British Journal of Pharmacology (1996) 117, 962–966

Micturition in conscious rats with and without bladder outlet obstruction: role of spinal α_1-adrenoceptors

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1 In normal rats and rats with bladder hypertrophy secondary to outflow obstruction, undergoing continuous cystometry, we examined the responses to the selective α_1 -adrenoceptor antagonist doxazosin given intrathecally (i.t.) and intra-arterially (i.a.). In addition, we investigated the effects of the drug on L-dopa-induced bladder hyperactivity in normal, unobstructed rats.

2 Doxazosin 50 nmol (approximately 60 $\mu g\ kg^{-1}$), given i.t., decreased micturition pressure in normal rats and in animals with post-obstruction bladder hypertrophy. The effect was much more pronounced in the animals with hypertrophied/overactive bladders. Doxazosin did not markedly affect the frequency or amplitude of the unstable contractions observed in obstructed rats. In contrast, however, doxazosin reduced L-dopa-induced bladder overactivity. When tested, the enantiomers of doxazosin produced qualitatively similar effects to doxazosin, but there was no evidence of stereoselectivity.

3 The results suggest that in addition to the well documented action on prostatic and lower urinary tract smooth muscle, and an effect on the sympathetic outflow to the bladder, bladder neck, prostate, and external urethral sphincter, doxazosin may have an action at the level of the spinal cord and ganglia, thereby reducing activity in the parasympathetic nerves to the bladder. This effect is more pronounced in rats with bladder hypertrophy than in normal rats.

Keywords: α-Adrenoceptor agonists; α-adrenoceptor antagonists; bladder; urethral obstruction

Introduction

Symptoms of benign prostatic hyperplasia (BPH) can be divided into obstructive (hesitancy, intermittency, decreased force of the urinary stream, dribbling retention), and irritative (urgency, urinary frequency, sense of incomplete voiding, nocturia, and incontinence). The former are due to the urethral obstruction caused by the physical mass of the enlarged gland and increased tension in prostatic smooth muscle; the latter are more closely associated with the induced bladder dysfunction. Indeed, bladder hypertrophy and bladder overactivity usually arise from the outflow obstruction secondary to BPH. On this basis, it is not unexpected that relief of outflow obstruction has often been shown to ameliorate both the obstructive and irritative symptoms of BPH. However, a significant number of patients who have undergone prostatectomy still experience persistent irritative symptoms although their obstruction is relieved. Not surprisingly, interest is beginning to focus on additional central nervous system-derived mechanisms particularly in the pathogenesis of the irritative symptoms previously attributed to localized aberrations in detrusor function.

Yoshimura *et al.* (1988) have analysed the physiology of bladder contraction subsequent to stimulation of the locus coeruleus in the anaesthetized cat. Based on the observation that the bladder contractions were antagonized by low doses of prazosin, they concluded that spinal α_1-adrenoceptors were involved in impulse transmission to the parasympathetic nuclei in the lumbosacral spinal cord. However, the role of spinal α_1-adrenoceptors in normal micturition has yet to be established. Equally, although changes in spinal neuronal activity have been demonstrated subsequent to outflow obstruction (Steers *et al.*, 1990), these have not been unequivocally linked to adaptive changes involving spinal α_1-adrenoceptors.

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The purpose of this study was to determine if spinal α_1-adrenoceptors were involved in the normal, volume-induced micturition process in the rat. A previous study in non-anaesthetized rats (Durant *et al.*, 1988) failed to show any dramatic effect of α-adrenoceptor antagonists on micturition, and concluded that spinal adrenergic systems were not active during a normal volume-evoked micturition reflex. Therefore, the effect of spinal α_1-adrenoceptor antagonism on bladder activity evoked by central activation (L-dopa) of the bulbospinal pathway mediating bladder contraction were also studied. For this purpose we administered the α_1-adrenoceptor antagonist, doxazosin, intrathecally (i.t.) and intra-arterially (i.a.), to conscious rats undergoing continuous cystometry. The effects of the drug were also studied in rats with bladder hypertrophy.

Methods

Animals

Female Sprague-Dawley rats, weighing 170–300 g, were used in this study. The experimental protocol was approved by the Animal Ethics Committee, University of Lund.

Procedures

Outlet obstruction procedure The methods used for establishing infravesical outflow obstruction, and the technique of cystometry in awake rats (Malmgren *et al.*, 1987) have been described in detail previously. Six weeks after partial ligature of the urethra, the animals were subjected to cystometrical evaluation. Partial obstruction of the urethra induces a significant bladder hypertrophy and bladder hyperactivity. One day after removal of the ligature, when the animals of this study were investigated, the bladder still exhibits a significant degree of hypertrophy and hyperactivity (Malmgren *et al.*, 1990).

Bladder catheter implantation Rats were anaesthetized with ketamine (75 mg kg^{-1}, i.m.) and xylazine (15 mg kg^{-1}, i.m.). The abdomen was opened through a midline incision, the ligature removed, and a polyethylene catheter (Clay-Adams PE-50, Parsippany, New Jersey, U.S.A.) implanted in the bladder through the dome as described previously (Malmgren *et al.*, 1987).

Intrathecal catheter implantation An intrathecal catheter was implanted at the same time as the bladder catheter. A polyethylene catheter (Clay-Adams PE-10) was inserted into the subarachnoid space at the level of L_6-S_1 spinal cord segments for intrathecal administration of drugs as described in detail previously (Igawa *et al.*, 1993). The injection sites in the spinal cord and the extent of dye distribution were confirmed by injection of dye (methylene blue) in every animal at the end of the experiment.

Cystometric investigations

Cystometric investigations were performed without any anaesthesia three days after the bladder catheter implantation in normal rats, and one day after in obstructed rats (Malmgren *et al.*, 1990). The bladder catheter was connected via a T-tube to a pressure transducer (P23 DC, Statham Instrument Inc., Oxnard, California, U.S.A.) and a microinjection pump (CMA 100, Carnegie Medicine AB, Solna, Sweden). The conscious rat was placed, without any restraint, in a metabolic cage which also enabled measurements of micturition volumes by means of a fluid collector connected to a Grass force displacement transducer (FT 03 C, Grass Instrument Co., Quincy, Massachusetts, U.S.A.). Room-temperature saline was infused into the bladder at a rate of 10 ml or 20 ml per hour in control animals and in animals with bladder hypertrophy, respectively. Intravesical pressure and micturition volumes were recorded continuously on a Grass polygraph (Model 7E; recording speed: 10 mm min^{-1}). Three reproducible micturition cycles, corresponding to a 20-min period, were recorded before drug administration and used as baseline values. The following cystometric parameters were investigated (Ishizuka *et al.*, 1994): basal pressure, micturition pressure (the maximum bladder pressure during micturition), bladder capacity (residual volume at the latest previous micturition plus volume of infused saline at the micturition), micturition volume (volume of expelled urine) and residual volume (bladder capacity minus micturition volume). Ten micturition cycles after administration of L-dopa in the presence or absence of doxazosin, and its enantiomers UK-35494-27(S) and UK-36528-27(R), were analysed and compared with the baseline values.

Administration of drugs

Stock solutions (10 mM) of doxazosin, UK-35494-27(S), and UK-36528-27(R) (Pfizer Central Research, Sandwich, UK) were made in dimethyl-sulphoxide (Sigma Chemical Company, St. Louis, Missouri, U.S.A.). The drugs were then stored at −70°C, and subsequent dilutions of the drugs were made on the day of experiments in saline. Carbidopa Merck Sharp and Dohme B.V., Haarlem, Netherlands) and L-dopa (Sigma Chemical Company) were dissolved in saline, adding a few drops of 1N HCL (pH 5–6) and slightly warmed. Carbidopa was given intra-peritoneally in the middle of a micturition cycle. After 15 min, L-dopa was given intra-peritoneally. Doxazosin, UK-35494-27(S), or UK-36528-27(R) was given intrathecally just after the administration of L-dopa. It was repeated 20 and 40 min after L-dopa. UK-35494-27(S) or UK-36528-27(R) was given intrathecally during bladder hyperactivity. The drug effects on cystometric parameters were followed for up to 120 min. The doses of the drugs used were chosen on the basis of our own pilot experiments, published data (Sillén *et al.*, 1979), and the known α_1-adrenoceptor activity of doxazosin *in vivo* (Kenny *et al.*, 1994).

Statistical analysis

The results are given as mean values ± standard error of the mean (s.e. mean). For comparisons between values obtained before and after the drug administration, Student's paired *t* test was used. One way factorial ANOVA was used for comparisons between doxazosin with and without outlet obstruction, L-dopa and L-dopa in the presence of doxazosin, UK-35494-27(S) or UK-36528-27(R), and was followed by Scheffe's *F* test. A probability level of $<5\%$ was accepted as significant.

Results

Effects of outlet obstruction

Repeated cystometries gave reproducible results in both control animals and animals with bladder hypertrophy. In animals with bladder hypertrophy, cystometry revealed spontaneous contractile activity during filling. In control animals, the bladder pressure was low and almost devoid of spontaneous fluctuations during the period of cystometry.

Partial obstruction of the urethra led to a significant increase in bladder weight (750 ± 73 mg, mean value ± s.e.mean, range from 230 to 1610 mg, $n=21$, $P<0.001$), compared to the normal controls (113 ± 6 mg, range from 70 to 189 mg, $n=23$).

Table 1 Effects of intrathecal (i.t.) or intra-arterial (i.a.) doxazosin on cystometric parameters in normal, conscious rats, and of i.t. doxazosin in rats with bladder hypertrophy

	MP	*BC*	*MV*	*RV*	*BP*
Doxazosin (50 nmol) *i.t.* ($n=7$); *normal rats*					
before	81.7 ± 7.3	0.79 ± 0.10	0.74 ± 0.13	0.07 ± 0.02	15.1 ± 1.8
after	68.9 ± 7.6**	0.79 ± 0.16	0.72 ± 0.14	0.08 ± 0.02	14.8 ± 2.0
Doxazosin (50 nmol) *i.a.* ($n=7$); *normal rats*					
before	61.5 ± 11.0	1.37 ± 0.11	1.25 ± 0.09	0.12 ± 0.03	8.7 ± 1.3
after	51.2 ± 10.1**	1.49 ± 0.07	1.27 ± 0.07	0.22 ± 0.06	8.9 ± 1.7
Doxazosin (50 nmol) *i.t.* ($n=8$); *bladder hypertrophy rats*					
before	93.2 ± 16.2	2.43 ± 0.62	2.15 ± 0.58	0.19 ± 0.06	7.5 ± 1.4
after	47.2 ± 10.7**†	2.64 ± 0.69	2.24 ± 0.53	0.48 ± 0.15	7.8 ± 1.2

MP: micturition pressure (cmH_2O), BC: bladder capacity (ml), MV: micturition volume (ml), RV: residual volume (ml), BP: basal pressure (cmH_2O). Results are expressed as mean ± standard error of the mean. Comparisons are made between values obtained before and after drug administration: **$P<0.01$ (Student's paired two tailed *t* test), and between normal rats and rats with bladder hypertrophy: †$P<0.05$ (ANOVA followed by Scheffe's *F* test).

Effects of doxazosin

Doxazosin, 50 nmol given i.t., decreased micturition pressure in normal rats ($n=7$; $P<0.01$; Table 1; Figure 1) as well as in rats with bladder hypertrophy ($n=8$; $P<0.01$; Table 1; Figure 1). Compared to the normal rats, changes in micturition pressure were significantly ($P<0.05$) more pronounced in rats with bladder hypertrophy (Table 1). In normal rats receiving 50 nmol doxazosin i.a., the drug also caused a significant ($P<0.01$) decrease in micturition pressure ($n=7$, Table 1), while not affecting the other cystometric parameters investigated.

Intrathecal doxazosin had no effect on the frequency or amplitude of the unstable contractions found in animals with bladder hypertrophy.

During and immediately after the administration of doxazosin, both normal animals and rats with bladder hypertrophy reacted with excitatory movements.

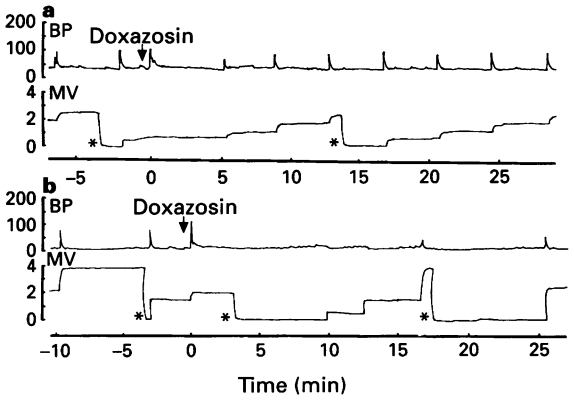

Figure 1 Effects of doxazosin administered intrathecally, at a dose of 50 nmol, on bladder pressure (BP; cmH_2O) and micturition volume (MV; ml) in a normal rat (a) and a rat with bladder hypertrophy (b). Note the variations in bladder pressure before the micturition contractions in the rat with bladder hypertrophy. Asterisk (*) indicates adjustment to baseline position.

Effects of doxazosin and its enantiomers on L-dopa-induced activity

L-Dopa, 50 mg kg^{-1} ($n=7$) decreased bladder capacity ($P<0.001$) and micturition volume ($P<0.001$), and increased basal pressure ($P<0.001$; Table 2; Figure 2a). There was no change in the micturition pressure and the residual volume. The effects of L-dopa appeared in about 10 min after the administration, and continued for about 120 min. Intrathecally administered doxazosin, UK-35494-27(S), or UK-36528-27(R), all given at a dose of 50 nmol per rat ($n=7$), attenuated the effects of L-dopa, both when administered just after L-dopa (Table 2, Figure 2b), and when hyperactivity had developed. There were no significant differences between the effects of the two enantiomers of doxazosin. Also when given i.a., doxazosin 50 nmol reduced the effects of L-dopa (Table 2).

Discussion

Descending spinal pathways concerned with micturition include 5-hydroxytryptamine and noradrenaline-containing projections from the raphe nuclei and the locus coeruleus, respectively (de Groat *et al.*, 1993). From the locus coeruleus, the noradrenergic neurones supply sympathetic and parasympathetic nuclei in the lumbosacral spinal cord. Bladder activation through these bulbospinal noradrenergic pathways may involve excitatory α_1-adrenoceptors. Thus, in the anaesthetized cat, electrical stimulation of the locus coeruleus induced bladder contractions that were antagonized by intrathecal administration of prazosin (Yoshimura *et al.*, 1988; 1990a,b). Destruction of noradrenergic cells in the locus coeruleus by microinjection of 6-OH-dopamine produced a hypoactive bladder, which could be partly reversed by intrathecal injection of the selective α_1-adrenoceptor agonist, phenylephrine. In the conscious cat, however, Downie *et al.* (1991) found that i.t. prazosin did not alter the micturition reflex. The reasons for these apparently conflicting results are unclear. Intravenous injection of prazosin or phentolamine in cats, depressed the external urethral sphincter activity and reduced reflex firing in pudendal nerve efferent pathways by a presumed central site of action (Gajewski *et al.*, 1984) Recently, central, facilitatory α_1-adrenoceptors, tonically active in both the sympathetic and somatic neural control of the lower

Table 2 Effects of intrathecal (i.t.) and intra-arterial (i.a.) doxazosin and its enantiomers on L-dopa induced bladder activity in normal, conscious rats

	MP	*BC*	*MV*	*RV*	*BP*
L-Dopa (50 mg kg^{-1}) ($n=7$)					
before	61.6 ± 6.8	0.96 ± 0.09	0.82 ± 0.06	0.13 ± 0.05	9.1 ± 1.0
after	58.9 ± 2.9	0.37 ± 0.03***	0.31 ± 0.02***	0.06 ± 0.02	16.7 ± 1.3***
L-Dopa (50 mg kg^{-1}) *plus i.t. doxazosin* (50 nmol) ($n=7$)					
before	61.0 ± 5.7	1.08 ± 0.12	0.91 ± 0.10	0.17 ± 0.04	12.2 ± 3.3
after	59.9 ± 6.9	0.85 ± 0.08††	0.67 ± 0.08††	0.17 ± 0.03	13.9 ± 2.2††
L-Dopa (50 mg kg^{-1}) *plus i.t. UK-35494-27(S)* (50 nmol) ($n=7$)					
before	57.5 ± 8.1	0.96 ± 0.08	0.81 ± 0.07	0.15 ± 0.02	6.3 ± 1.1
after	45.0 ± 3.9	0.70 ± 0.02*††	0.57 ± 0.03**††	0.13 ± 0.02	6.8 ± 0.7†††
L-Dopa (50 mg kg^{-1}) *plus i.t. UK-36528-27(R)* (50 nmol) ($n=7$)					
before	77.2 ± 14.0	0.93 ± 0.07	0.81 ± 0.06	0.12 ± 0.03	15.1 ± 3.0
after	67.8 ± 14.3	0.60 ± 0.07**†	0.47 ± 0.05**†	0.12 ± 0.01	14.4 ± 2.9†††
L-Dopa (50 mg kg^{-1}) *plus i.a. doxazosin* (50 nmol) ($n=7$)					
before	58.2 ± 7.7	1.07 ± 0.11	0.95 ± 0.11	0.13 ± 0.02	8.1 ± 1.8
after	67.0 ± 11.8	0.72 ± 0.08**†	0.58 ± 0.08**	0.14 ± 0.01	8.9 ± 1.2††

MP: micturition pressure (cmH_2O), BC: bladder capacity (ml), MV: micturition volume (ml), RV: residual volume (ml), BP: basal pressure (cmH_2O).

Results are expressed as mean ± standard error of the mean. Comparisons are made between values obtained before and after drug administration: *$P<0.05$, **$P<0.01$, ***$P<0.001$ (Student's paired two tailed t test), and between L-dopa and L-dopa plus i.t. or i.a. doxazosin or enantiomers. †$P<0.05$, ††$P<0.01$, †††$P<0.001$ (ANOVA followed by Scheffe's F test).

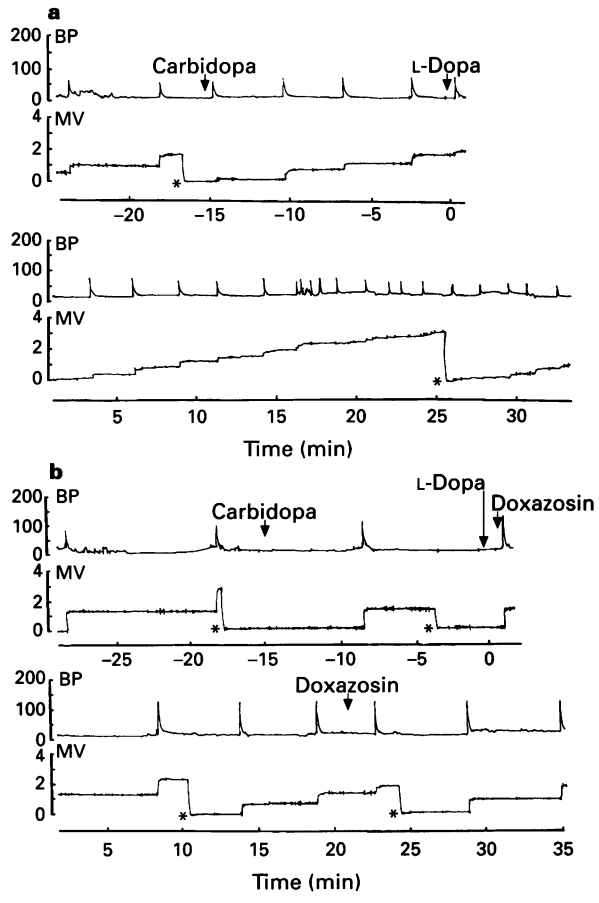

Figure 2 (a) Effects of i.p. L-dopa at a dose of 50 mg kg^{-1}, on bladder pressure (BP; cmH_2O) and micturition volume (MV; ml). Carbidopa, at a dose of 50 mg kg^{-1}, was given i.p. 15 min before L-dopa. Asterisk (*) denotes adjustment to baseline position. (b) Effects of i.p. L-dopa administered, at a dose of 50 mg kg^{-1}, on bladder pressure (BP; cmH_2O) and micturition volume (MV; ml) in the presence of i.t. doxazosin at a dose of 50 nmol per rat. Carbidopa, at a dose of 50 mg kg^{-1}, was given i.p. 15 min before L-dopa. Asterisk (*) denotes adjustment to baseline position.

urinary tract, were demonstrated in the cat (Ramage & Wyllie, 1994; Danuser & Thor, 1995).

All experiments in this study were carried out in conscious animals with varying levels of sympathetic drive in an attempt to resolve some of these ambiguities. The study showed that in normal rats, the only effect of spinal doxazosin on micturition induced by bladder filling, was a consistent decrease in micturition pressure. Since this effect was also found after i.a. administration of the drug, a role for spinal α_1-adrenoceptors was not conclusively demonstrated. A drug-induced decrease in micturition pressure may reflect not only depression of the micturition reflex at a spinal site, but also peripheral effects. Theoretically, antagonism at the α_1-adrenoceptors on the detrusor muscle, or antagonism at prejunctional α_1-adrenoceptors facilitating acetylcholine release in the bladder, would produce a decreased micturition pressure. Doxazosin can be expected also to antagonize the α_1-adrenoceptors of the urethral smooth muscle with a consequent decrease in outflow resistance. This effect would be expected to be more pronounced on i.a. than i.t. administration. However, the magnitude of the effect on micturition pressure was similar when the same dose of doxazosin was given i.t. and i.a., which seems to favour the view that at least part of the action of i.t. doxazosin was exerted at the spinal level, in addition to the action at the neuroeffector junction on the urethral smooth muscle.

Facilitatory α_1-adrenoceptors have been demonstrated on cholinergic neurones in the vesical ganglia of the cat (de Groat & Booth, 1980; Akasu *et al.*, 1985; Keast *et al.*, 1990), on dissociated bladder neurones from the rat major pelvic ganglion (Yoshimura & de Groat, 1992), and on cholinergic terminals in the rat bladder (Somogyi *et al.*, 1995). An effect of doxazosin at the ganglionic and/or prejunctional level, leading to a decrease of acetylcholine release cannot therefore be excluded. However, a direct antagonism at α_1-adrenoceptors in the detrusor smooth muscle seems less likely, since α_1-adrenoceptors do not seem involved in normal bladder contraction (Andersson, 1993).

Overall, therefore, it can be concluded that both central and peripheral effects of doxazosin may contribute to the decrease in micturition pressure seen after i.t. as well as i.a. administration.

The doxazosin-induced decrease in micturition pressure was significantly more pronounced in rats with bladder hypertrophy than in normal rats. Urethral obstruction facilitates certain reflex pathways to the urinary bladder (Steers & de Groat, 1988; Steers *et al.*, 1990), changes the peptide content in bladder nerves (Andersson *et al.*, 1988), and alters the responses of bladder smooth muscle to autonomic transmitters (Mattiasson *et al.*, 1987; Speakman *et al.*, 1987). Steers *et al.* (1990) demonstrated a significant increase in the size of bladder postganglionic neurones in the major pelvic ganglion of rats with bladder hypertrophy, as compared to normal controls. The contribution of these changes in neural function to the increased sensitivity to doxazosin in animals with bladder hypertrophy is unclear.

In fact, Mattiasson *et al.* (1987) concluded on the basis of radioligand binding data that the number of α-adrenoceptors in the detrusor was reduced in rats with bladder outflow obstruction; a functional correlate was observed in so far as α-adrenoceptor agonist-induced contraction was much reduced in detrusor derived from these animals. Assuming that detrusor contraction is linked to the facilitatory effect of α_1-adrenoceptor activation on acetylcholine release (see above), doxazosin would not be expected to have an enhanced effect via an interaction at this locus; by inference, an indirect action on detrusor contractility at the spinal level would be a more plausible explanation of the sensitization to the drug in obstructed animals.

After pretreatment with i.p. carbidopa, i.p. L-dopa will stimulate micturition or induce bladder hyperactivity in both anaesthetized rats (Sillén *et al.*, 1979; 1981), and in normal, conscious rats. Based on the observation that the effects were abolished by prior i.p. administration of the centrally acting dopamine receptor antagonist, spiroperidol, Sillén *et al.* (1979) suggested that the L-dopa-induced hyperactivity was elicited mainly via stimulation of central dopamine receptors. L-Dopa was assumed to act on the dopamine receptors in the locus coeruleus. From the locus coeruleus, which has been implicated in the supraspinal control of micturition (Elam *et al.*, 1986), noradrenergic neurones supply sympathetic and parasympathetic nuclei in the lumbosacral spinal cord. These bulbospinal noradrenergic pathways are of importance for micturition. Thus, Elam *et al.* (1986) showed that distension of the rat urinary bladder and the concomitant increase in bladder pressure, was associated with an increase in the firing rate of noradrenergic neurones in the locus coeruleus.

The present findings demonstrate that i.t. doxazosin as well as its enantiomers reduce the bladder hyperactivity induced by L-dopa. The effect was more pronounced than that of i.a. administration of the drugs, which supports the view of a central site of action, but does not exclude a peripheral contribution. The results also support the view that the spinal adrenergic system is activated by L-dopa treatment, and contributes to the evoked bladder activity. This is in contrast to the volume-induced bladder contraction, where spinal α_1-adrenoceptor antagonism had effects restricted to changes in micturition pressure.

The present study demonstrates the complexity of the action of doxazosin on the micturition reflex. Almost certainly α_1-adrenoceptors are involved in the control of micturition at

several different levels, all of which may contribute to the overall profile of the drug on the dynamic component of obstruction. Thus, in addition to the well documented action on prostatic and lower urinary tract smooth muscle, and an effect on the sympathetic outflow to the bladder, bladder neck, prostate, and external urethral sphincter (Gajewski *et al.*, 1984; Ramage & Wyllie, 1994; Danuser & Thor, 1995), α_1-adrenoceptor antagonists may have an additional action at the level of the spinal cord and ganglia, thereby reducing activity in the parasympathetic nerves to the bladder. The clinical significance has yet to be established, but the potential importance of these extra-prostatic actions of α_1-adrenoceptor antagonists should be borne in mind in the search for the new generation of prostate selective agents.

This project was supported by the Swedish Medical Research Council (No. 6837 and 10399), by the Medical Faculty of Lund, Sweden and by a Pfizer Pre-clinical Research Award.

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(Received July 12, 1995
Revised October 18, 1995
Accepted November 7, 1995)