–8.53)	6.69 (6.19–7.20)	6.86 (6.34–7.37)
CL316243	5.04 (4.59–5.49)	8.18 (7.95–8.41)	8.03 (7.59–8.46)

Results are expressed as mean with 95% confidence intervals (in parentheses).

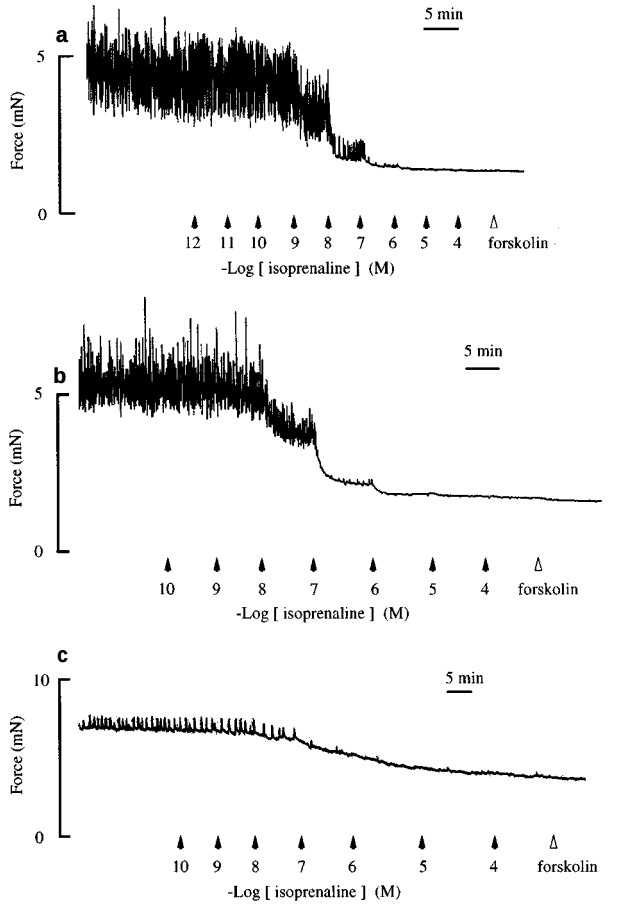

Figure 1 Representative recordings of the effect of isoprenaline on resting tension in rabbit (a), rat (b) and canine (c) detrusor preparations.

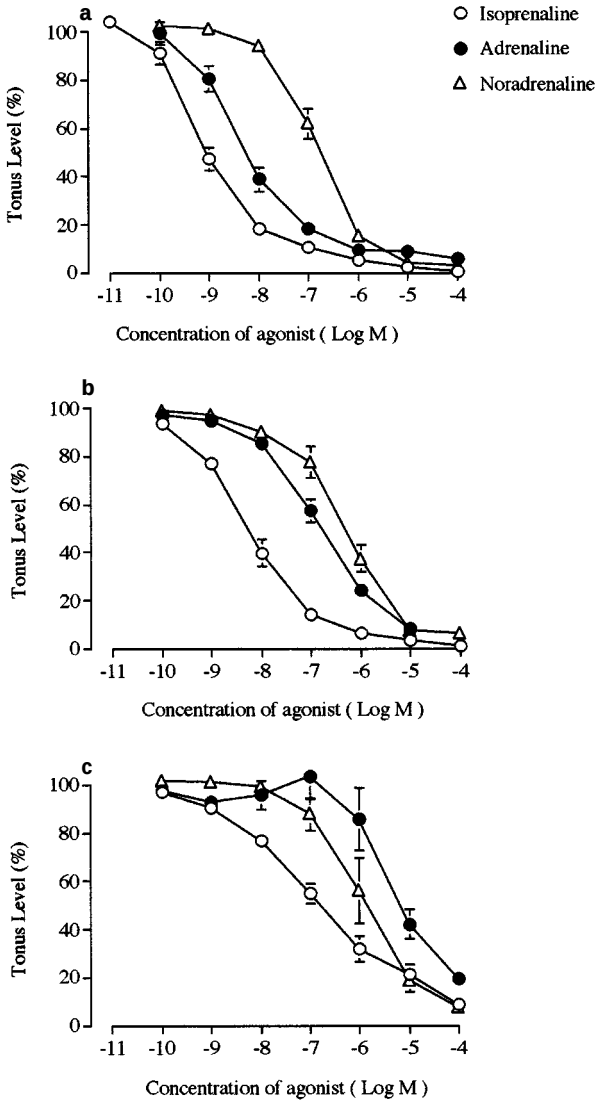

Figure 2 Effects of isoprenaline, adrenaline and noradrenaline on resting tension in rabbit (a), rat (b) and canine (c) detrusor preparations. Each value is the mean of 5–7 experiments; vertical lines show s.e.mean.

β-Adrenoceptor agonist activity in rabbit, rat and canine detrusors

In the rabbit detrusor, the selective β_2-AR agonist, procaterol, was the most potent relaxant, isoprenaline and the selective β_1-AR agonist, dobutamine, being 3 times and 660 times, respectively, less potent than procaterol (Figure 3a). The selective β_3-AR agonist, CGP-12177A exhibited a relatively high activity, but another β_3-AR agonist, CL316243, had an apparently low activity in the detrusor in this species. In the rat detrusor, procaterol and CL316243 were almost as potent in inducing relaxation as isoprenaline, which was about 1,000 times more potent than dobutamine (Figure 3b). By contrast, CGP-12177A induced only a slight relaxation. The rank order for the relaxing activity of these β-AR agonists in the canine detrusor was CL316243 > isoprenaline and CGP-12177A > procaterol and dobutamine (Figure 3c). The pD_2 values obtained for all the β-AR agonists are shown in Table 1.

Effect of β-AR antagonists on the relaxation induced by isoprenaline in the rabbit, rat and canine detrusors

In the rabbit and rat detrusors, the selective β_1-AR antagonist, CGP-20712A failed to affect the relaxation induced by isoprenaline (Figure 4a,b). Although CGP-20712A at concentrations of 10^{-9} and 3×10^{-9} M caused a rightward shift of the concentration-response curve for isoprenaline in the canine detrusor, further antagonism was not observed after application of the agent at concentrations over 10^{-8} M (pA_2 9.41 (9.00–9.91), slope 0.69 (0.02–1.36): Figure 4c). In the rabbit detrusor, the selective β_2-AR antagonist, ICI-118,551 (10^{-9} to 10^{-7} M), produced a parallel rightward shift of the concentration-response curve for isoprenaline without altering the maximal response (pA_2 9.45 (9.21–9.69), slope 0.59 (0.39–0.79): Figure 5a). In the rat detrusor, ICI-118,551 at concentrations of 10^{-9} to 10^{-7} M produced a relatively small rightward shift of the curve for isoprenaline (pA_2 9.05 (8.61–9.49), slope 0.28 (0.10–0.46): Figure 5b). By contrast, ICI-118,551 had no effect on the relaxation induced by isoprenaline in the canine detrusor (Figure 5c).

The non-selective β-AR antagonist, bupranolol (10^{-9} to 10^{-5} M), caused a rightward shift of the concentration-response curve for isoprenaline in the detrusors of both rabbit (pA_2 9.32 (9.21–9.44), slope 0.86 (0.77–0.94): Figure 6a) and rat (pA_2 8.98 (8.77–9.19), slope 0.63 (0.53–0.74): Figure 6b). Although bupranolol at concentrations from 10^{-9} to 10^{-8} M had only small effects on the response to isoprenaline in the canine detrusor, higher concentrations produced a rightward

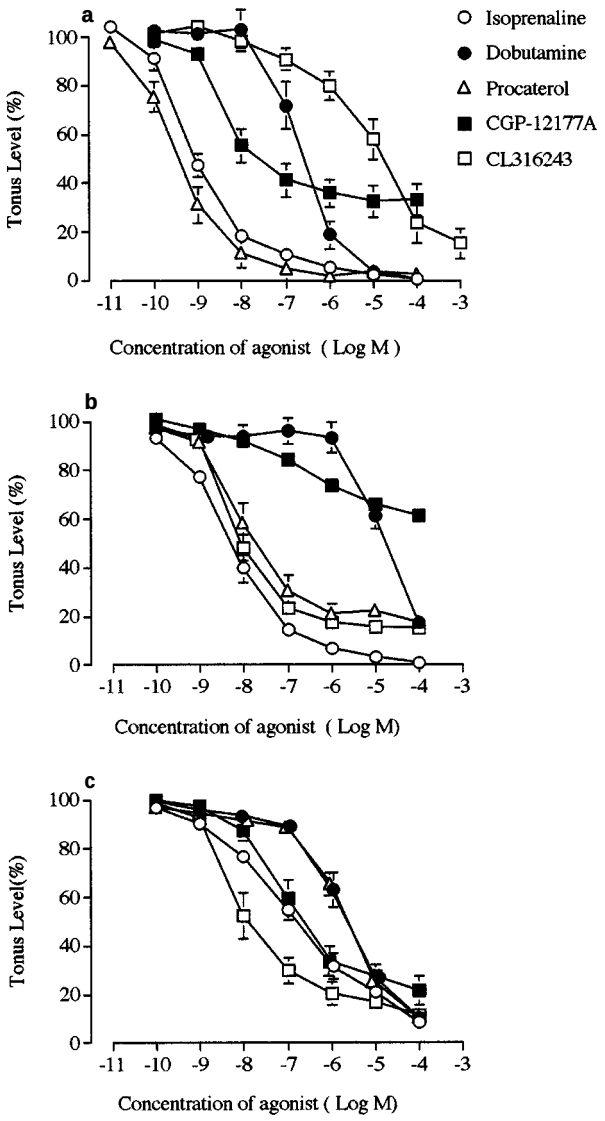

Figure 3 Effects of isoprenaline, dobutamine, procaterol, CGP-12177A and CL316243 on resting tension in rabbit (a), rat (b) and canine (c) detrusor preparations. Each value is the mean of 5–7 experiments; vertical lines show s.e.mean.

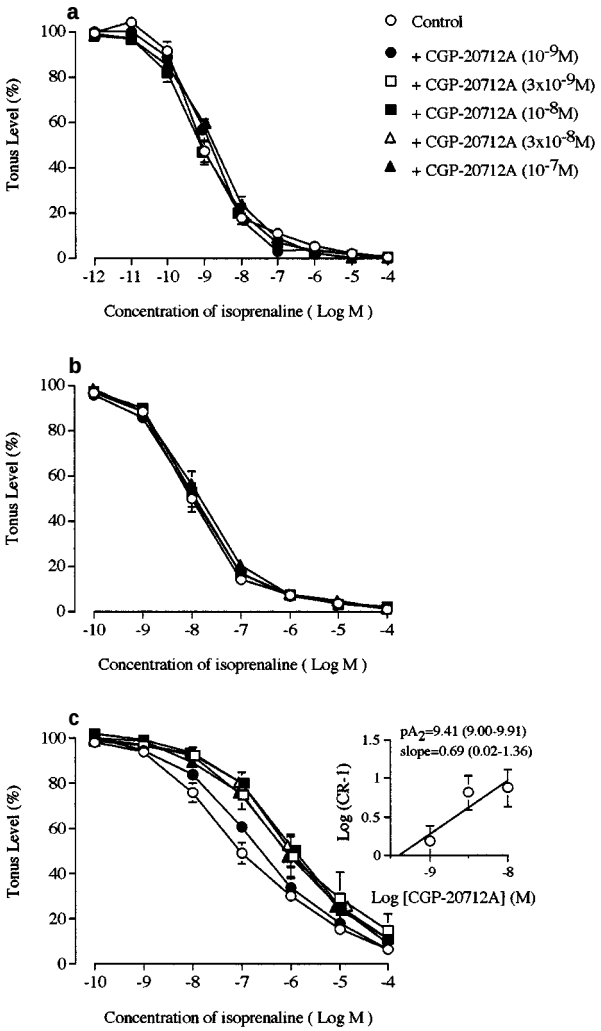

Figure 4 Effect of CGP-20712A on isoprenaline-induced relaxation in rabbit (a), rat (b) and canine (c) detrusor preparations. Each value is the mean of 6 experiments; vertical lines show s.e.mean. Inset: Schild plot of CGP-20712A against isoprenaline-induced relaxation in the dog. The slope of the regression line did not differ significantly from unity in the dog.

shift of this curve (pA_2 8.19 (7.88–8.50), slope 0.53 (0.31–0.75): Figure 6c).

Discussion

The present study has confirmed that the distribution of β-AR subtypes in the detrusor differs considerably among the species tested (rabbit, rat and dog), and provides the first functional evidence for the existence of the β_3-AR subtype in the detrusor.

The β-ARs present in a given tissue can be classified as β_1 or β_2 subtypes on the basis of their different sensitivities to a series of structurally-related sympathomimetic amines, including both endogenous and synthetic ones (Lands *et al.*, 1967). The rank order of potency for those catecholamines producing β-AR-mediated responses is isoprenaline > noradrenaline ≥ adrenaline for β_1-AR and isoprenaline > adrenaline > noradrenaline for β_2-AR. A few years ago, β_3-AR, an additional β-AR subtype, was identified (Emorine *et al.*, 1989), and the stimulating effects of catecholamines were evaluated on adenosine 3′ : 5′-cyclic monophosphate (cyclicAMP) accumulation in Chinese hamster ovary cells expressing human β_3-AR. In such tests, the rank order of potency was isoprenaline > noradrenaline > adrenaline. This has been confirmed in several species in other tissues containing β_3-ARs (Mohell *et al.*, 1983; McLaughlin & MacDonald, 1990).

In our first experiment, we examined the relaxing effects of the same catecholamines to enable us to characterize the β-AR subtypes present in the detrusor in rabbits, rats and dogs. Isoprenaline was the most potent relaxant in all three species. However, the relaxing potency of noradrenaline and adrenaline was species-dependent. Adrenaline was more effective than noradrenaline in rabbits and rats, but it was less effective than noradrenaline in dogs. These results seemed to suggest the existence of β_2-ARs in rabbit and rat detrusors, but of β_1 and/or β_3-ARs in the canine detrusor.

In our next experiment, we evaluated the relaxing effects of several β-AR agonists on the detrusors. Dobutamine, supposedly a β_1-AR-selective agonist, produced a concentration-dependent relaxation at higher concentrations (over 10^{-7} M) in all three species. In our preliminary experiments on rat tissues: (i) dobutamine produced an increase in the

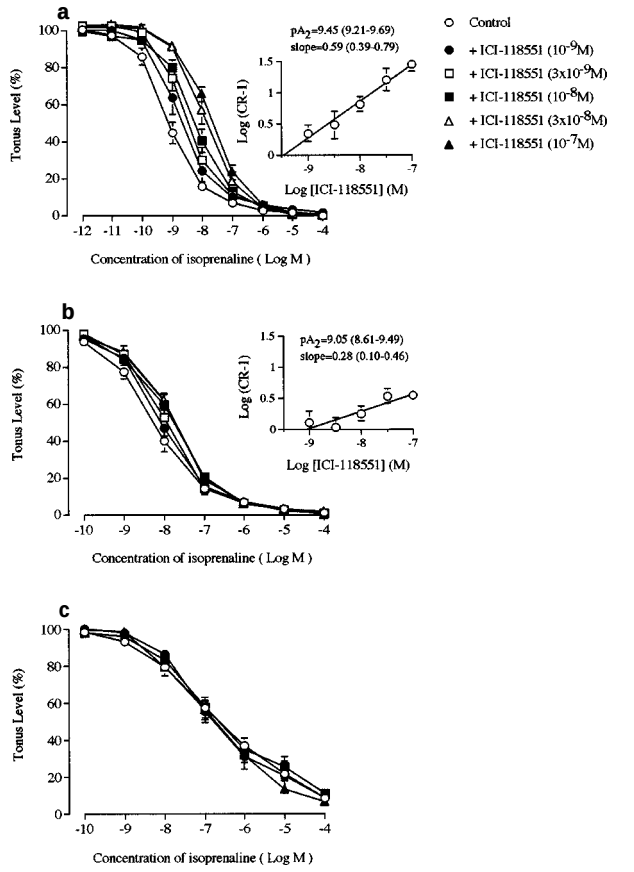

Figure 5 Effect of ICI-118,551 on isoprenaline-induced relaxation in rabbit (a), rat (b) and canine (c) detrusor preparations. Each value is the mean of 6–7 experiments; vertical lines show s.e.mean. Inset: Schild plots of ICI-118,551 against isoprenaline-induced relaxation in rabbit and rat. The slope of the regression line differed significantly from unity in both rabbits and rats.

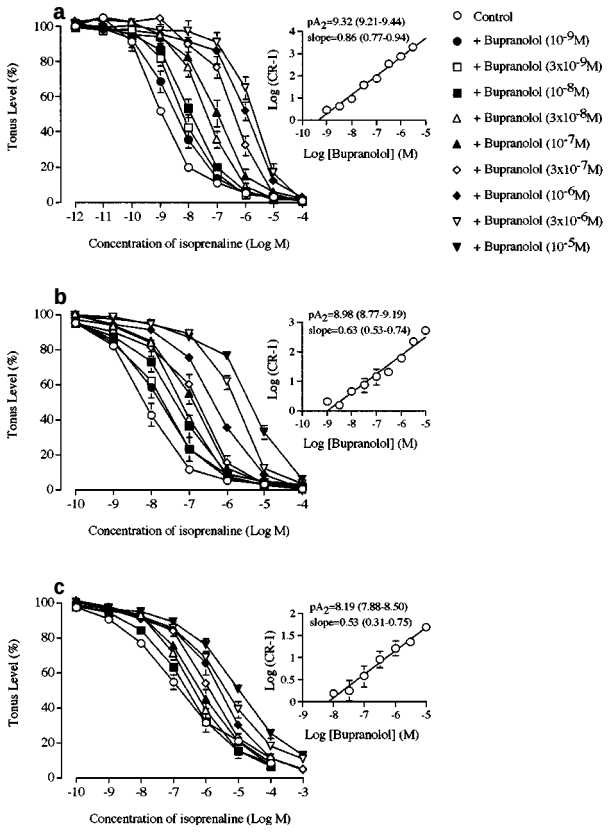

Figure 6 Effect of bupranolol on isoprenaline-induced relaxation in rabbit (a), rat (b) and canine (c) detrusor preparations. Each value is the mean of 6 experiments; vertical lines show s.e.mean. Inset: Schild plots of bupranolol against isoprenaline-induced relaxations. The slope of the regression line differed significantly from unity in rabbits, rats and dogs.

spontaneous rate of beating of the isolated atrium (β_1-AR-mediated response) at concentrations over 10^{-8} M, the pD_2 value being 7.0, and (ii) it produced an inhibition of spontaneous contractions in the pregnant uterus (β_2-AR-mediated response) and in the proximal colon (β_3-AR-mediated response), the pD_2 values being 6.6 and 6.7, respectively. It seems likely that the β_1-AR is of little functional importance in the relaxation of the rat detrusor, on the basis of the effects of dobutamine. As the β_1-AR selectivity of dobutamine is not great enough to enable us reliably to distinguish β_1-AR from the other β-ARs, we cannot exclude a contribution of β_1-AR to the relaxation of the rabbit or canine detrusor. The selective β_2-AR agonist, procaterol, also relaxed all the detrusors. In fact, procaterol was almost as potent as isoprenaline in both the rabbit and rat, but less potent in the dog. Since procaterol produced an apparent relaxation of the rabbit and rat detrusors at 10^{-7} M, a dose at which it does not exert any significant stimulating effect on β_1- or β_3-ARs (our preliminary experiments data on rat tissues), these results suggest a functional importance for the β_2-AR subtype in the detrusor of both species.

We next examined the relaxing effects of the selective β_3-AR agonists CGP-12177A (Kaumann, 1996) and CL316243 (Bloom *et al*., 1992) on the various detrusors. Although both compounds produced a relaxation in all three species, the functional importance of the β_3-AR in this response appears to differ significantly from species to species. The greatest apparent relaxation was observed in the canine detrusor, where CGP-12177A and CL316243 exhibited potencies comparable to and 10 times greater than isoprenaline, respectively. As both compounds are devoid of β_1-AR- and β_2-AR-stimulating effects even at 10^{-5} M (Kaumann, 1996; Bloom *et al*., 1992), the present results indicate a predominance of β_3-AR-mediated relaxation in the canine detrusor. In the rat detrusor, CL316243 produced a relaxation comparable to that induced by isoprenaline, but the maximal relaxation induced by CGP-12177A was only about 40% of that induced by isoprenaline. This result agrees well with findings that CGP-12177A is only a partial agonist for β_3-AR both in the rat proximal colon (Kaumann & Molenaar, 1996) and in rat and human adipocytes (Méjean *et al*., 1995). CGP-12177A and CL316243 also relaxed the rabbit detrusor, but the rank order of potency was CGP-12177A > CL316243, whereas it was CL316243 > CGP-12177A in the rat. CGP-12177A also behaved as a partial agonist in the rabbit detrusor. One possible explanation for the difference between the rabbit and rat detrusors in terms of the relative relaxing potencies of CGP-12177A and CL316243 is that there are constitutional differences between β_3-ARs, leading to species–specific differences in their affinity for a given β_3-agonist (Zaagsma & Nahorski, 1990; Blin *et al*., 1994). Another species difference was indicated by the finding that the β_3-agonist-induced relaxation of the rabbit detrusor was considerably less significant than that induced by the β_2-AR-agonist, procaterol, suggesting a greater functional importance

of β_2-AR than of β_3-AR in the rabbit detrusor. On the other hand, our results suggest that both β_2-AR and β_3-AR may play important roles in the relaxation of the rat detrusor, since procaterol and CL316243 produced almost equipotent relaxation in this species.

In an attempt to build on the findings obtained in the agonist experiment, we next examined which types of β-antagonists were effective in counteracting isoprenaline-induced relaxation in the various detrusors. CGP-20712A, a selective β_1-AR antagonist, had no significant effect on the concentration-response curve for isoprenaline in either the rabbit or rat. This result effectively excludes the possibility suggested by the β-AR agonist experiment that β_1-AR may play a functional role in the relaxation of the rabbit detrusor. In the dog detrusor, low concentrations of CGP-20712A (10^{-9} and 3×10^{-9} M) exerted an antagonistic effect on the isoprenaline-induced relaxation, but no further antagonism was observed when higher concentrations of the agent (over 10^{-8} M) were applied. On this basis, it seems unlikely that β_1-ARs play an important functional role in the relaxation of the canine detrusor. Unlike CGP-20712A, ICI-118,551, a selective β_2-AR antagonist, antagonized the isoprenaline-induced relaxation of the rabbit detrusor, with a high pA_2 value of 9.45. ICI-118,551 also produced a slight rightward shift of the concentration-response curve for the isoprenaline-induced relaxation of the rat detrusor, again with a relatively high pA_2 value (9.05). However, the slopes of 0.59 (rabbit) and 0.28 (rat) obtained from Schild plots were significantly different from unity, indicating a non-competitive form of antagonism. It has been recognized that the coexistence of two or more receptor subtypes, each of which can bind with both an agonist and an antagonist, results in a slope value in the Schild plot of less than 1.0 in competition experiments (Kenakin, 1987). Such a situation may well exist in the rabbit and rat detrusors, because the functional data from the present agonist experiment also suggested the coexistence of β_2- and β_3-ARs in the detrusors of these two species. However, the fact that a higher pA_2 value was obtained for ICI-118,551, is indicative of a functional predominance of β_2-AR in the rabbit detrusor. On the other hand, the isoprenaline-induced relaxation of the canine detrusor was not influenced by ICI-118,551, indicating the presence of a β-AR subtype other than the β_2-AR, presumably the β_3-AR.

Bupranolol, a non-selective β-AR antagonist, has been shown to exhibit β_3-AR antagonistic activity at higher concentrations, in addition to the β_1- and β_2-AR-antagonistic activities it shows at lower concentrations (Koike *et al*., 1995). The concentration-response curves for the isoprenaline-induced relaxation of the detrusor in rabbit and rats were antagonized by bupranolol with high pA_2 values of 9.32 and 8.98, respectively. However, the slopes calculated from the Schild plots were significantly lower than 1.0 in rabbit and rat detrusors (0.86 and 0.63, respectively), again suggesting the coexistence of β_2- and β_3-ARs, as concluded from the experiments with the β_2-AR-antagonist ICI-118,551. In the canine detrusor, bupranolol induced an apparent rightward shift of the concentration-response curve for the isoprenaline-induced relaxation only at higher concentrations (10^{-8} to 10^{-5} M), which is additional evidence for the predominant distribution of the β_3-AR in the canine detrusor. As the slope value for this agent (0.53) differed significantly from unity, a β-AR subtype other than the β_3-AR, possibly the β_1-AR, may coexist in the canine detrusor.

In conclusion, the present study has (a) confirmed that there are significant species differences in the distribution of the β-AR subtypes among mammalian bladder smooth muscle tissues, and (b) provided the first functional evidence for the presence of the β_3-AR in the rabbit, rat and canine detrusors, while indicating that the functional importance of this subtype varies significantly between species. The relaxation response to adrenergic stimulation of the urinary bladder, which physiologically is induced by endogenous noradrenaline, seems to be exerted via mainly β_2-ARs ($\beta_2>\beta_3$) in rabbits, via both β_2- and β_3-ARs ($\beta_2=\beta_3$) in rats, and via mainly β_3-ARs ($\beta_3>\beta_1$) in dogs. Identification of the subtype-specific mRNAs in those detrusors is needed to provide molecular biological confirmation of the present functional data.

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(Received November 6, 1997
Revised March 3, 1998
Accepted March 9, 1998)