ELSEVIER

European Journal of Pharmacology 294 (1995) 645–650

ejp

A comparison of the effects of doxazosin and terazosin on the spontaneous sympathetic drive to the bladder and related organs in anaesthetized cats

Andrew G. Ramage [a,*], Michael G. Wyllie [b]

[a] *Academic Department of Pharmacology, Royal Free Hospital School of Medicine, Rowland Hill Street, Hampstead, London, NW3 2PF, UK*
[b] *Discovery Biology, Pfizer Central Research, Sandwich, Kent, CT13 9NJ UK*

Received 29 May 1995; revised 13 September 1995; accepted 22 September 1995

Abstract

The effects of i.v. infusion of the α_1-adrenoceptor antagonists doxazosin and terazosin (2 mg kg^{-1} h^{-1}) on spontaneous hypogastric, renal and inferior cardiac nerve activity, spontaneous bladder contractions, blood pressure, heart rate and femoral arterial flow were investigated separately in α-chloralose-anaesthetized cats. Both drugs caused a reduction in hypogastric nerve activity associated with no overt changes in spontaneous bladder contractions. Doxazosin was more potent than terazosin, in that there was a significant reduction in hypogastric nerve activity after 20 min (0.67 mg kg^{-1}) of infusion, while for terazosin this occurred after 40 min (1.33 mg kg^{-1}). Both drugs also caused significant falls in blood pressure of 34 ± 3 mm Hg and 33 ± 4 mm Hg after 60 min. This was associated with no change in heart rate for doxazosin while terazosin caused an initial and significant increase in heart rate of 20 ± 3 beats min^{-1} by 5 min, declining by 30 min to 1 ± 5 beats min^{-1}. This terazosin-induced tachycardia was associated with a significant increase in cardiac nerve activity of $128 \pm 22\%$. Both drugs caused increases in renal nerve activity however only for doxazosin was this increase significant. Femoral arterial conductance was also increased by both drugs, however, for doxazosin this increase was immediate and larger over the infusion period. These results demonstrate that α_1-adrenoceptor antagonists can reduce sympathetic drive to the bladder and related organs.

Keywords: α_1-Adrenoceptor antagonist; Doxazosin; Terazosin; Sympathetic nerve activity; Bladder; (Anesthetized cat)

1. Introduction

Benign prostatic hyperplasia is a hormone-dependent, non-cancerous enlargement of the prostate gland. The disease process leading to the development of symptoms has three components: histological prostatic hyperplasia, an increase in urethal outflow resistance and an adaptive response of the bladder (detrusor) muscle to the obstruction. Symptomatic benign prostatic hyperplasia is usually associated with obstructive symptoms related to prostatic mass-induced changes in urethral resistance and irritative symptoms to the associated bladder hypertrophy. A number of functional studies indicate that the α_1-adrenoceptors (Hieble et al., 1985; Chapple et al., 1989) are involved in the control of urethral resistance (peri-urethral stromal tone) and in this respect drugs which block α_1-adrenoceptors have been shown to improve urinary flow rates (Caine et al., 1976; Lepor et al., 1991; Christensen et al., 1993) in patients with benign prostatic hyperplasia. This has been suggested to be also due to a reduction in tone to the prostatic capsule and bladder base as well as proximal urethal smooth muscle which would overcome the effects of mechanical compression of the urethra by an enlarged prostate. An additional possibility is that these drugs also interfere with central sympathetic drive to these organs and in this respect changes in sympathetic drive to bladder have been implicated in urinary storage as well as facilitation of voiding (see De Groat et al., 1993); during micturition this reflex pathway is inhibited (De Groat and Lalley, 1972). It is therefore possible that mechanical compression of the urethra activates afferents which increase sympathetic tone to the bladder and thereby contribute to bladder instability. It has been demonstrated that α_1-adreno-

* Corresponding author. Tel.: 00 44 171 794 0500 ext. 4323; fax: 00 44 171 794 6854.

SSDI 0014-2999(95)00599-4

ceptor antagonists can cause a reduction in central sympathetic tone involved in cardiovascular regulation (McCall and Humphrey, 1981; Persson et al., 1981; Ramage, 1984a; McCall and Schutte, 1984; Ramage, 1986a, b) by a central mechanism. Further central sudo-motor sympathetic tone (Rybarczyk and Walland, 1985; Ito et al., 1988), a non-baroreceptor-modulated sympathetic pathway, is also attenuated by a central action of α_1-adrenoceptor antagonists. It is therefore possible that these drugs are also having their effect by reducing central sympathetic tone to the bladder. Thus the purpose of the present study was to determine if central sympathetic drive to the bladder, hypogastric nerve activity (this nerve supplies the sympathetic innervation to the bladder and associated structures, see De Groat et al., 1993) is reduced by the α_1-adrenoceptor antagonists, doxazosin and terazosin. In addition, sympathetic outflow to the heart (inferior cardiac nerve activity) and to the kidneys (renal nerve activity) were recorded for comparison along with blood pressure, heart rate, femoral arterial flow and bladder pressure. A preliminary report of some of these observations has been made (Ramage and Wyllie, 1994).

2. Materials and methods

Experiments were performed on 15 male adult cats (2.5–3.5 kg) anaesthetized with a mixture of α-chloralose (70 mg kg^{-1}) and pentobarbitone sodium (6 mg kg^{-1}) i.v.; supplementary doses of α-chloralose (10–15 mg kg^{-1}) were given as assessed by the cardiovascular responses to paw pinch and the state of the pupil. Following a tracheotomy low in the neck, the animals were intubated and artificially ventilated (rate 30 per min, tidal volume 17–20 ml) with oxygen-enriched room air using a positive pressure ventilator (Harvard 665A) after neuromuscular blockade with vecuronium bromide (200 μg kg^{-1}). Arterial blood pressure, heart rate, right femoral arterial flow (from which conductance was calculated) were also recorded as previously described (Ramage, 1984a). A constant infusion of a solution comprising 500 ml H_2O, 500 ml Gelofusine, 8.4 g $NaHCO_3$ and 2 g of glucose was given at a rate of 6 ml kg^{-1} h^{-1} into the brachial vein to maintain blood volume and counteract the development of non-respiratory acidosis. Arterial blood gases and pH were kept within the following ranges, P_{CO2} 41–48 mm Hg; P_{O2} 112–130 mm Hg and pH 7.24–7.35, by varying the rate and tidal volume of the ventilator or by a slow infusion, i.v., of $NaHCO_3$ (1 M) during the experiment.

Simultaneous recordings were made of left inferior cardiac, renal and hypogastric nerve activities. The left inferior cardiac nerve was exposed by deflecting the scapula and removing the second rib retropleurally. The renal and hypogastric nerves were exposed by a retroperitoneal approach through the left flank. The left hypogastric nerve was identified as the major branch leaving the inferior mesenteric ganglia. Whole nerve activity was recorded from the nerves using bipolar silver hook electrodes as previously described (Ramage and Wilkinson, 1989). In all experiments sympathetic nerve activity was tested to see if it was under baroreceptor modulation by checking that activity in the nerves decreased during a rise in blood pressure induced by noradrenaline (0.25 μg per animal, i.v.). Spontaneous activity in the cardiac and renal nerves was found to be consistently inhibited by the increase in blood pressure evoked by i.v. noradrenaline while spontaneous nerve activity in the hypogastric nerve was hardly effected. Changes in bladder smooth muscle tension were assessed by measuring changes in the pressure of a fluid-filled (15 ml) balloon placed inside the bladder and connected to a pressure transducer. The bladder was also cannulated to allow the free flow of urine. In all experiments an initial infusion of vehicle (0.04 M lactic acid) was carried out 20 min before infusion of the test solution. The test solutions were vehicle alone, doxazosin or terazosin. These solutions were infused over 1 h. The volume of the infusion was the same for each test solution; 3 ml.

2.1. Analysis of data

Baseline values from which changes were measured were taken just prior to beginning the test infusion. All sympathetic nerve activities were quantified by rectifying and integrating the signals above background noise over 10 s periods using solid state electronic integrators. The outputs were then displayed on a Grass polygraph recorder and were calibrated in arbitrary units. The validity of the threshold settings used to quantify the nerve activities was verified at the end of each experiment after administration of pentobarbitone sodium (60 mg per animal) or by crushing the nerves centrally to block all activity. All nerve activity is reported as the mean level over 1 min in arbitrary units. All results are expressed as changes from baseline values. In order to normalise the data, changes in integrated nerve activity are given as percentage changes from baseline. The changes in all other variables are presented as actual changes. Changes (means $\pm$ S.E.) in variables evoked by either doxazosin or terazosin were compared with the changes caused by the vehicle infusion by two way analysis of variance and the least significant difference test for comparisons between the means (Sokal and Rohlf, 1969). Differences were considered significant when $P < 0.05$. As no obvious changes in bladder contractions were observed these data were not further analysed.

2.2. Drugs and solutions

The following drugs were used: α-chloralose (Sigma Chemical Co., Poole, Dorset, UK); Gelofusine (Con-

solidated Chem., Wrexham, Clwyd, UK); pentobarbitone sodium (May and Baker, UK); vecuronium bromide (Organon Teknika, Cambridge, UK); doxazosin meyslate and terazosin HCl (supplied by Pfizer Central Research. UK). All drugs were dissolved in 0.9% w/v saline except doxazosin and terazosin which were dissolved in 0.04 M lactic acid and infused at a rate of 2 mg kg^{-1} h^{-1} (3 ml h^{-1}). All doses refer to the salts of the compounds.

3. Results

3.1. Baseline values

The mean baseline values for vehicle, doxazosin and terazosin for mean arterial blood pressure were 124 ± 12, 139 ± 7 and 131 ± 6 mm Hg, for heart rate 238 ± 5, 197 ± 11 and 212 ± 6 beats min^{-1} and for femoral arterial conductance 51 ± 12, 69 ± 7 and 52 ± 5 ml min^{-1} mm $Hg^{-1} \times 10^{-3}$ respectively.

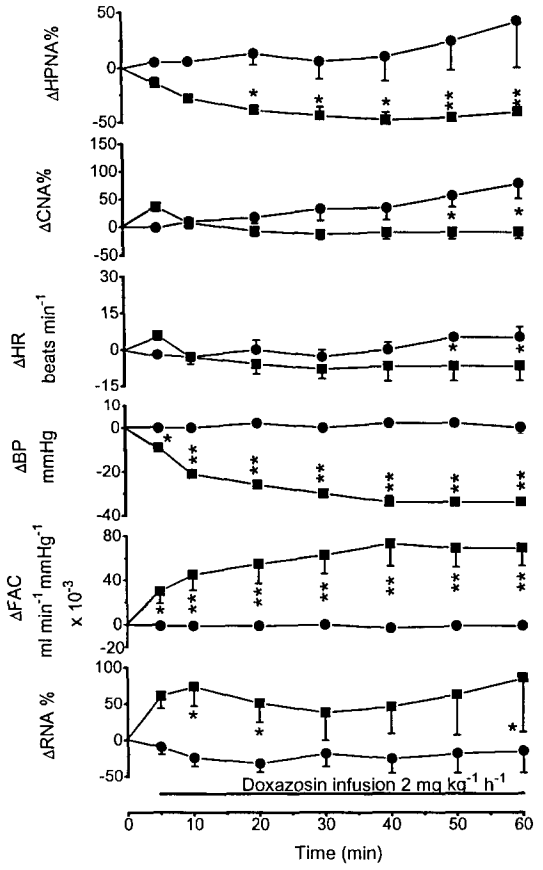

Fig. 1. Anaesthetized cats: comparison of the effects of infusions (dotted line) of doxazosin (■) 2 mg kg^{-1} h^{-1} with those of vehicle (0.04 M lactic acid; 3 ml h^{-1}; ●) on changes (Δ) in hypogastric nerve activity (HPNA; %), cardiac nerve activity (CNA; %), heart rate (HR; beats min^{-1}), mean blood pressure (BP; mm Hg), femoral arterial conductance (FAC; ml min^{-1} mm Hg^{-1} x 10^{-3}) and renal nerve activity (RNA; %). Each point represents the mean value ($n = 5$) with S.E. Comparison of changes caused by doxazosin with those produced by vehicle were made by two way analysis of variance and the least significant difference test to compare the means; * $P < 0.05$; ** $P < 0.01$.

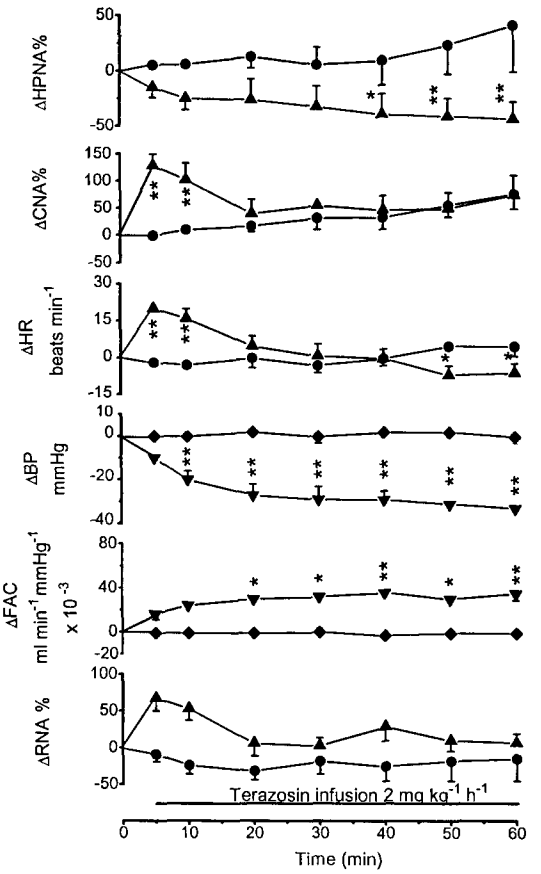

Fig. 2. Anaesthetized cats: comparison of the effects of infusions (dotted line) of terazosin (▲) 2 mg kg^{-1} h^{-1} with those of vehicle (0.04 M lactic acid; 3 ml h^{-1}; ●) on changes (Δ) in hypogastric nerve activity (HPNA; %), cardiac nerve activity (CNA; %), heart rate (HR; beats min^{-1}), mean blood pressure (BP; mm Hg), femoral arterial conductance (FAC; ml min^{-1} mm Hg^{-1} x 10^{-3}) and renal nerve activity (RNA; %). Each point represents the mean value ($n = 5$) with S.E. Comparisons of changes caused by terazosin with those produced by vehicle were made by two way analysis of variance and the least significant difference test to compare the means; * $P < 0.05$; ** $P < 0.01$.

3.2. Infusion of vehicle 0.04 M lactic acid over 1 h

Vehicle infusion (3 ml h^{-1}; $n = 5$) had very little effect on blood pressure, heart rate and femoral arterial conductance. Cardiac nerve activity tended to increase over the period of infusion reaching 77 ± 27% while renal nerve activity tended to decrease reaching −15 ± 30% after 60 min. Changes in hypogastric nerve activity were very variable, however overall nerve activity tended to increase reaching 42 ± 42% by 60 min (Fig. 1).

3.3. Infusion of doxazosin and terazosin over 1 h

Both doxazosin ($n = 5$) and terazosin ($n = 5$) infusion (2 mg kg^{-1} h^{-1}) caused a slow reduction in

hypogastric nerve activity which was significantly different from vehicle after 20 min ($-39 \pm 5\%$) for doxazosin and after 40 min ($-39 \pm 19\%$) for terazosin (Figs. 1 and 2). Doxazosin had little effect on cardiac nerve activity only causing small but significant sympathoinhibition after 50 min of $-10 \pm 12\%$ compared with vehicle. This was associated with a small but significant bradycardia of 7 ± 6 beats min^{-1} compared with vehicle. However, terazosin caused, after 5 min, a significant increase in cardiac nerve activity and heart rate of $128 \pm 22\%$ and 20 ± 3 beats min^{-1}, respectively, both changes declining by 20 min to non-significant levels and by 50 min terazosin had caused a significant fall in heart rate of 7 ± 4 beats min^{-1} compared with vehicle. Both drugs tended to increase renal nerve activity. These increases were only significantly different from vehicle for doxazosin at 10, 20 and 60 min of infusion (Fig. 1).

Both doxazosin and terazosin infusion (Figs. 1 and 2) also caused a significant fall in blood pressure after 5 min of 9 ± 2 and 10 ± 2 mm Hg respectively but only for doxazosin was this associated with a significant increase in femoral arterial conductance of 30 ± 11 ml min^{-1} mm $Hg^{-1} \times 10^{-3}$ when compared with the vehicle infusion (Fig. 1). However, by 20 min terazosin had also caused a significant increase in femoral arterial conductance reaching a maximum after 40 min of 36 ± 4 ml min^{-1} mm $Hg^{-1} \times 10^{-3}$ as did doxazosin, 73 ± 20 ml min^{-1} mm $Hg^{-1} \times 10^{-3}$. From 30 min until the end of the infusions the changes in femoral arterial conductance caused by doxazosin were significantly greater than those caused by terazosin (data not illustrated). Doxazosin also caused a maximum fall in blood pressure after 40 min of 34 ± 3 mm Hg while terazosin caused a similar fall in blood pressure by the end of the infusion of 33 ± 4 mm Hg.

Neither drug caused any obvious effect on spontaneous changes in bladder balloon pressure or resting tone. A trace showing the effect of doxazosin infusion on all variables that were recorded is shown in Fig. 3.

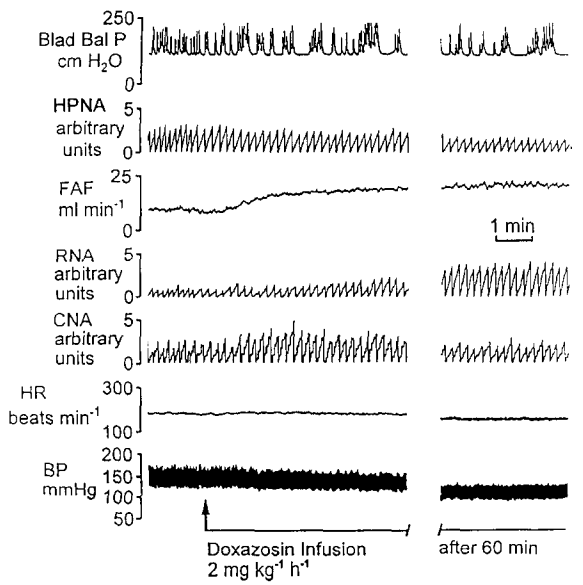

Fig. 3. Traces showing recordings of bladder balloon pressure (Blad Bal P), integrated hyogastric nerve activity (HPNA), femoral arterial flow (FAF), integrated renal (RNA), cardiac (CNA) nerve activities and blood pressure (BP) in the anaesthetized cat. The first panel shows the effect of the beginning at the doxazosin infusion while the second panel shows the effect of 60 min of this infusion on these recordings.

4. Discussion

Intravenous infusions of the α_1-adrenoceptor antagonists doxazosin and terazosin into anaesthetized neuromuscular blocked cats caused a reduction in sympathetic nerve activity i.e., hypogastric nerve activity to the bladder and related tissues. Doxazosin was found to have a more potent sympathoinhibitory action on hypogastric nerve activity than terazosin, in that there was a significant reduction in hypogastric nerve activity after 20 min (0.67 mg kg^{-1}) of infusion while for terazosin this occurred after 40 min (1.33 mg kg^{-1}). The contribution of this indirect action to the overall clinical profile of α_1-adrenoceptor antagonists on bladder function has yet to be established, although the present data suggest that resting bladder tone is unaffected by these drugs. However, this sympathoinhibitory action, additional to a direct action on stromal smooth muscle, would be entirely consistent with the overall clinical profile of doxazosin; which has been shown to have a greater effect on irritative symptoms than could be expected from a drug acting exclusively on the prostate (Chapple et al., 1994).

Doxazosin and terazosin had no apparent sympathoinhibitory action on cardiac or renal nerve activity, except for the small sympathoinhibitory effect near the end of the doxazosin infusion. However both drugs caused significant falls in blood pressure and since these sympathetic outflows are under baroreceptor modulation (i.e. activity was inhibited in these nerves, but not in the hypogastric nerve, by the rise in blood pressure induced by i.v. noradrenaline) a baroreceptor-mediated reflex rise in nerve activity should be observed in both these nerves. Indeed, terazosin did initially cause increases in cardiac nerve activity and heart rate. However, no significant increases in cardiac nerve activity or heart rate were observed for doxazosin. Further, these initial increases caused by terazosin returned to near baseline values after 20 min of infusion although the fall in blood pressure remained fairly constant. It is possible that the effects of terazosin are due to baroreceptor unloading but, as a

maintained fall in blood pressure caused by a peripheral acting vasodilator, such as nitroprusside, over this period causes maintained sympathoexcitation in sympathetic nerve activity under baroreceptor modulation (Ramage, 1984b), this is unlikely. Therefore a certain level of sympathoinhibition must have occurred in the cardiac nerve as the fall in blood pressure failed to cause any sympathoexcitation in the case of doxazosin and failed to cause maintained sympathoexcitation in the case of terazosin. However, neither drug inhibited renal nerve activity. In fact, doxazosin caused significant increases at various time points during the infusion. A similar observation in anaesthetized dogs led Laubie and Schmitt (1988) to conclude, at least in this species, that there is no evidence for a central action of α_1-adrenoceptor antagonists, although previous data in dogs had shown that prazosin caused a fall in blood pressure without causing a reflex tachycardia (Massingham and Hayden, 1975). This latter observation would support a central action for α_1-adrenoceptor antagonists in the dog, at least at the level of cardiac sympathetic outflow. Another interpretation of these data on renal sympathetic nerve activity is that renal sympathetic outflow can be modulated by other physiological factors which can override the central sympathoinhibitory effect of α_1-adrenoceptor antagonists, such as autoregulatory mechanisms involved in the control of renal blood flow. These mechanisms would try to compensate for the vasodilator action of doxazosin and terazosin; the present data on femoral arterial conductance suggest that this is greater for doxazosin. This latter explanation would also explain why the effects of doxazosin on renal nerve activity were more variable and at various time points caused a significant increase in renal nerve activity compared with vehicle, whereas terazosin only tended to cause an initial non-significant increase in renal nerve activity. Overall the present observations are consistent with the view that α_1-adrenoceptor antagonists have a central sympathoinhibitory action (see Introduction). Further the initial sympathoexcitation in the cardiac nerve observed with terazosin and the delayed sympathoinhibitory effect on hypogastric nerve activity, may reflect a difference in CNS penetration between these drugs as both drugs have similar α_1-adrenoceptor potency and selectivity (Kenny et al., 1994).

A possible site at which doxazosin and terazosin are having this sympathoinhibitory action is the intermediolateral nucleus in which the preganglionic sympathetic motoneurones are located. These neurones are densely innervated by catecholamine-containing nerve terminals originating from neurones in the C1, C2 and C3 group and the A5,A6 and A7 cell groups (see Dampney, 1994). Further, ionophoretic studies, in vivo (Marks et al., 1990) and in vitro (Yoshimura et al., 1987), microinjection (Sundaram et al., 1991; Marks and Gilbey, 1992) and intrathecal studies (Gradin et al., 1992) have shown that preganglionic sympathetic motoneurones can be excited by activation of α_1-adrenoceptors. However, it is possible that doxazosin and terazosin are also acting at other sites within the CNS, such as nucleus tractus solitarii where activation of α_1-adrenoceptors can cause sympathoexcitation (Kubo et al., 1987) and/or by inhibiting the α_1-adrenoceptor-mediated excitatory drive to the dorsal raphe (Menkes et al., 1981) which, when stimulated evokes a pressor response (Kuhn et al., 1990).

In conclusion the present data demonstrate that the α_1-adrenoceptor antagonists, doxazosin and terazosin, can reduce the sympathetic nerve activity to the bladder and related organs which may contribute to their ability to improve urinary flow rates in patients with benign prostatic hyperplasia. The present data also suggest that doxazosin would cause fewer untoward cardiovascular effects than terazosin.

Acknowledgements

We wish to thank Mr. S. Wilkinson for technical support.

References

Caine, M., A. Pfau and S. Perlberg, 1976, The use of alpha-adrenergic blockers in benign prostatic obstruction, Br. J. Urol. 48, 255.

Chapple, C.R., M.L. Aubrey, S. James, P.M. Greengrass, G. Burnstock, R.T. Turner-Warwick, E.J. Milroy and M.J. Davey, 1989, Characterisation of human prostatic adrenoceptors using pharmacology, receptor binding and localization, Br. J. Urol. 63, 487.

Chapple, C.R., P. Carter, T.J. Christmas, R.S. Kirby, J. Bryan, E.J.G. Milroy and P. Abrams, 1994, A three-month double-blind study of doxazosin as a treatment for benign prostatic bladder outlet obstruction, Br. J. Urol. 74, 50.

Christensen, M.M., J. Bendix-Holmes, P.C. Rasmussen, F. Jacobsen, J. Neilswen, J.P Norgaard, S. Olesen, I. Noer, H. Wolfe and S.E. Husted, 1993, Doxazosin treatment in patients with prostatic obstruction. A double-bind placebo-controlled study, Scand. J. Urol. Nephrol. 27, 39.

Dampney, R.A.L., 1994, Functional organization of central pathways regulating the cardiovascular system, Physiol. Rev. 74, 323.

De Groat, W.C. and P.M. Lalley, 1972, Reflex firing in the lumbar sympathetic outflow to activation of vesical afferent fibres, J. Physiol. 226, 289.

De Groat, W.C., A.M. Booth and N. Yoshimura, 1993, Neurophysiology of micturition and its modification in animal models of human disease, in: Nervous Control of Urogenital System, ed. C.A. Maggi (Harwood, Switzerland) p. 227.

Gradin, K., A.P. Nicholas, P. Hjemdahl, T. Svensson and T. Hokfelt, 1992, Contrasting cardiovascular responses from intrathecal administration of epinephrine and norepinephrine in conscious rats: role of α_1- and α_2-adrenoceptors, J. Cardiovasc. Pharmacol. 20, 367.

Hieble, J.P., M. Caine and E. Zalazanik, 1985, In vitro characterisa-

tion of the alpha-adrenoceptors in human prostrate, Eur. J. Pharmacol. 107, 111.

Ito, T., J.A. Hey and M.C. Koss, 1988, Studies on the mechanism of prazosin induced sympatho-inhibition, Eur. J. Pharmacol. 158, 225.

Kenny, B.J., A.M. Read, A.M. Naylor, P.M. Greengrass, P.J. Carter and M.G. Wyllie, 1994, Effect of alpha$_1$ adrenoceptor antagonists on prostatic pressure and blood pressure in anaesthetised dogs, J. Urol. 44, 52.

Kubo, T., M. Kihara, H. Hata and Y. Misu, 1987, Cardiovascular effects in rats of alpha$_1$ and alpha$_2$ adrenergic agents injected into the nucleus tractus solitarii, Naunyn-Schmied. Arch. Pharmacol. 335, 274.

Kuhn, D.M., W.A. Wolff and W. Lovenburg, 1990, Pressor effects of electrical stimulation of the dorsal raphe and median raphe nuclei in anaesthetized rats, J. Pharmacol. Exp. Ther. 214, 403.

Laubie, M. and H. Schmitt, 1988, Prazosin produces a sustained and reflex-mediated increase in renal sympathetic nerve activity in anaesthetized dogs, Eur. J. Pharmacol. 151, 75.

Lepor, H., D. Henry and A.R. Laddu, 1991, The role and safety of terazosin for the treatment of symptomatic BPH. The BPH-ALF Group, Prostrate 18, 345.

Marks, S.A. and M.P. Gilbey, 1992, Effect on cardiac sympathetic nerve activity of phenylephrine microinjected into the cat intermediolateral cell column, J. Physiol. 453, 185.

Marks, S.A., R.D. Stein, M.R. Dashwood and M.P. Gilbey, 1990, [^{3}H]Prazosin binding in the intermediolateral cell column and the effects of iontophoresed methoxamine on sympathetic preganglionic neuronal activity in the anaesthetized rat and cat, Brain Res. 530, 312.

Massingham, R. and M.L. Hayden, 1975, A comparison of the effects of prazosin and hydrallazine on blood pressure, heart rate and plasma renin activity in conscious renal hypertensive dogs, Eur. J. Pharmacol. 30, 121.

McCall, R.B. and S.J. Humphrey, 1981, Evidence for a central depressor action of post-synaptic α_1-adrenergic receptor antagonists, J. Auton. Nerv. Syst. 3, 245.

McCall, R.B. and M.R. Schutte, 1984, Evidence for an alpha-1 mediated central sympathoinhibitory action of ketanserin, J. Pharmacol. Exp. Ther. 228, 704.

Menkes, D.B., J.M. Baraban and G.K. Aghajanian, 1981, Prazosin selectively antagonizes neuronal responses mediated by alpha1-adrenoceptors in the brain, Naunyn-Schmied. Arch. Pharmacol. 317, 273.

Persson, B., T. Yao and P. Thoren, 1981, Correlation between decreased heart rate and central inhibition of sympathetic discharge after prazosin administration in the spontaneously hypertensive rat, Clin. Exp. Hypertens. 3, 245.

Ramage, A.G., 1984a, Effect of prazosin, indoramin and phentolamine on sympathetic nerve activity, Eur. J. Pharmacol. 106, 507.

Ramage, A.G., 1984b, Effect of pinacidil, hydralazine and sodium nitroprusside on sympathetic nerve activity of the cat, in: IUPHAR 9th International Congress of Pharmacology (Macmillan Presss, London) p. 1719P.

Ramage, A.G., 1986a, A comparison of the effects of doxazosin and alfuzosin with those of urapidil on preganglionic sympathetic nerve activity in anaesthetised cats, Eur. J. Pharmacol. 129, 307.

Ramage, A.G., 1986b, Evidence for a central sympathoinhibitory action of prazosin and indoramin, Eur. J. Pharmacol. 121, 83.

Ramage, A.G. and S.J. Wilkinson, 1989, Evidence that different regional sympathetic outflows vary in their sensitivity to the sympathoinhibitory actions of putative 5-HT$_{1A}$ and α_2 adrenoceptor agonists in anaesthetised cats, Br. J. Pharmacol. 98, 1157.

Ramage, A.G. and M.G. Wyllie, 1994, Effects of doxazosin and terazosin on inferior mesenteric nerve activity, spontaneous bladder contraction and blood pressure in anaesthetized cats, Br. J. Pharmacol. 112, 526P.

Rybarczyk, M.C. and A. Walland, 1985, Permissive role of spinal α_1-adrenoceptors in sudomotor efferents, Eur. J. Pharmacol. 112, 339.

Sokal, R.R. and F.J. Rohlf, 1969, Biometry: The Principles and Practice of Statistics in Biological Research (CA: Freeman, San Francisco).

Sundaram, K., J. Murugaian and H. Sapru, 1991, Microinjections of norepinehrine into the intermediolateral cell column of the spinal cord exert excitatory as well as inhibitory effects on the cardiac function, Brain Res. 544, 227.

Yoshimura, M., C. Polosa and S. Nishi, 1987, Slow epsp and the depolarizing action of noradrenaline on sympathetic preganglionic neurons, Brain Res. 414, 138.