Br. J. Pharmac. (1974), **50**, 525-529

DISTRIBUTION OF α- AND β-ADRENOCEPTORS IN HUMAN URINARY BLADDER

S.A. AWAD, A.W. BRUCE, G. CARRO-CIAMPI, J.W. DOWNIE & M. LIN
Department of Urology, Faculty of Medicine, Queen's University, Kingston, Ontario, Canada

G.S. MARKS
Department of Pharmacology, Faculty of Medicine, Queen's University, Kingston, Ontario, Canada

1 The distribution of α- and β-adrenoceptors in isolated preparations of human bladder neck and detrusor muscle has been studied.

2 Adrenaline caused contraction of the bladder neck which was blocked by phenoxybenzamine but unaltered by propranolol.

3 Isoprenaline caused relaxation of the bladder neck which was blocked by propranolol. High concentrations caused contraction which was enhanced by propranolol but blocked by phenoxybenzamine.

4 Detrusor muscle was relaxed by isoprenaline and this effect was blocked by propranolol. Phenylephrine caused relaxation of detrusor which was unaffected by phenoxybenzamine; in some cases contraction was produced in the presence of propranolol.

5 It is concluded that the bladder neck contains mainly α-receptors and the detrusor mainly β-receptors but both regions possess both types of adrenoceptor.

Introduction

Recently, Taira (1972) has reviewed some of the attempts to clarify the role of the sympathetic nervous system in the control of the bladder. The effect of stimulation of the hypogastric nerve or of sympathomimetic drugs has been examined in the intact bladder (e.g. Gjone, 1966; Boyarsky, Labay, Gregg & Levie, 1968; Edvardsen, 1968a, 1968b; Carpenter, 1970). In these preparations, however, the responses are the sum of effects on both detrusor and bladder neck. There is reason to believe that these two areas of the bladder might react differently.

Some evidence concerning the distribution of α- and β-adrenoceptors in urinary bladder has been obtained in single-dose studies on strips from urinary bladder of experimental animals (Edmunds & Roth, 1920; Young & Macht, 1923; Edvardsen & Setekleiv, 1968; Salimi, Setekleiv & Skobba, 1969; Malin & Boyarsky, 1970; Rohner, Raezer, Wein & Schoenberg, 1971; Nergardh & Boreus, 1972) and of man (Wesson, 1920; Young & Macht, 1923; Coupar & Turner, 1969; Todd & Mack, 1969; Nergardh & Boreus, 1972). Few studies, however, have compared detrusor and bladder neck in man (Young & Macht, 1923; Nergardh & Boreus, 1972). In general, it is evident that α-adrenoceptor responses predominate in bladder neck, while β-adrenoceptor responses predominate in the detrusor. Some authors have also found evidence for α-adrenoceptors in detrusor of cat, rabbit and guinea-pig (Edvardsen & Setekleiv, 1968; Salimi *et al.*, 1969); others, however, have detected β-adrenoceptors in the bladder neck, but found no evidence of α-adrenoceptors in the detrusor (Edmunds & Roth, 1920; Nergardh & Boreus, 1972). This confusion could be due in part to the difference in methodology employed by the various workers.

The purpose of this work was to compare the distribution of adrenoceptors in the detrusor and bladder neck of man. We felt that such comparisons would be more meaningful if complete dose-response curves were studied.

Methods

Specimens from human bladder were usually obtained during retropubic prostatectomy. Detrusor samples were obtained from the anterior wall of the bladder without disturbing the mucosa. Other samples were obtained from the anterior part of the bladder neck. The surgery was performed under various general anaesthetics and the

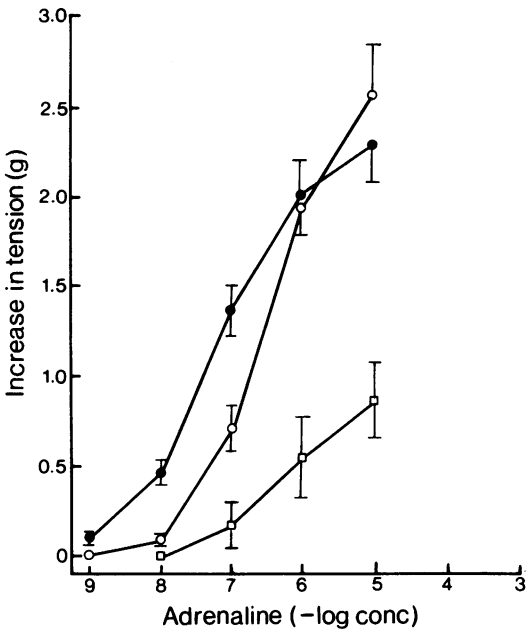

Fig. 1 Adrenaline increased the muscle tone of strips from human bladder neck (•; 10 strips). This response was not altered appreciably by propranolol (10 μg/ml) (○; five strips), but was reduced in the presence of phenoxybenzamine (10 ng/ml) (□; five strips). Vertical bars represent the standard errors of the means.

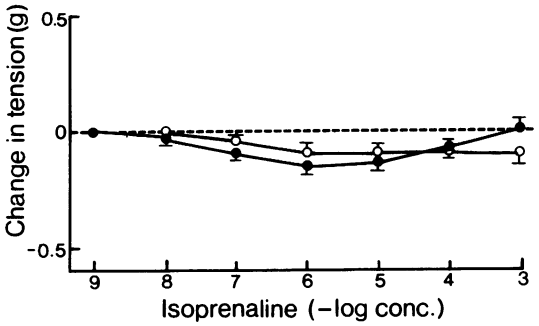

Fig. 2 Isoprenaline reduced the muscle tone of strips from human bladder neck (•; 17 strips). In the presence of phenoxybenzamine (10 ng/ml) (○; six strips) there was no reduction in maximum at high doses. Vertical bars represent standard errors of the means.

patients had received several drugs prior to surgery. The bladders of patients undergoing prostatectomy often exhibited considerable muscular hypertrophy. The samples were placed in ice-cold modified Krebs solution for transport to the laboratory, and were further dissected within 30 minutes. Wherever possible, two strips of approximately 10 mm long and 4 mm wide (unstretched) were cut from each biopsy specimen.

Tissues were suspended under 1 g tension in a 20 ml organ bath containing a modified Krebs solution of the following composition (mM): NaCl 116, KCl 4.6, $MgSO_4$ 1, NaH_2PO_4 1, $CaCl_2$ 2.4, $NaHCO_3$ 21, glucose 45. The bathing fluid was bubbled with 95% oxygen and 5% carbon dioxide. The temperature was maintained at 37°C. The tissues were allowed to equilibrate for 2 h, during which the bathing solution was changed several times.

Measurements of isometric tension were made by means of Grass FTO3C force-displacement transducers and a Grass Model 7PCPB polygraph.

Freshly prepared solutions of the following drugs were used: (−)-adrenaline bitartrate, (−)-noradrenaline bitartrate, (−)-phenylephrine hydrochloride, (±)-isoprenaline hydrochloride (Winthrop Laboratories), acetylcholine chloride (Welcker-Lyster Ltd), phenoxybenzamine hydrochloride (Smith, Kline and French, Canada Ltd), propranolol hydrochloride (Ayerst Laboratories) and sotalol (Mead Johnson and Co.). Concentrations are expressed as g/ml of free base in the bath. Antagonists were added to the bath 20 min before the agonist and were not washed out. Responses in cumulative dose-response curves are expressed as change in resting tension, in grams.

Results

Muscle strips cut from detrusor showed spontaneous contractions usually of greater amplitude and frequency than strips cut from bladder neck.

Tissue responsiveness

Nineteen strips out of 42 (45%) from human bladder neck and 26 strips out of 45 (58%) from human detrusor were unresponsive to sympathomimetic drugs. Even the long period of equilibration may not have been sufficient to allow the muscle to recover from surgical trauma and the effects of the various drugs used prior to and during surgery. Infection, which was evident in some samples, might have influenced tissue reactivity.

Responses to sympathomimetic amines in strips from human bladder neck

In strips from bladder neck, noradrenaline, phenylephrine (not shown) and adrenaline (Fig. 1) produced contractions which could be antagonized by

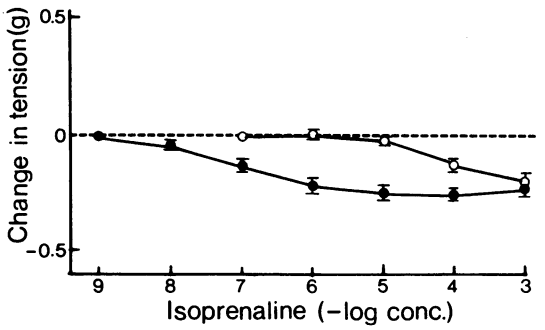

Fig. 3 Isoprenaline reduced the muscle tone of strips from human detrusor (•; 22 strips). In the presence of propranolol (10 μg/ml) (○; nine strips) the dose-response curve for isoprenaline was shifted to the right. Vertical bars represent standard errors of the means.

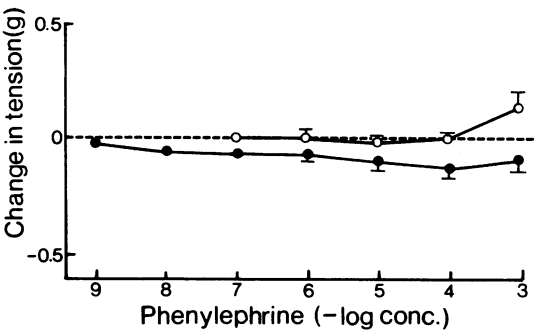

Fig. 4 Phenylephrine reduced the muscle tone of strips from human detrusor (•; 11 strips). This response was abolished by propranolol (10 μg/ml) (○; five strips). Vertical bars represent standard errors of the means.

phenoxybenzamine (10 ng/ml). No reversal of the adrenaline-induced response was seen in the bladder neck in the presence of this concentration of phenoxybenzamine. In preliminary experiments, phenoxybenzamine up to 1 μg/ml failed to reverse the adrenaline response. Although propranolol (10 μg/ml) appeared to alter the rising portion of the dose-response curve of both phenylephrine and adrenaline, there was no significant difference in the maximum contraction reached before and after propranolol (Figure 1).

Isoprenaline caused relaxation which reached a maximum at about 1 μg/ml (Figure 2). An increase in the concentration of isoprenaline caused a reduction in this maximum in 13 out of 17 strips. Five strips eventually showed a contraction at a high concentration (100 μg/ml). This behaviour is reflected in the average curve (Fig. 2) by the return toward control resting tension at doses greater than 10 μg/ml. After phenoxybenzamine (10 ng/ml), the maximum relaxation was maintained even at higher doses of isoprenaline (Fig. 2), suggesting that the reduction in maximum seen in unblocked strips was α-adrenoceptor-mediated. Although the maximum relaxation reached in the presence of phenoxybenzamine appeared to be slightly lower than that for the control, the difference is not statistically significant. After propranolol (10 μg/ml), isoprenaline produced less relaxation and contractile responses were evident at much lower concentrations (four strips out of six contracted at 1 μg/ml).

Responses to sympathomimetic amines in strips from human detrusor

Isoprenaline produced a relaxation in strips from detrusor (Figure 3). After propranolol (10 μg/ml), the dose-response curve of isoprenaline was shifted to the right (Figure 3). After phenoxybenzamine (10 ng/ml), detrusor strips showed a reduced maximum in response to isoprenaline similar to that seen in blader neck.

In strips from detrusor, both phenylephrine (Fig. 4) and adrenaline (not shown) caused relaxation which was unaffected by phenoxybenzamine (10 ng/ml) (not shown). Propranolol (10 μg/ml) caused a shift to the right in the dose-response curve of adrenaline. The response to phenylephrine in the presence of propranolol (10 μg/ml) was variable. In one strip, the dose-response curve was shifted to the right. In another strip, the initial relaxation (at 10 μg/ml) was followed by a contraction (at 1 mg/ml). In the remaining three strips, the response to phenylephrine was contraction only. The average curve obtained from these data (Fig. 4) shows only the contraction at very high doses.

Discussion

Atypical sympathomimetic drug actions

Isoprenaline exhibited significant action on α-adrenoceptors in human bladder neck. Other workers have reported a weak stimulating action of isoprenaline on α-adrenoceptors in the smooth muscle of the guinea-pig genitourinary tract (Large, 1965; Spedding & Weetman, 1972).

Phenylephrine produced relaxation in detrusor strips from man. The dose-response curve was unaffected by phenoxybenzamine (10 ng/ml) and reversed to contraction by propranolol (10 μg/ml). Our results thus suggest a significant β-agonist activity for phenylephrine. A similar β-agonist

activity for phenylephrine has been demonstrated in guinea-pig trachea (Chahl & O'Donnell, 1969).

Human bladder

The contractile response seen in human bladder neck was evidently mediated by α-adrenoceptors, since it was antagonized by phenoxybenzamine. However, it was not completely resistant to propranolol. In preliminary experiments in rabbit bladder neck and detrusor (unpublished observations), propranolol was found to reduce contractions produced by acetylcholine, though sotalol (MJ 1999), which is reported to have little (Davis, 1970) or no (Raper & Wale, 1968) direct cardiac depressant activity, did not alter the acetylcholine response. We therefore have attributed the depressant effects of propranolol on α-adrenoceptor agonists in this study to direct, non-specific effects on smooth muscle. The predominance of α-adrenoceptor-mediated contraction in human bladder neck has been reported previously (Nergardh & Boreus, 1972).

The presence of β-adrenoceptors in human bladder neck is confirmed by the finding of a direct isoprenaline-induced relaxation which was antagonized by propranolol but not significantly altered by phenoxybenzamine. Nergardh & Boreus (1972) reached the same conclusion from their observation that isoprenaline antagonized an acetylcholine-induced contraction in strips from human bladder neck. Relaxation in response to adrenaline in human bladder neck was not reported by Wesson (1920) or by Young & Macht (1923). In contrast to our observations in rabbit (unpublished), it was not possible to demonstrate in human bladder neck the reversal of adrenaline-induced responses with phenoxybenzamine, even at doses up to 1 μg/ml.

The predominant effect observed in human detrusor was relaxation. In the presence of propranolol, the dose-response curves of adrenaline and isoprenaline were shifted to the right. These findings confirm that the relaxation was mediated by β-adrenoceptors. The prevalence of β-adrenoceptor-mediated relaxation in human detrusor has been reported previously (Nergardh & Boreus, 1972).

The presence of α-adrenoceptors in human detrusor is suggested by the reversal of the phenylephrine response in the presence of propranolol. Nergardh & Boreus (1972) found no evidence of α-adrenoceptors in human detrusor, but Todd & Mack (1968) showed contraction in human detrusor with a single dose (10 μg/ml) of phenylephrine and Coupar & Turner (1969) reported potency ratios in the presence of propranolol (0.5 μg/ml) for various α-adrenoceptor agonists in a single strip of human detrusor.

In this study we were able to verify that the bladder of man shows a predominance of α-adrenoceptors in the bladder neck and β-adrenoceptors in the detrusor. It was possible also to demonstrate the presence of α-adrenoceptors in the detrusor and β-adrenoceptors in the bladder neck.

This investigation was supported by a grant from the Medical Research Council of Canada. Gifts of phenylephrine (Winthrop Laboratories), phenoxybenzamine (Smith, Kline and French, Canada Limited), propranolol (Ayerst Laboratories) and sotalol (Mead Johnson and Co.) are gratefully acknowledged.

References

BOYARSKY, S., LABAY, P., GREGG, R. & LEVIE, B. (1968). Pharmacologic studies of the nature of the sympathetic nerves of the urinary bladder. *Paraplegia*, **6**, 136-150.

CARPENTER, F.G. (1970). Antagonism of smooth muscle contractility by catecholamines. *Am. J. Physiol.*, **219**, 1539-1543.

CHAHL, L.A. & O'DONNELL, S.R. (1969). Actions of phenylephrine on β-adrenoceptors in guinea-pig trachea. *Br. J. Pharmac.*, **37**, 41-51.

COUPAR, I.M. & TURNER, P. (1969). Relative potencies of sympathetic amines in human smooth muscle. *Br. J. Pharmac.*, **36**, 213P-214P.

DAVIS, W.G. (1970). A comparison of the local anaesthetic-, 'quinidine-like'- and adrenergic β-blocking-activities of five β-receptor antagonists. *J. Pharm. Pharmac.*, **22**, 284-290.

EDMUNDS, C.W. & ROTH, G.B. (1920). The point of attack of certain drugs acting on the periphery. I. Action on the bladder. *J. Pharmac. exp. Ther.*, **15**, 189-199.

EDVARDSEN, P. (1968a). Nervous control of urinary bladder in cats. I. The collecting phase. *Acta physiol. scand.*, **72**, 157-171.

EDVARDSEN, P. (1968b). Nervous control of urinary bladder in cats. II. The expulsion phase. *Acta physiol. scand.*, **72**, 172-182.

EDVARDSEN, P. & SETEKLEIV, J. (1968). Distribution of adrenergic receptors in the urinary bladder of cats, rabbits and guinea-pigs. *Acta pharmac. tox.*, **26**, 437-445.

GJONE, R. (1966). Peripheral autonomic influence on the motility of the urinary bladder in the cat. II. 'Tone'. *Acta physiol. scand.*, **66**, 72-80.

LARGE, B.J. (1965). Sympathetic β-receptors and the guinea-pig vas deferens. *Br. J. Pharmac. Chemother.*, **24**, 194-204.

MALIN, J.M. Jr. & BOYARSKY, S. (1970). The effects

of cholinergic and adrenergic drug stimulation of detrusor muscle. *Invest. Urol.*, 8, 286-291.

NERGARDH, A. & BOREUS, L.O. (1972). Autonomic receptor function in the lower urinary tract of man and cat. *Scand. J. Urol Nephrol.*, 6, 32-36.

RAPER, C. & WALE, J. (1968). Propranolol MJ 1999 and CIBA 39089 Ba in ouabain and adrenaline induced cardiac arrhythmias. *Eur. J. Pharmac.*, 4, 1-12.

ROHNER, T.J., RAEZER, D.M., WEIN, A.J. & SCHOENBERG, H.W. (1971). Contractile responses of dog bladder neck muscle to adrenergic drugs. *J. Urol.*, 105, 657-661.

SALIMI, M., SETEKLEIV, J. & SKOBBA, T.J. (1969). The sensitivity of adrenergic excitatory and inhibitory receptors in the smooth muscle of rabbit urinary bladder. *Acta pharmac. tox.*, 27, 213-224.

SPEDDING, M. & WEETMAN, D.F. (1972). The presence of β-adrenoceptors in the guinea-pig seminal vesicle. *Br. J. Pharmac.*, 45, 21-28.

TAIRA, N. (1972). The autonomic pharmacology of the bladder. *Ann. Rev. Pharmac.*, 12, 197-208.

TODD, J.K. & MACK, A.J. (1969). A study of human bladder detrusor muscle. *Br. J. Urol.*, 41, 448-454.

WESSON, M.B. (1920). Anatomical, embryological and physiological studies of the trigone and neck of the bladder. *J. Urol.*, 4, 279-307.

YOUNG, H.H. & MACHT, D.I. (1923). A contribution to the physiology and pharmacology of the trigonum vesicae. *J. Pharmac. exp. Ther.*, 22, 329-354.

(Received September 18, 1973)