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Effect of Doxazosin on Rat Urinary Bladder Function After Partial Outlet Obstruction

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Hypoxia induced by partial outlet obstruction is believed to play a major role in both the hypertrophic and degenerative effects of partial outlet obstruction. Doxazosin (dox) is a clinically effective α-adrenergic antagonist used in the treatment of symptomatic benign prostatic hyperplasia (BPH). Although the major therapeutic effect of the agent is believed to occur on the smooth muscle components of the prostate by reducing prostatic urethral resistance and thus improving emptying, dox may have part of its clinical action via effects mediated by other actions, including via spinal α-adrenergic receptors or direct effects on the bladder, possibly via inhibition of vascular alpha receptors. The specific aim of the current study was to determine whether dox pretreatment on rats affects blood flow to the bladder and reduces the level of bladder dysfunction induced by partial outlet obstruction. In part 1, eight rats were separated into two groups of four rats each. Group 1 received oral administration of dox (30 mg/kg) for 4 weeks; group 2 received vehicle (5% dimethyl sulfoxide). After 4 weeks of treatment, blood flow studies were performed using fluorescent microspheres and the bladders excised, frozen, and submitted to Interactive Medical Technologies (IMT) for blood flow analysis. In part 2, 32 adult male rats were separated into four groups of eight rats each. Groups 1 and 2 received oral administration of dox (30 mg/kg) for 4 weeks, groups 3 and 4 received vehicle (5% dimethyl sulfoxide). At 4 weeks, the rats in groups 1 and 3 received partial outlet obstructions and treatment continued for an additional 2 weeks. After 6 weeks of treatment (total), each rat was anesthetized, the bladder excised, weighed, and isolated strips mounted and contractility studies performed. 1) Four weeks pretreatment of rats with dox increased blood flow to the bladder in both the control and obstructed groups. 2) Partial outlet obstruction induced a mild decrease in blood flow. 3) The magnitude of the increased bladder weight in the vehicle-treated obstructed group was significantly greater than in the dox-treated obstructed group. 4) Partial outlet obstruction resulted in significant decreases in the contractile response to field stimulation in both treated and non-treated rats. The magnitude of the decreased response was significantly greater in the non-treated rats. 5) The response to potassium chloride was significantly reduced by partial outlet obstruction in the vehicle-treated group but not in the dox-treated group. 6) The time to maximal tension was significantly increased in response to carbachol, adenosine triphosphate, and potassium chloride. However, the magnitude of the increase was significantly greater for the vehicle-treated obstructed groups stimulated by potassium chloride than for the dox-treated groups. Dox treatment of rats increased blood flow to the bladder and reduced the severity of the response to partial outlet obstruction. These beneficial effects would be due to pharmacological effects on α-adrenergic systems outside those present in the prostate. These include effects on blood flow to the bladder, effects on the micturition centers of the central nervous system, spinal reflexes, and α-adrenergic receptors in the urethra and bladder. *Neurourol. Urodynam. 21:160–166, 2002.* © 2002 Wiley-Liss, Inc.

Key words: doxazosin; bladder; rat; obstruction

INTRODUCTION

Doxazosin (dox) is an α-adrenergic blocking agent used in the treatment of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) [Janknegt and Chapple, 1993; Martin et al., 1997]. Although dox has been shown to have a relative selectivity in the treatment of LUTS than for the cardiovascular system, it is clear that this α-adrenergic blocker lowers blood pressure, reduces vascular resistance, and can increase blood flow under specific conditions

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[Tewari and Narayan, 1999; Weingerger and Fawzy, 2000]. Although the mechanism of action of dox in the treatment of BPH has been assumed to be primarily via relaxation of prostatic smooth muscle, there may be other biological actions of the agent that contribute to its clinical efficacy. These actions include effects on the spinal reflexes that modulate micturition, stimulation of apoptosis, and α-adrenergic inhibition of vascular and urethral tone [Cai et al., 1995; Ishizuka et al., 1997; Kyprianou et al., 1998; Persson et al., 1998; Rimoldi et al., 2000].

It is clear that obstructive symptoms including decreased voiding pressure and flow, incomplete emptying and irritative symptoms such as urgency, frequency, and nocturia are related to the enlarged prostate. However, it is not clear whether improvement in these symptoms with the use of alpha antagonists is primarily due to actions on the prostatic smooth muscle, urethral smooth muscle, or other sites of action. One of the etiological factors in the response to partial outlet obstruction is reduced blood flow and hypoxia [Greenland et al., 2000; Greenland and Brading, 2001; Schröder et al., 2001].

The specific aim of the current project was to determine whether dox given orally to rats has beneficial effects on bladder function in both normal control rats and rats subjected to partial outlet obstruction. Because this is a mechanical obstruction, the mechanism of action relating to a beneficial effect would be independent of actions on the prostate.

METHODS

In part 1, 16 adult male rats were separated into two groups of eight rats each. Group 1 received oral administration of dox (30 mg/kg) for 4 weeks; group 2 received vehicle [5% dimethyl sulfoxide (DMSO)]. After 4 weeks of treatment, four rats per group were subjected to partial outlet obstructions. After 2 weeks of obstruction, blood flow studies were performed using fluorescent microspheres, and the bladders excised, frozen, and submitted to Interactive Medical Technologies, Ltd. (IMT) (North Hollywood, CA) for blood flow analysis. In part 2, 32 adult male rats were separated into four groups of eight rats each. Groups 1 and 2 received oral administration of dox (30 mg/kg dissolved in 30% DMSO) for 4 weeks; groups 3 and 4 received vehicle (30% DMSO). At 4 weeks, the rats in groups 1 and 3 received partial outlet obstructions and treatment continued for an additional 2 weeks. The dosage and duration of treatments were based on consultation with Pfizer who has extensive experience in the treatment of rats with dox.

Blood Flow Studies

The right femoral and left carotid arteries of each rat were surgically exposed under anesthesia. The femoral artery was cannulated with a 28-gauge catheter filled with normal saline and 20 U/mL heparin. This catheter was connected to a Harvard automatic syringe infusion/withdrawal pump to obtain reference blood samples. The left carotid artery was cannulated with a 24-gauge catheter filled with saline and 20 U/ml heparin and was inserted down into the aortic arch. The carotid catheter was likewise attached to an automatic syringe infusion/withdrawal pump and used to infuse 2,000,000 NuFlow fluorescent red microspheres (IMT) 15-μm in diameter well suspended in 0.4 mL 0.9% saline and 0.01% Tween 80 (Sigma Chemical Co., St. Louis, MO) into the circulation as previously described. Delivery of the microspheres was timed for a 10-second period, and residual beads were flushed through the catheter by a subsequent 0.5-mL volume of saline/heparin. A reference blood sample was simultaneously withdrawn at a rate of 0.7 mL/min from the right femoral artery commencing 10 seconds before the injection of the microspheres. Blood was withdrawn continuously during the period of microsphere injection continuing to 22 seconds after the flush of the carotid catheter and collected in an ethylenediaminetetraacetic acid-coated tube to prevent coagulation. Five minutes after the infusion, the rat was euthanized (a lethal cocktail of pentobarbital) fluid given intravenously. The bladder was removed and frozen in liquid nitrogen for blood-flow measurements. Because of the small size of the rat bladder, the entire bladder is required for accurate blood-flow measurements. The blood samples and frozen tissue were processed for immediate shipment to IMT, Investigative Partner Services, where the samples were digested in an alkaline solution. Microspheres from individual tissues were subsequently collected on a filter, resuspended, and quantified in a flow cytometer measuring red fluorescence.

Surgical Creation of Obstruction

Each rat was sedated with ketamine-xylazine (80–10 mg/kg i.p.) and surgical anesthesia was maintained with 25 mg/kg Nembutal. The bladder was exposed through a mid-line incision and a partial outlet obstruction created by tying a 2-0 silk ligature loosely around a length of PE-20 tubing placed on the urethra (above the pubis). The incision was closed with 3-0 Vicryl sutures. Treatment was stopped 24 hours before surgery and started immediately after recovery from surgery.

After 6 weeks of treatment (total), each rat was anesthetized with pentobarbital, and the bladder was exposed, excised, and weighed. The bladder was then transected above the trigone. Full-thickness (including urothelium) strips were then cut longitudinally from the dome toward the base. The strips were then mounted in isolated baths containing 15 mL Tyrode's solution maintained at 37°C and equilibrated with 95% O_2, 5% CO_2. After 1 hour of incubation, 2 g of passive tension was placed on each strip, and the contractile responses to the following were determined: field stimulation (FS) at 1, 2, 4, 8, 16, and 32 Hz, 80 V, 1-millisecond duration; 10 mM carbachol, 1 mM adenosine triphosphate (ATP), and 120 mM potassium chloride (KCl). Tension was recorded on a Grass polygraph and digitized by Polyview digital analysis system. The maximal tension, maximal rate of tension generation, and time

to maximal tension for each stimulation were quantitated. All data are presented as mean ± SEM; the tension was recorded as g tension/100 mg tissue weight. Statistical analysis used analysis of variance followed by Newman-Keuls test for individual groups. A $P < 0.05$ was required for significance. Data are presented for 2, 8, and 32 Hz as representative of low-, intermediate-, and high-frequency stimulation.

RESULTS

Blood flow to the rat bladder was increased following 4 weeks of dox treatment in both the control and the obstructed groups (Fig. 1). Blood flow in the vehicle-treated rats was decreased by approximately 25% by partial outlet obstruction and by approximately 20% in the dox-treated rats. Partial outlet obstruction resulted in a significant increase in bladder mass in both vehicle- and dox-treated groups (Fig. 2). However, the magnitude of the increase in the vehicle-treated group was significantly greater than in the dox-treated group (Fig. 2).

Partial outlet obstruction induced a significant decrease in the both the magnitude of the contractile response to FS and the rate of tension generation at all frequencies (Figs. 3 and 4). Interestingly, the magnitude of the decreases in the vehicle-treated group was significantly greater than the magnitude of the decreases in the dox-treated group, indicating that the level of dysfunction was less in the dox-treated rats. Partial outlet obstruction resulted in a significant increase in the time to maximal tension for 32 Hz; dox treatment had no significant effects on the time to maximal tension (Fig. 5).

The contractile response to ATP was increased after partial outlet obstruction for both vehicle- and dox-treated groups (Fig. 6). The response to KCl was significantly reduced by partial outlet obstruction in the vehicle-treated group but not in the dox-treated group, showing that the response to KCl was significantly greater for the dox-treated obstructed group when compared with the vehicle-treated obstructed group (Fig. 6). Partial outlet obstruction had no significant effects on the contractile response to carbachol (Fig. 6).

There were no effects of either obstruction or dox treatment on the rate of contractile response for ATP, KCl, or carbachol (Fig. 7). For all three contractile agents, partial outlet obstruction resulted in an increase in the time to maximal tension

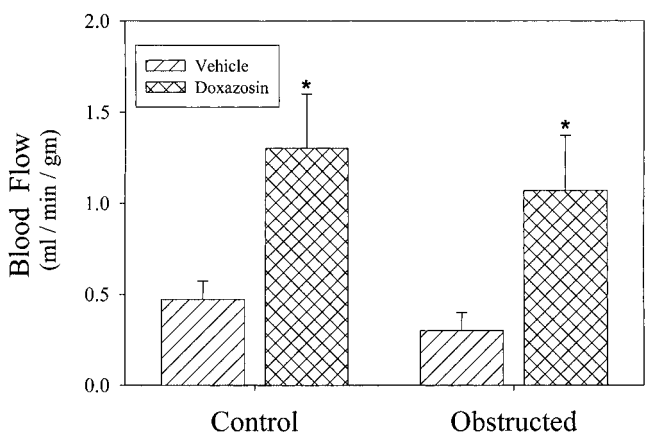

Fig. 1. Effect of doxazosin on blood flow. Each bar is the mean ± SEM of four individual rats. *Significantly different from vehicle; $P < 0.05$.

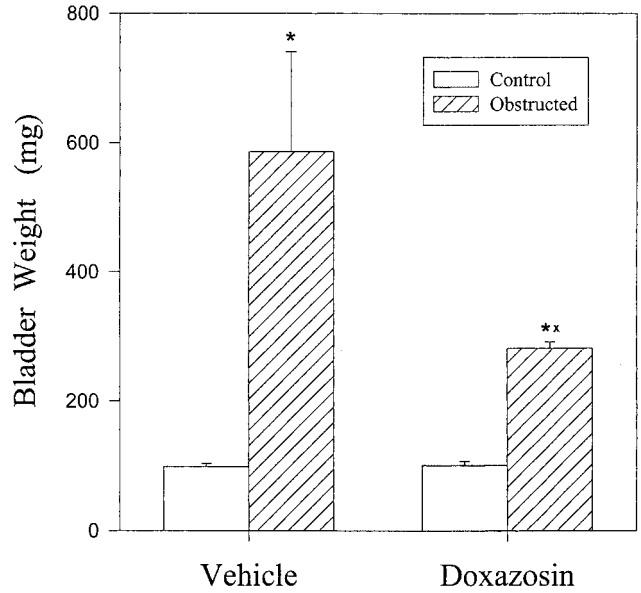

Fig. 2. Effect of doxazosin on bladder weight. Each bar is the mean ± SEM of eight individual rats. *Significantly different from control; ˣsignificantly different from vehicle; $P < 0.05$.

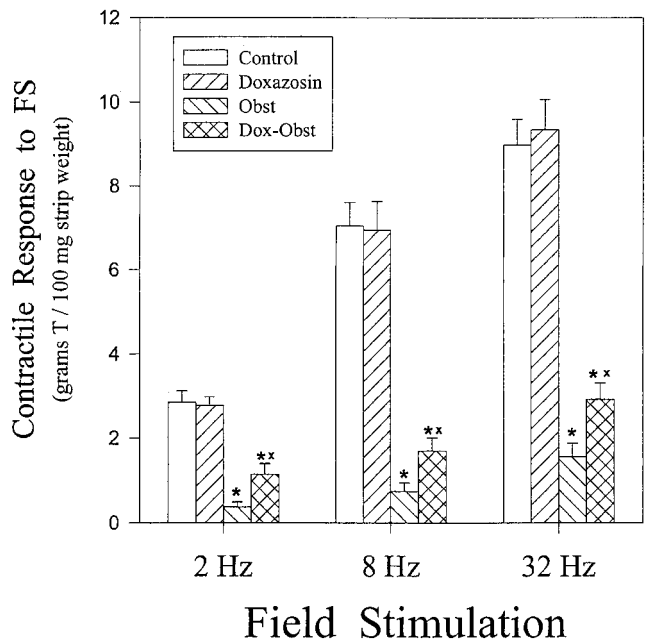

Fig. 3. Effect of doxazosin on the response to field stimulation: maximal contractile response. Each bar is the mean ± SEM of eight individual rats. *Significantly different from non-obstructed; ˣsignificantly different from obstructed; $P < 0.05$.

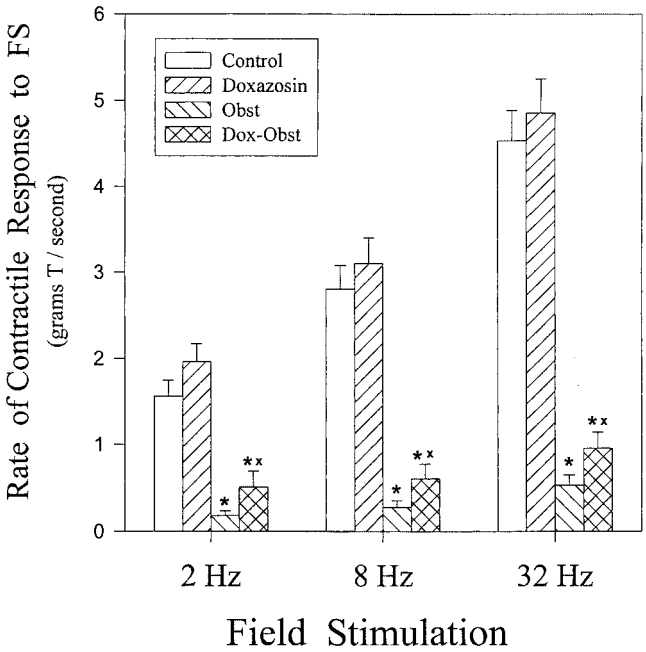

Fig. 4. Effect of doxazosin on the response to field stimulation: rate of tension generation. Each bar is the mean ± SEM of eight individual rats. *Significantly different from non-obstructed; ˣsignificantly different from obstructed; $P < 0.05$.

(Fig. 7); however, the time to maximal contraction for all three agonists was significantly shorter for the obstructed group receiving dox than for the obstructed group receiving vehicle (Fig. 8).

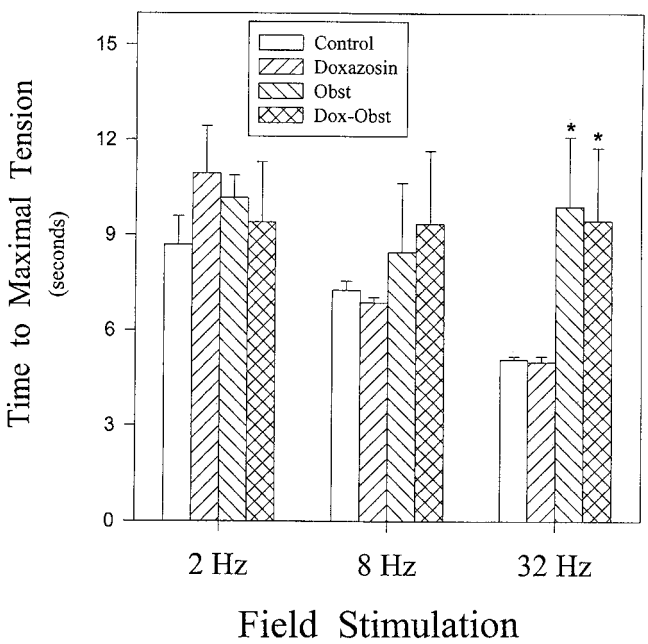

Fig. 5. Effect of doxazosin on the response to field stimulation: time to maximal tension. Each bar is the mean ± SEM of eight individual rats. *Significantly different from non-obstructed; $P < 0.05$.

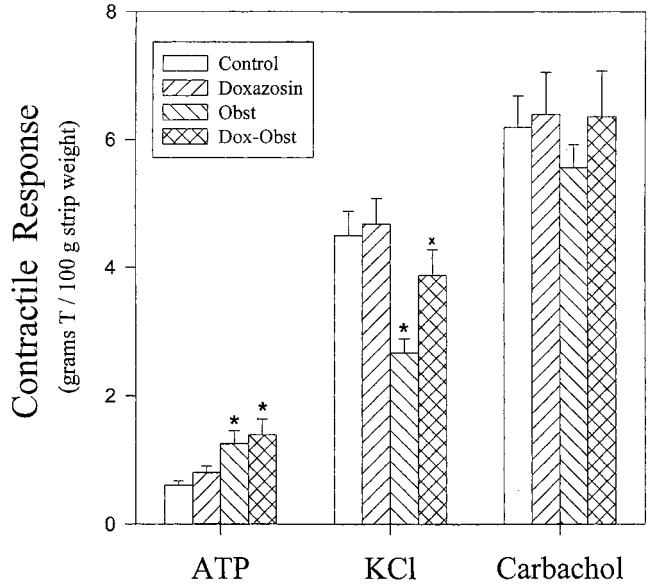

Fig. 6. Effect of doxazosin on the response to adenosine triphosphate (ATP), potassium chloride (KCl), and carbachol: maximal contraction. Each bar is the mean ± SEM of eight individual rats. *Significantly different from non-obstructed; ˣsignificantly different from obstructed; $P < 0.05$.

DISCUSSION

The results of the study demonstrated that dox pretreatment of rats increased blood flow to the bladder in both the control and the obstructed rats, reduced the degree of bladder hypertrophy after partial outlet obstruction, and partially protected the bladder against the contractile dysfunctions induced by partial outlet obstruction. In the rat model of

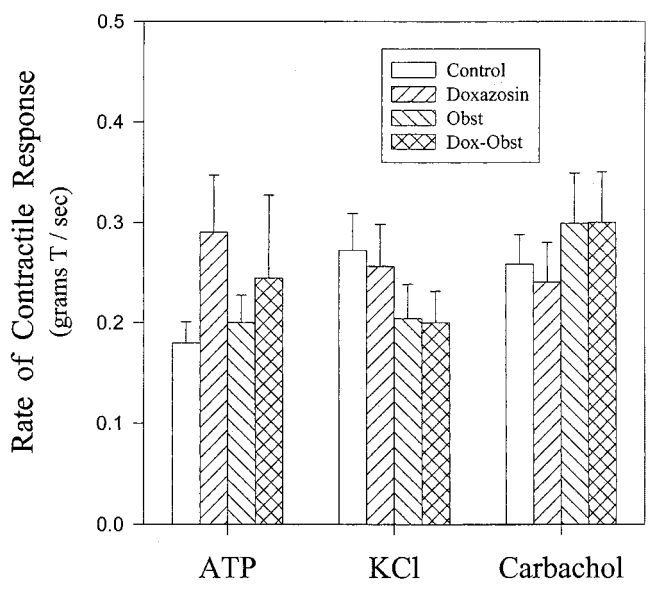

Fig. 7. Effect of doxazosin on the response to adenosine triphosphate (ATP), potassium chloride (KCl), and carbachol: rate of tension generation. Each bar is the mean ± SEM of eight individual rats.

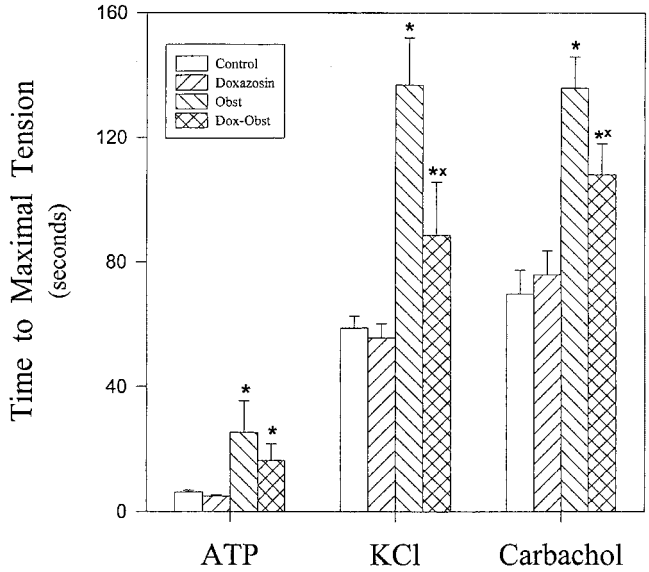

Fig. 8. Effect of doxazosin on the response to adenosine triphosphate (ATP), potassium chloride (KCl), and carbachol: time to maximal tension. Each bar is the mean ± SEM of eight individual rats. *Significantly different from non-obstructed; ˣsignificantly different from obstructed; $P < 0.05$.

obstruction, the increase in bladder mass is related to both hypertrophy and hyperplasia of the smooth muscle elements, urothelial and fibroblast hyperplasia, and expansion of the connective tissue components of the bladder [Uvelius and Mattiasson, 1984; Levin et al., 1990; Saito et al., 1994].

In both rats and rabbits, reduced blood flow and hypoxia have been shown to be involved in the response to partial outlet obstruction [Saito et al., 1997; Greenland et al., 2000; Greenland and Brading, 2001]. In studies recently published, the blood flow to the rabbit bladder per unit bladder mass was not changed in compensated bladders. That is, although the compensated bladders were significantly hypertrophied, there was no decrease in blood flow. However, in decompensated bladders, there was a clear decrease in blood flow to the detrusor smooth muscle [Schröder et al., 2001]. The decrease in blood flow to the bladder observed in these studies is consistent with the cited published studies.

Hypoxia in a variety of in vitro and in vivo settings stimulates cellular proliferation, angiogenesis, and collagen synthesis and deposition [Lee et al., 2000; Takahashi et al., 2000; Vincent et al., 2000]. The response of the bladder to partial outlet obstruction includes all three of the above: urothelial and fibroblast hyperplasia [Monson et al., 1992], angiogenesis [Chichester et al., 2000], and collagen synthesis and deposition [Monson et al., 1988; Schrder et al., 2001]. Our hypothesis for the etiology of the response to obstruction is as follows: 1) Partial outlet obstruction increases urethral resistance and results in an initial overdistension of the bladder. 2) Overdistension of the bladder compresses the capillary blood vessels in both the urothelium and smooth muscle compartments, resulting in a mild to moderate tissue hypoxia. 3) This hypoxia results in the increased expression of growth factors including an increase in basic fibroblast growth factor, increased activation of epidermal growth factor receptors [Buttyan et al., 1992; Chen et al., 1994], and decreased expression of transforming growth factor β, resulting in the observed hyperplasia. 4) Hypoxia also results in the activation of fibroblast and smooth muscle synthesis of collagen, resulting in the observed increased deposition and redistribution of connective tissue after partial outlet obstruction. 5) Although it is generally thought that hypoxia is a stimulant for apoptosis [Matsushita et al., 2000], there is recent literature that clearly demonstrates that hypoxia can also result in the direct inhibition of apoptosis [Baek et al., 2000].

We recently demonstrated that the molecular response to partial outlet obstruction [Chen et al., 1994], overdistension [Matsushita et al., 2000], and ischemia [Chen et al., 1996] are very similar except for the time course. All three respond with hyperplasia of the urothelium and fibroblasts and increased collagen synthesis. A recent study showed that the degree of bladder hypertrophy and the severity of contractile dysfunctions after partial outlet obstruction can be significantly reduced by intermittent catheterization, thus demonstrating that if the initial period of overdistension is reduced, the structural and functional responses to partial outlet obstruction are significantly reduced [Ohnishi et al., 2000].

The current study is consistent with the above theory, that is, if the hypoxia after partial outlet obstruction is reduced via increasing blood flow to the bladder, the severity of the structural and functional responses to partial outlet obstruction will be reduced. Future studies will look at the relationships among blood flow, tissue hypoxia, and the structural and functional responses to both overdistension and partial outlet obstruction.

A recent study demonstrated that bladder distension stimulated increased sympathetic activity that resulted in increased coronary resistance and reduced coronary blood flow. Dox pretreatment reversed the distension-induced increased vascular resistance [Lee et al., 2000]. Similar reductions in vascular resistance have been reported in other studies [Cai et al., 1995; Rimoldi et al., 2000]. In other studies, dox has been demonstrated to both inhibit growth-factor stimulated proliferation of vascular smooth muscle cells [Hu et al., 1998] and to stimulate apoptosis [Yang et al., 1997; Kyprianou et al., 1998], both of which may play a part in the reduced bladder mass in the dox-treated obstructed bladders.

We present three parameters of the contractile responses: maximal tension, the rate of tension generation, and the time to maximal tension. Previously, we observed that the first noticeable change in the contractile response to FS or to pharmacological stimulation induced by partial outlet obstruction was not in the maximal tension generated but in the rate of tension [Levin et al., 1997]. Partial outlet obstruction results in marked changes in excitable membrane properties and in calcium transport, release, and storage mechanisms, which

can affect the rate of tension generation before affecting the maximal tension developed [Levin et al., 1997; Geloso and Levin, 1998; Fry et al., 1999]. The time to maximal tension in response to FS is related to the release of transmitters, diffusion across the synapse, activation of postsynaptic receptors, and release and diffusion of calcium within the smooth muscle cells. With pharmacological agents, the diffusion of the agent to the receptor is directly related to the time to maximal tension. The contractile response to FS (at all frequencies) was reduced by more than 70% by partial outlet obstruction. Dox treatment resulted in a limited improvement in the response to FS compared with the vehicle treated. Because the response to FS is a measure of the magnitude of denervation present [Seki et al., 1992; Steers, 1994], this may indicate that the level of denervation induced by partial outlet obstruction was somewhat less severe in the dox-treated group than in vehicle-treated animals.

It is clear from these studies that the contractile response to KCl was protected by dox treatment. There was no significant decrease in the magnitude of the contractile response, and the time to maximal tension, although increased, was significantly less (closer to control values) when compared with the vehicle-treated obstructed rats. Neither obstruction nor dox treatment affected the contractile responses to carbachol. It is interesting to note that the contractile response to ATP was significantly increased after obstruction. Because the obstructed bladders showed clear signs of denervation, perhaps the increased response to ATP represents a form of denervation supersensitivity.

Dox has been shown to affect bladder function in both normal and obstructed rats in part by inhibition of spinal α-receptors [Ishizuka et al., 1997; Persson et al., 1998]. The effects after partial outlet obstruction were more pronounced than the effects in normal rats. This demonstration may indicate that the beneficial effect of dox in this study may be in part due to inhibition of spinal reflexes to the bladder and perhaps a reduction in the level of spontaneous activity (hyperreflexia) that is induced by partial outlet obstruction. Future studies will evaluate the effect of dox on hyperreflexia induced by partial outlet obstruction.

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