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Excitatory and Inhibitory Influence of Pathways in the Pelvic Nerve on Bladder Activity in Rats with Bladder Outlet Obstruction

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Abstract

Objectives—This study was undertaken to investigate whether chronic bladder outlet obstruction (BOO) in female rats influences the tonic parasympathetic excitatory or inhibitory reflex control of bladder activity.

Methods—Bladder activity during isovolumetric cystometry (1.5–12 mL) was examined after transection of dorsal and ventral lumbosacral spinal roots (L4–S4) and administration of hexamethonium, a ganglionic blocking agent, in urethane anesthetized female rats with sympathectomy and BOO.

Results—Lumbosacral dorsal root transection abolished reflex bladder contractions, but did not influence intravesical baseline pressure. However, ventral root transection after dorsal root transection decreased baseline intravesical pressure (y: % change) at low bladder volumes (x) and increased pressure at high volumes. The calculated ($y = 1.9x - 16.5$) transition volume was 9 mL. Administration of hexamethonium (100 mg/kg, intraperitoneally) after dorsal and ventral root transection increased the amplitude and decreased the frequency of myogenic bladder contractions.

Conclusion—The bladder is tonically excited or inhibited depending upon bladder volume by the interactions between a parasympathetic preganglionic pathway in the pelvic nerve and a peripheral reflex. However, in rats with BOO, the volume at which the response shifts from excitation to inhibition was very large, and tonic function of the parasympathetic preganglionic pathway was weak compared to previously reported results in rats without BOO. The persistence of reflex tonic excitatory control of bladder tone over a broad range of bladder volumes may be one of the reasons for overactivity of the bladder with outlet obstruction.

Keywords

bladder outlet obstruction; bladder tone; local reflex; pelvic nerve; ventral and dorsal roots

1. INTRODUCTION

Nerve terminals in the bladder wall contain many neurotransmitters or modulators.¹ Some of these substances can induce bladder contraction and others can inhibit contraction.¹ Recent experiments^{2–4} using a neonatal rat *in vitro* brainstem-spinal cord-bladder preparation or a spinal cord-bladder preparation have revealed tonic inhibitory input to the urinary bladder that arises in the spinal cord at L6–S1 and passes through a peripheral ganglionic synapse. This inhibitory pathway is not dependent upon afferent input from the dorsal roots⁴ or from supraspinal sites.^{2,3} A previous study in adult rats with sympathectomy⁵ revealed that the bladder is also tonically excited or inhibited by a parasympathetic reflex pathway that depends on connections with the lumbosacral spinal cord and the pelvic nerves, and by a local reflex pathway that may be composed of afferent fibers, afferent collaterals and parasympathetic postganglionic neurons. Both the excitatory and inhibitory reflex mechanisms are influenced by bladder volume. Therefore, parasympathetic pathways seem to have important roles, not only during micturition, but also during urine storage.

Bladder outlet obstruction (BOO) in several species, including the rat, is known to induce bladder hypertrophy and hyperactivity.^{6–12} The rat model with BOO has been used to investigate the pathophysiology of human unstable bladder resulting from urethral obstructive diseases, such as benign prostatic hyperplasia.^{6,7} This bladder hyperactivity is related to changes in central reflexes,¹⁰ peripheral changes in the bladder wall, such as alterations in innervation, transmitter content⁸ and receptors,¹² and in the smooth muscle cells.^{9,13,14} Bladder hyperactivity after BOO is accompanied by an increase in acetylcholine and adenosine triphosphate (ATP) release from bladder epithelium.^{15,16} Increased acetylcholine and ATP could activate afferent terminals and subepithelial cells through muscarinic and purinergic receptors, and facilitate the micturition reflex.¹⁷

We examined whether BOO in rats influenced the tonic excitation or inhibition of bladder activity mediated by parasympathetic and peripheral reflex mechanisms. The experiments were performed by transecting the dorsal and ventral lumbosacral spinal roots and by administering a ganglionic blocking agent in rats with sympathectomy and BOO.

2. METHODS

Adult female Sprague–Dawley rats ($n = 10$) weighing 285–350 g were used for the study. The bladder and the proximal urethra were exposed through a lower midline abdominal incision while the animal was under halothane (2%) anesthesia. A double 4-0 silk ligature was placed around the urethra and loosely tied in the presence of an extraluminal plastic rod with a diameter of 1 mm to achieve bladder outlet obstruction.¹¹ The plastic rod was removed after urethral ligation, and the abdominal wall was closed. After 6–8 weeks, the abdomen was opened while the animal was under urethane anesthesia (0.3 g/kg, intraperitoneally and 0.9 g/kg, subcutaneously; total dose 1.2 g/kg) and hypogastric nerves and sympathetic chains were transected bilaterally near the bifurcation of the abdominal aorta. The ureters were transected and their distal ends were ligated. A transurethral bladder catheter (PE-90, 1.27 mm outside diameter; Becton Dickson, Sparks, MD, USA) was used to record the bladder pressure isovolumetrically with the proximal urethral ligated. The catheter was connected to 5 or 20 mL syringes and a pressure transducer through a three-way stopcock. A chart recorder was used to display bladder pressure. As the rat bladder is permeable to saline, but not to soybean oil,¹⁸ the bladder was filled slowly with soybean oil (Food Club) to various volumes (1.5–12.0 mL), which in some experiments evoked isovolumetric bladder contractions, but in all animals maintained intravesical baseline pressure at ≤ 30 cmH₂O. Laminectomy (L1–L4) was performed to expose the spinal roots. When bladder activity stabilized 1 h after bladder infusion, the amplitude and frequency of

spontaneous bladder contractions and intravesical baseline pressure were measured for 10 min intervals to obtain an estimate of control bladder activity. To evaluate tonic functions of the dorsal and ventral roots individually, dorsal root transections were performed first, followed by ventral root transections. Changes in the amplitude and frequency of isovolumetric spontaneous bladder contractions and intravesical baseline pressure were recorded following (i) transection of dorsal or ventral spinal roots (L4–S4) and (ii) administration of hexamethonium bromide (Sigma, St. Louis, MO, USA; 100 mg/kg, intraperitoneally), a ganglionic blocking agent, after the spinal root transections. Transection of the roots and administration of hexamethonium were performed at 30 min intervals, and data after each procedure were obtained for at least 10 min intervals when recordings were stable.

Results are reported as means $\pm$ standard error. Linear regression and Student's *t*-test for paired data were used for statistical data analysis. $P < 0.05$ was considered statistically significant.

3. RESULTS

3.1. Effects of transection of dorsal roots on bladder activity

Dorsal root transections (L4–S4), which were performed first in 10 rats, significantly decreased the amplitude of spontaneous bladder contractions (from 21.2 ± 5.5 cmH₂O to 3.2 ± 0.6 cmH₂O, $P < 0.0001$) and increased the frequency of these contractions (from 1.5 ± 0.3 /min to 2.6 ± 0.2 /min, $P = 0.0053$). Intravesical baseline pressure before transection of dorsal roots ranged from 13 to 30 cmH₂O (mean, 18.3 ± 1.8 cmH₂O). These baseline pressures did not significantly depend upon bladder volume of each animal (x : bladder volume, y : intravesical baseline pressure, $y = 0.8x + 13.9$, $r = 0.5578$, $P = 0.0939$). Changes in intravesical baseline pressure (-2 to $+5$ cmH₂O, -12 to $+33\%$ change) after transection of dorsal roots also did not depend upon bladder volume (Fig. 1).

3.2. Effects of transection of ventral roots on bladder activity after transection of dorsal roots

Transection of ventral roots (L4–S4) after dorsal root transection did not influence the amplitude (3.6 ± 0.7 cmH₂O) and frequency (2.6 ± 0.1 /min) of spontaneous bladder contractions. However, baseline intravesical pressure was affected in a volume dependent manner. In rats in which bladder volumes were ≤ 9 mL, baseline pressure decreased ($n = 8$) or did not change ($n = 1$) (range, 0–3 cmH₂O; 0–15% decrease, $n = 9$) after transection of the ventral roots. When bladder volume was very large (12 mL), which was tested in only one rat, baseline pressure increased (3 cmH₂O increase, 23% increase) after transection of ventral roots. The percent change in intravesical baseline pressure (y) after transection of ventral roots significantly depended upon bladder volumes (x) ($y = 1.9x - 16.5$, $r = 0.6508$, $P = 0.0457$) (Fig. 2). However, the percent change in intravesical baseline pressure (y) (-3 to $+3$ cmH₂O change, -19 to $+23\%$ change) from control conditions with the roots intact to the condition after combined dorsal and ventral root transection did not depend upon bladder volume (x) ($y = 1.8x - 16.1$, $r = 0.5005$, $P = 0.1406$).

3.3. Effect of hexamethonium on bladder activity after dorsal and ventral root transection

Administration of hexamethonium (100 mg/kg, intra-peritoneally) after transection of dorsal and ventral roots in 10 rats significantly increased the amplitude of spontaneous bladder contractions (from 3.6 ± 0.7 cmH₂O to 6.6 ± 0.9 cmH₂O, $P < 0.0001$), but significantly decreased their frequency (from 2.6 ± 0.1 /min to 2.0 ± 0.2 /min, $P = 0.0367$) (Fig. 3). These changes in amplitude and frequency did not depend upon bladder volume. Intravesical

baseline pressure was not influenced (from 17.3 ± 1.6 cmH₂O to 15.7 ± 1.4 cmH₂O) by administration of hexamethonium.

4. DISCUSSION

Our results demonstrate that in the absence of bladder afferent input to the spinal cord, parasympathetic preganglionic pathways in the pelvic nerves and a hexamethonium-sensitive peripheral mechanism tonically regulate bladder activity. The regulation of baseline tone by preganglionic pathways was bladder volume dependent; whereas the regulation of spontaneous contractile activity by a peripheral reflex mechanism was volume independent.

The sympathetic pathways in the hypogastric nerves and sympathetic chains were transected bilaterally in all rats. After transection of the L4–S4 dorsal and ventral roots, which include all afferent and efferent fibers from the pelvic nerves,¹⁹ the bladder was decentralized. In this state, administration of the ganglionic blocking agent hexamethonium resulted in an increase in the amplitude of small spontaneous bladder contractions. This effect of hexamethonium suggested the existence of a peripheral reflex pathway,^{5,20,21} which might be composed of bladder afferents and their collaterals projecting to the pelvic ganglia and postganglionic neurons projecting back to the bladder through the pelvic nerves. This finding is consistent with the results of our previous study using rats with a normal bladder⁵ and an *in vitro* study⁴ using a neonatal rat spinal cord-bladder preparation with transection of the lumbosacral ventral roots, in which electrical stimulation of the lumbosacral afferent roots inhibited spontaneous bladder contractions induced by bladder distension. This inhibition was blocked by administration of hexamethonium, suggesting that afferents activate a peripheral cholinergic inhibitory mechanism. However, because the effects of hexamethonium were not dependent on bladder volume in this study, it is possible that the local reflex pathway does not depend on mechano-sensitive afferent activity induced by bladder distension. Seki et al.²² reported that detrusor smooth muscle cell membranes showed spontaneous electrical activity in a study of normal guinea pig muscle strips. Therefore, the increase in the amplitude of small spontaneous bladder contractions after administration of hexamethonium may mean that desynchronized intrinsic contractile activity of bladder smooth muscle cells was released from the control of inhibitory local reflexes after treatment by hexamethonium.²¹

In our previous study using rats with a normal bladder,⁵ administration of hexamethonium after transection of the dorsal and ventral roots increased the amplitude of spontaneous bladder contractions from 2.6 ± 0.3 cmH₂O to 3.6 ± 0.8 cmH₂O (38% increase). However, in the present study, administration of hexamethonium increased the amplitude from 3.6 ± 0.7 cmH₂O to 6.6 ± 0.9 cmH₂O (83% increase). Igawa et al.²³ also reported that administration of hexamethonium increased the amplitude of spontaneous bladder contractions in awake rats with BOO. Seki et al.²² reported that spontaneous electrical activity of bladder smooth muscle cells obtained from guinea pigs with BOO occurred in only 17.9% of the tissues studied. A gap junction protein, connexin 43, and its mRNA increase in bladder smooth muscle cells of rats with BOO.^{13,14} Therefore, in decentralized conditions after administration of hexamethonium, spontaneous electrical activity of a small number of cells in a bladder with outlet obstruction could spread to many silent smooth muscle cells through gap junctions,^{13,14,24} and this spreading and synchronous electrical activity of many smooth muscle cells could increase the amplitude of spontaneous bladder contractions. This increase in the amplitude of intrinsic spontaneous bladder contractions could increase their duration and result in their decrease in frequency. Therefore, a hexamethonium-sensitive local inhibitory reflex is also tonically functioning in rats with BOO.

When bladder volume was relatively small, transection of the ventral roots after dorsal root transection decreased the baseline pressure. This result implies that inhibitory postganglionic neurons are tonically inhibited, or excitatory postganglionic neurons are tonically facilitated, by afferent collaterals and preganglionic neurons (Fig. 4).⁵ However, when the bladder volume was large, which was tested in only one rat, transection of the ventral roots after dorsal root transection increased the baseline pressure. This result indicates that inhibitory postganglionic neurons were tonically facilitated, or excitatory postganglionic neurons were tonically inhibited, by afferent collaterals and preganglionic neurons under our experimental conditions. After transection of dorsal and ventral roots, postganglionic neurons could only receive input from afferent collaterals. Under these conditions the input to the local efferent neurons may be only partially dependent upon bladder volume. Possible transmitters in the afferent collaterals are acetylcholine, substance P, calcitonin gene-related peptide (CGRP), nitric oxide, pituitary adenylate cyclase-activating polypeptide (PACAP), or ATP, which could activate hexamethonium-sensitive and -resistant receptors.^{8,9,20,25}

When the ventral roots were still intact after dorsal root transection, it is presumed that postganglionic neurons received input from afferent collaterals and preganglionic neurons. In this state, our results indicate that the parasympathetic system has both excitatory and inhibitory effects on bladder activity, depending on the bladder volume. One efferent pathway having two opposing volume-dependent influences on bladder activity may mean that multiple neurotransmitters (inhibitory and excitatory) are released from the same neurons and that the release of these transmitters is differentially regulated by the level of activity in the two input pathways, one or both of which could be influenced by bladder volume. For example, after dorsal root transection, if postganglionic neurons receive a small input from afferent collaterals and a constant input from preganglionic neurons, the total input to postganglionic neurons would not induce bladder volume-dependent excitatory or inhibitory effects. However, ventral root transection after dorsal root transection did actually induce a volume-dependent change of bladder activity, so the constant preganglionic neuronal output may amplify the volume-dependent input from afferent collaterals. In this state, amplified excitatory or inhibitory inputs to postganglionic neurons may induce excitation or inhibition of these neurons, depending on the bladder volume. During the micturition reflex, large-amplitude bladder contractions occur and there is massive firing of preganglionic axons in the pelvic nerves,^{26,27} so the small reflex mechanisms identified by the present study may have a minimal effect on bladder activity.

As mentioned above, preganglionic axons in the pelvic nerves arising in the ventral lumbosacral roots have both excitatory and inhibitory tonic influence on bladder tone in rats. The volume at which the response shifts from excitation to inhibition was calculated to be 9 mL ($y = 1.9x - 16.5$, $x = 1.5 - 12.0$ mL, $y = -15$ to $+23\%$ change, when $y = 0$, $x = 8.7$). In our previous study using rats with a normal bladder,⁵ the volume at which the response shifts from excitation to inhibition after dorsal and ventral root transection was calculated to be 0.9 mL ($y = 44.7x - 40.4$, $x = 0.25 - 1.8$ mL, $y = -56$ to $+46\%$ change, when $y = 0$, $x = 0.9$), which is the same as micturition volume (0.9 mL) in awake rats²⁸ and near threshold volume (0.6 mL) that evokes reflex micturition in urethane-anesthetized rats.²⁹ Therefore, the parasympathetic pathway may act in an excitatory or inhibitory manner, respectively, when the bladder volume is below or above the threshold volume that evokes reflex micturition in rats with a normal bladder.⁵ However, in rats with BOO, tonic efferent output of parasympathetic pathways might be considerably decreased. Dorsal root transection before ventral root transection did not change intravesical baseline pressure in rats with BOO, although in rats with a normal bladder dorsal root transection before ventral root transection changed intravesical baseline pressure in a bladder volume dependent manner.⁵ Therefore, in rats with BOO, the influence of the parasympathetic pathway on bladder tone may be considerably weaker. The inhibitory efferent element of this pathway is speculated

to promote urine storage by keeping the baseline intravesical pressure low. However, the excitatory effect of this pathway on bladder tone seems to be less important, except for reflex contractions induced through this pathway. However, it is possible that the excitatory effect also promotes urine storage by closing the bladder neck and ureteral orifices. In rats with BOO, the pelvic nerve seems to have an excitatory influence on bladder tone until the bladder is filled to a very large volume. Only one rat with a very large intravesical volume (12 mL) showed parasympathetic/peripheral tonic inhibition. The reflex bladder contraction is thought to occur easily when there is the tonic excitation to the bladder, even if the excitation is weak. This may be one of the reasons for overactivity of the bladder with outlet obstruction, as identified in patients with benign prostatic hyperplasia.

5. CONCLUSION

Bladder tone is tonically controlled by a peripheral reflex pathway and a central parasympathetic pathway, both in the pelvic nerve in rats with sympathectomy. These tonic excitatory or inhibitory efferent functions of the pelvic nerve depend upon bladder volume. However, in rats with BOO, excitatory or inhibitory functions of the pelvic nerve on bladder tone are altered so that the bladder volume at which tonic function of the pelvic nerve on bladder tone changes from excitatory to inhibitory is very large. Therefore, tonic excitatory function of the pelvic nerve on bladder tone may contribute to overactivity of the bladder with outlet obstruction.

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Fig. 1. Effect of bilateral L4–S4 dorsal root transection on intravesical baseline pressure in rats with bladder outlet obstruction and intact ventral roots ($n = 10$). Changes in baseline pressure (-2 to $+5$ cmH₂O, -12 to $+33\%$ change) after dorsal root transection did not depend upon bladder volume.

Fig. 2.

Effect of bilateral L4–S4 ventral root transection after dorsal root transection on intravesical baseline pressure in rats with bladder outlet obstruction ($n = 10$). After ventral root transection following dorsal root transection, baseline pressure changed by -3 to $+3$ cmH₂O (-15 to $+23\%$ change). Changes in baseline pressure (fitted by equation $y = 1.9x - 16.5$, where y = bladder pressure and x = bladder volume) depended upon the bladder volume of each animal.

Fig. 3. Effect of hexamethonium after dorsal and ventral root transection on intravesical pressure in a rat with bladder outlet obstruction. The rat bladder was filled with 9.0 mL soybean oil. Intraperitoneal hexamethonium (100 mg/kg) increased the amplitude and decreased the frequency of small myogenic spontaneous bladder contractions in the rat. IVP, intravesical pressure.

Fig. 4.

Potential contribution of bladder afferent fibers and parasympathetic preganglionic and postganglionic fibers in the pelvic nerve to the regulation of bladder activity in the rat with bladder outlet obstruction (BOO). Postganglionic neurons receive a small input from afferent collaterals and a constant input from preganglionic neurons during the urine storage phase. The constant preganglionic neuronal output may amplify the volume dependent input from afferent collaterals. In this state, amplified excitatory or inhibitory inputs to postganglionic neurons may induce excitation or inhibition of these neurons depending on the input volume, although preganglionic neuronal output is weak in rats with BOO. Excitatory and inhibitory synaptic connections indicated by (+) and (-), respectively. DRG, dorsal root ganglion; PG, pelvic ganglion.