Spinal and peripheral mechanisms contributing to hyperactive voiding in spontaneously hypertensive rats

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PERSSSON, Katarina, Raj K. Pandita, John M. Spitsbergen, William D. Steers, Jeremy B. Tuttle, and Karl-Erik Andersson. Spinal and peripheral mechanisms contributing to hyperactive voiding in spontaneously hypertensive rats. Am. J. Physiol. 275 (Regulatory Integrative Comp. Physiol. 44): R1366–R1373, 1998.—The influence of noradrenergic mechanisms involved in micturition in spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats was investigated using continuous cystometry in vivo and in vitro studies on isolated bladder and urethral tissues. Compared with WKY rats, SHR had a significantly lower bladder capacity (SHR: 0.7 ± 0.05 ml; WKY rats: 1.3 ± 0.06 ml; P < 0.001), micturition volume (SHR: 0.4 ± 0.04 ml, WKY rats: 1.2 ± 0.05 ml; P < 0.001), and an increased amplitude of nonvoiding (unstable) bladder contractions. The effects of intrathecal and intra-arterial doxazosin on cystometric parameters were more pronounced in SHR than in WKY rats. There was a marked reduction in nonvoiding contractions after intrathecal (but not intra-arterial) doxazosin in SHR. Norepinephrine (0.1 µM–1 mM) failed to evoke contractions in bladder strips from WKY rats, in contrast to a weak contractile response in SHR. The response to electrical field stimulation was significantly less in bladder strips from SHR than from WKY rats. In WKY rats, norepinephrine produced concentration-dependent inhibition (87 ± 5%, n = 6) of nerve-evoked bladder contractions. Almost no inhibition (11 ± 8%, n = 6) was found in SHR. Alterations in bladder function of SHR appear to be associated with changes in the noradrenergic control of the micturition reflex, in addition to an increased smooth muscle and decreased neuronal responsiveness to norepinephrine. The marked reduction in nonvoiding contractions after intrathecal doxazosin suggests that the bladder hyperactivity in SHR has at least part of its origin in supraspinal and/or spinal structures.

bladder; urethra; α-adrenoceptors; sympathetic nervous system

SPONTANEOUSLY HYPERTENSIVE rats (SHR) have been widely studied as a genetic model of hypertension. Vascular abnormalities in SHR are thought to derive from arterial cell hypertrophy and hyperplasia and sympathetic hyperinnervation (14). An increased norepinephrine content has been found in nonvascular tissue of SHR (9), implying that hyperinnervation is not restricted to the vasculature and may include other sympathetically innervated tissues. Increased tissue concentrations of norepinephrine and neuropeptide Y in the bladders and urethras of SHR when compared with control tissues from Wistar-Kyoto (WKY) rats have been demonstrated (23, 24, 28, 29). Compared with WKY rats, SHR exhibit increased voiding frequency, increased bladder sympathetic innervation (23, 24), and hypertrophy in both afferent and efferent neurons supplying the bladder (5). The mechanism for the increased voiding frequency in SHR is not known. Thus urodynamic studies and pharmacological investigations of the lower urinary tract were undertaken to clarify the functional consequences of the sympathetic hyperinnervation in SHR.

The sympathetic input to the bladder shows a wide variation between species (1). Because SHR have hyperexcitable sympathetic neuronal pathways (27), this animal model may be helpful to elucidate bladder dysfunctions associated with disturbances in the sympathetic nervous system. The enhanced nerve activity in SHR seems to involve increased excitability in both postganglionic (32) and preganglionic neurons (15). Obstruction and decentralization of the lower urinary tract have been linked to changes in the peripheral adrenergic innervation and responsiveness. An increased contractile response to α-adrenoceptor stimulation was found in the obstructed dog bladder (20) and in patients with benign prostatic hyperplasia (16). In bladder strips from parasympathetically decentralized patients, an increase in fluorescent adrenergic fibers was reported (26).

The influence of central sympathetic pathways for micturition has recently gained more attention. Autoradiographic studies have revealed a widespread distribution of α1-adrenoceptors in the rat spinal cord (21), including areas in the lumbar sacral cord involved in the micturition reflex (33). The precise role of spinal α1-adrenoceptors in micturition is not known. In normal rats, blockade of spinal α1-adrenoceptors has been found to have no effect (6) or to decrease the micturition pressure (11). The effect of α1-adrenoceptor antagonism on the micturition pressure was more pronounced in rats with bladder hypertrophy than in normal rats (11), implying plasticity in spinal α1-adrenoceptors with alterations at the bladder level.

To compare the influence of noradrenergic mechanisms involved in micturition in SHR and WKY rats, the effects of spinal and peripheral administration of an α1-adrenoceptor antagonist were studied in animals undergoing continuous cystometry, and in vitro studies were performed on isolated bladder and urethral tissues. A preliminary report of some of the present findings was previously published (18).

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METHODS

Animals

Female SHR and the genetically normotensive control strain, the WKY rat, weighing between 180 and 220 g were used. The experimental protocol was approved by the Animal Ethics Committee, University of Lund.

Cystometry

Catheter implantations. Rats were anesthetized with ketamine (Ketalar; Parke-Davis, Barcelona, Spain; 75 mg/kg im) and xylazine (Rompun; Bayer, Leverkusen, Germany; 15 mg/kg im). The abdomen was opened through a midline incision, and a polyethylene catheter (PE-50; Clay-Adams, Parsippany, NJ) was implanted into the bladder through the dome as previously described (13).

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 the atlantooccipital joint through the dura, and the tip was advanced caudally until it reached the L₅–S₁ level of the spinal cord segments. The injection site in the spinal cord and the extent of dye distribution were confirmed by injection of dye (methylene blue) in every animal at the completion of the experiment.

One day before cystometry, the rats were again anesthetized, and through an inguinal approach a heparinized polyethylene catheter (Clay Adams PE-50) was placed in one of the femoral arteries. The tip of the catheter reached the aortic bifurcation, and the catheter was tunnelled subcutaneously and secured with a silk suture on the back of the animal.

Cystometric investigations. Cystometric investigations were performed without any anesthesia 3 days after the bladder catheter implantation. The bladder catheter was connected via a T tube to a pressure transducer (P23 DC; Statham Instruments, Oxnard, CA) and to a microinjection pump (CMA 100; Carnegie Medicine, Solna, Sweden). The rats were placed without any restraint in metabolic cages, which also enabled measurement of the micturition volumes by means of a fluid collector connected to a fluid displacement transducer (FT03; Grass Instrument, Quincy, MA). Room temperature saline was infused into the bladder continuously at a rate of 10 ml/h. Intravesical pressure and micturition volumes were recorded continuously on a Grass polygraph (model 7E). Transmural adjustment of passive tension. Isometric tension was recorded using a Grass polygraph (model 7D). Stimulation of nerves was performed with a Grass S48 stimulator delivering single square wave pulses (duration 0.8 ms) at the voltage giving maximal contractile response. The train duration was 5 s, the stimulation interval was 120 s, and the polarity of the electrodes was shifted after each pulse by means of a polarity changing unit.

Experimental procedure. During an equilibration period of 45–60 min the preparations were stretched to a stable passive tension of 4 mN. Spontaneous, phasic bladder contractions generally developed during the equilibration period, and in separate experiments the effects of norepinephrine (0.1 µM–1 mM) and isoprenaline (10 µM) were examined on these contractions.

After the equilibration period, each experiment was started by exposing the preparations to a K⁺ (124 mM)–Krebs solution. In bladder preparations, frequency-response relations (1–40 Hz) to electrical field stimulation (EFS) and concentration-response relations to K⁺ (18–124 mM), carbachol (10 nM–0.1 mM), α₁β-hydroxy-ATP (MeATP; 1 µM–0.1 mM), substance P (10 nM–100 nM), and norepinephrine (0.1 µM–1 mM) were recorded. Relaxant responses to norepinephrine (0.1 µM–1 mM) were recorded in preparations precontracted by carbachol (100 µM). The EFS-induced contractile response (at 20 Hz) was further characterized by addition of scopolamine (1 µM), propranolol (1 µM), rauwolscine (1 µM), and phenylephrine (0.1 µM–30 µM).

In urethral preparations, the contractile responses to EFS (2–50 Hz) and norepinephrine (10 nM–0.1 mM) were recorded. Due to the pronounced influence of inhibitory nitric oxide (NO), contractile responses to EFS were studied in the presence of the NO synthase inhibitor N′-nitro-L-arginine (l-NNA; 0.1 mM). Relaxant responses to EFS (0.5–30 Hz) and the NO donor 5-nitroso-N-acetyl-lysine (SNAP; 10 nM–0.1 mM) were studied in urethral preparations precontracted by arginine vasoressin (AVP; 10 nM).

Drugs and solutions. The Krebs solution used had the following composition (in mM): 119 NaCl, 4.6 KCl, 1.5 CaCl₂, 1.2 MgCl₂, 15 NaHCO₃, 1.2 NaH₂PO₄, and 5 glucose. The following drugs were used in functional in vitro studies: carbachol, scopolamine hydrochloride, substance P, l-NNA, α₁β-MeATP, phenylephrine, isoprenaline, propranolol, and norepinephrine (Sigma Chemical), AVP acetate (Peninsula Laboratories, Belmont, CA), rauwolscine (Carl Roth KG, Karlsruhe, Germany).
Germany), and SNAP (a generous gift from Dr. M. Feelisch, Schwarz Pharma, Monheim, Germany). Stock solutions were prepared and then stored at −70°C. SNAP was dissolved in ethanol, and all other drugs were dissolved in saline or distilled water. K+ Krebs solution (124 mM) was prepared by replacing NaCl with equimolar amounts of KCl.

Statistical analyses. The results are given as mean values ± SE. Student’s unpaired t-test was used for comparisons between SHR and WKY rats. For comparison between values obtained before and after drug administration, Student’s paired t-test was used. A probability level of <5% was accepted as significant.

RESULTS

The body and bladder weights were less in SHR (body: 185 ± 2 g; bladder: 55 ± 1.4 mg) compared with WKY rats (body: 208 ± 5 g; bladder: 63 ± 1.3 mg). However, the ratio of bladder weight to body weight was identical in the two strains (SHR 0.031%; WKY rats 0.030%).

Cystometries

Differences between SHR and WKY rats. Repeated cystometries gave reproducible results in both strains, but there was a marked difference in cystometrograms (Fig. 1 and Table 1). SHR had a significantly (P < 0.001) reduced micturition volume (0.4 ± 0.04 ml, n = 8) compared with WKY rats (1.2 ± 0.05 ml, n = 8). The bladder capacity (SHR 0.7 ± 0.05 ml; WKY rats 1.3 ± 0.06 ml) was also reduced in SHR (P < 0.001). The amplitude of nonvoiding bladder contractions, in between micturitions, was significantly (P < 0.05) higher in SHR than in WKY rats (Table 1). The threshold pressure to trigger micturition was slightly, although not significantly, lower in SHR.

Effects of doxazosin in SHR. The hyperactive bladder activity in SHR was reduced by administration of doxazosin (50 nmol). Both intra-arterial (P < 0.05) and intrathecal (P < 0.001; Table 2) doxazosin decreased the micturition pressure and increased bladder capacity (P < 0.001 and P < 0.01, respectively). However, micturition volume remained unchanged, which resulted in an increase (P < 0.01) in residual volume (Table 2). The amplitude of nonvoiding bladder contractions was promptly attenuated (P < 0.01) by intrathecal, but not intra-arterial, administration of doxazosin (Fig. 2). After intrathecal doxazosin, there was an increase in basal (P < 0.001) pressure.

Effects of doxazosin in WKY rats. In WKY rats, the only effect of intra-arterial (n = 6) and intrathecal (n = 6) doxazosin was a decrease in micturition pressure from 75 ± 9 to 67 ± 9 cmH2O (P < 0.05) and from 111 ± 16 to 101 ± 16 cmH2O (P < 0.05), respectively.

Responses in Isolated Tissue

Effects of agonists and nerve stimulation in bladder tissue. There was no difference in K+ (124 mM)-induced bladder contractions between WKY rats and SHR (WKY rats: 26.3 ± 2.0 mM, n = 6; SHR: 24.7 ± 1.6 mM, n = 6). The contractile responses to K+ (18–124 mM), carbachol (0.1 µM–30 µM), substance P (10 nM–10 µM), or α-β-MeATP (0.1 µM–0.1 mM) did not differ between the strains (data not shown). Norepinephrine (0.1 µM–1 mM) did not evoke contractions in bladders from WKY rats, but a weak contractile response to this amine (4.9 ± 1.2% of K+, n = 6, P < 0.01) was found in SHR. In carbachol-precontracted preparations, norepinephrine elicited a relaxant response of −35%. The relaxant response to norepinephrine did not differ between SHR and WKY rats (data not shown).

When norepinephrine was applied to spontaneously developed, myogenic bladder contractions, a concentration-dependent decrease of the activity occurred in WKY rats. At a norepinephrine concentration of 10 µM, the myogenic activity was abolished (n = 6; Fig. 3). In SHR bladders, the response to norepinephrine was biphasic. A decrease of the activity was found at low concentrations, whereas concentrations ≥10 µM stimulated the bladder contractions (Fig. 3). The norepinephrine-stimulated bladder activity in SHR was not affected by isoprenaline (10 µM).

EFS (1–40 Hz) of isolated bladder strips produced frequency-dependent contractions. The response in bladder strips from SHR was significantly lower than in strips from WKY rats at frequencies ≥16 Hz (Fig. 4A). The EFS-evoked bladder contractions were reduced by scopolamine (1 µM) in both SHR and WKY, but ~40% of the response was unaffected by scopolamine. The decrease response to EFS in SHR compared with WKY persisted after treatment with scopolamine (data not shown). In separate experiments (n = 4), it was shown that propranolol (1 µM) and rauwolscine (1 µM) had no
Table 1. Cystometric parameters in awake, freely moving WKY and SHR

<table>
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<tr>
<th></th>
<th>MP, cmH2O</th>
<th>BP, cmH2O</th>
<th>TP, cmH2O</th>
<th>BC, ml</th>
<th>MV, ml</th>
<th>RV, ml</th>
<th>FNVC, min⁻¹</th>
<th>ANVC, cmH2O</th>
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<tr>
<td>WKY (n = 8)</td>
<td>87 ± 12</td>
<td>11 ± 1.5</td>
<td>21 ± 2.6</td>
<td>1.3 ± 0.06</td>
<td>1.2 ± 0.05</td>
<td>0.19 ± 0.03</td>
<td>1.6 ± 0.08</td>
<td>7.1 ± 0.53</td>
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<tr>
<td>SHR (n = 8)</td>
<td>111 ± 14</td>
<td>11 ± 2.4</td>
<td>16 ± 2.0</td>
<td>0.7 ± 0.05*</td>
<td>0.4 ± 0.04*</td>
<td>0.28 ± 0.04</td>
<td>2.8 ± 0.09</td>
<td>28 ± 2.3†</td>
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Results are expressed as means ± SE; n, no. of rats. WKY, Wistar-Kyoto; SHR, spontaneously hypertensive rats; MP, micturition pressure; BP, basal pressure; TP, threshold pressure; BC, bladder capacity; MV, micturition volume; RV, residual volume; FNVC, frequency of nonvoiding contractions; ANVC, amplitude of nonvoiding contractions. For statistical comparisons of data, Student's unpaired t-test (2-tailed) was used. *P < 0.001 and †P < 0.05.

Table 2. Effects of intra-arterial and intrathecal doxazosin (50 nmol) on cystometric parameters in SHR

<table>
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<tr>
<th></th>
<th>MP, cmH2O</th>
<th>BP, cmH2O</th>
<th>TP, cmH2O</th>
<th>BC, ml</th>
<th>MV, ml</th>
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<th>FNVC, min⁻¹</th>
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<tr>
<td><strong>Intra-arterial doxazosin (n = 12)</strong></td>
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<td>Before</td>
<td>131 ± 4</td>
<td>10 ± 0.4</td>
<td>16 ± 0.6</td>
<td>1.0 ± 0.06</td>
<td>0.8 ± 0.04</td>
<td>0.26 ± 0.05</td>
<td>2.1 ± 0.09</td>
<td>19 ± 1.0</td>
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<tr>
<td>After</td>
<td>119 ± 7†</td>
<td>11 ± 0.7</td>
<td>17 ± 1.3</td>
<td>1.4 ± 0.09*</td>
<td>0.8 ± 0.04</td>
<td>0.63 ± 0.07†</td>
<td>2.2 ± 0.16</td>
<td>14 ± 2.4</td>
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| **Intrathecal doxazosin (n = 12)** |
| Before         | 160 ± 9   | 13 ± 1.4  | 20 ± 1.3  | 1.1 ± 0.06 | 0.7 ± 0.04 | 0.31 ± 0.04 | 2.1 ± 0.07  | 24 ± 3.6    |
| After          | 137 ± 7†  | 16 ± 1.2* | 24 ± 2.6  | 1.3 ± 0.04‡ | 0.8 ± 0.03 | 0.52 ± 0.03‡ | 1.8 ± 0.18  | 11 ± 1.4‡   |

Results are expressed as means ± SE; n, no. of rats. For statistical comparisons of data before and after drug administration, Student's paired t-test (2-tailed) was used. *P < 0.001, †P < 0.05, and ‡P < 0.01.
on interneurons in the sacral intermediolateral cell column may mediate the excitatory input to preganglionic parasympathetic neurons (33). In normal Sprague-Dawley rats (11), as well as in SHR and WKY rats (this study), intrathecal or intra-arterial doxazosin decreased micturition pressure. The intrathecal response may be explained by reduced sympathetic outflow to the urethra or by reduced parasympathetic activity, reducing the strength of the micturition contraction. With intra-arterial drug, antagonism of urethral $\alpha_1$-adrenoceptors, decreasing outflow resistance, can be expected to decrease the micturition pressure. Because the same dose of doxazosin (50 nmol) was given intrathecally and intra-arterially, the fact that the intrathecal administration was at least as effective as the intra-arterial administration suggests that part of the effect was exerted at the spinal cord level. In SHR, both intrathecal and intra-arterial doxazosin had pronounced effects and, besides a decrease in micturition pressure, doxazosin increased basal pressure, bladder capacity, and residual volume. The fact that the residual volume increased after administration of doxazo-

Fig. 2. Cystometrogram showing bladder pressure and micturition volume in conscious SHR after intrathecal (it) administration of doxazosin (50 nmol). Note the attenuation of nonvoiding bladder contractions after doxazosin treatment.

Fig. 3. Isolated bladder preparation. Tracings from original recordings of bladder activity in WKY rats (A) and SHR (B), showing the effects of norepinephrine (L-NA) and isoprenaline on spontaneously developed, myogenic bladder contractions.

Fig. 4. Isolated bladder preparations. A: responses to electrical field stimulation in bladder strips from SHR (●) and WKY rats (○). Contractile response is expressed as percent of the response to K$^+$ (124 mM). Effects of norepinephrine (B) and phenylephrine (C) on the contractile response induced by submaximal EFS (20 Hz) in bladder strips from SHR (●) and WKY rats (○). Results are compared with the response before administration of agonists and are expressed as percentage inhibition or increase. Data are given as means ± SE. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$, Student's t-test (SHR vs. WKY rats).
lumbosacral cord involved in the micturition reflex express α₁-adrenoceptors (33). Previous studies have shown that spinal α₁-adrenoceptors were more important in the bulbospinal voiding reflex than in the vesicospinal vesical reflex as revealed by L-dopa- and capsaicin-stimulated hyperactivity, respectively (10). Intrathecally α₁-adrenoceptor blockade was particularly effective in the present study, supporting the view that the bladder hyperactivity in SHR may originate within the bulbospinal voiding pathway. The locus ceruleus has been implicated in the supraspinal control of micturition (7), and the density of α₁-adrenoceptors in this region is higher in young SHR than normal controls (19). Thus the possibility exists that the alteration in bladder function in SHR may be mediated in part by α₁-adrenoceptors in the brain.

The excitatory nerve-evoked responses in isolated bladder strips were impaired in SHR compared with WKY rats. The cause of the decreased response to EFS in SHR is unlikely to be due to postjunctional changes, because no difference was found in response to exogenous administration of carbachol or β-MeATP. The α₂-adrenoceptor selective antagonist rauwolscine did not change the EFS-induced contraction either in SHR or in WKY rats. A decreased concentration of synaptosomal acetylcholine has been reported in bladders obtained from SHR (29), and, therefore, a general decrease of excitatory innervation in bladders from SHR is plausible. However, the mechanisms of the observed changes in neuromuscular regulation of bladder contractility in SHR are presently unknown.

Norepinephrine failed to contract strips of detrusor from WKY rats but elicited weak contractions in preparations from SHR, in line with an increased postjunctional α-adrenoceptor function in SHR. Supporting this, norepinephrine in high concentrations enhanced the spontaneous bladder contractions of strips from SHR, whereas the amine abolished such contractions from WKY rats. The relaxant effects of norepinephrine in carbachol-contracted strips were similar in SHR and WKY rats, suggesting that the adrenoceptor-mediated relaxation (presumably via β-adrenoceptors) was not changed. It has been shown that stimulation of prejunctional α₂-adrenoceptors on cholinergic neurons inhibits acetylcholine release in lower urinary tract smooth muscle (1). In our study, norepinephrine produced a pronounced concentration-dependent inhibition of nerve-evoked bladder contractions in strips from WKY rats while having only minor effects in strips from SHR. This suggests an impaired function of inhibitory prejunctional α₂-adrenoceptors on cholinergic neurons of the SHR bladder. Moreover, facilitatory α₁-adrenoceptors on cholinergic nerves have been described in the rat bladder (22), consistent with findings in the present study. Phenylephrine, selective for α₁-adrenoceptors, caused a concentration-dependent enhancement of electrically evoked bladder contractions in both SHR and WKY rats, the maximal increase being more pronounced in SHR than in WKY rats.

Fig. 5. Isolated urethral preparations. Contractile response to norepinephrine (A) and electrical field stimulation (B) in urethral strips from SHR (●) and WKY rats (○). Contractile responses are expressed as mN/100 mg tissue and are given as means ± SE. *P < 0.05, Student's t-test (SHR vs. WKY).
Higher tissue contents of norepinephrine are found in urethras from SHR compared with WKY rats (28), suggesting increased sympathetic innervation of the bladder outlet. In the present study, urethral preparations from SHR exhibited an increased responsiveness to norepinephrine and an increased contractile activity to nerve stimulation. A similar increased contractile response to norepinephrine is found in several vessels (8) and particularly after inhibition of the neuronal uptake process (4). The mechanisms of the increased urethral contractility were not examined in the present study, but enhanced inositol phosphate formation (30) and increased receptor density (3) have been suggested to contribute to the pronounced α-adrenergic response in SHR smooth muscle. Thus the possibility of an increased urethral resistance contributing to bladder dysfunction in the SHR has to be considered.

NO is the main inhibitory transmitter in the female rat urethra (2, 17). A general alteration in the NO synthesis system appears to exist in vascular smooth muscle of SHR (31), although discrepancies are found in the literature as to whether NO production is increased or decreased in SHR. In the urethra, no differences in sensitivity to SNAP or in NO-mediated neurotransmission were observed between the strains to suggest changes in the urethral NO system.

In conclusion, SHR show cystometric changes including bladder instability. The alterations in SHR bladder function appear to be associated with changes in the noradrenergic control of the micturition reflex. Peripherally, an increased smooth muscle and decreased neuronal responsiveness to norepinephrine was found in SHR. The marked reduction of nonvoiding contractions after intrathecal doxazosin suggests that the bladder overactivity in SHR has its origin, at least in part, in supraspinal and/or spinal structures.

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