Bladder inflammation and hypogastric neurectomy influence uterine motility in the rat

Natalia Dmitrieva, Orenda L. Johnson, Karen J. Berkley*

Program in Neuroscience, Florida State University, Tallahassee, FL 32306-1270, USA

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Abstract

How pathophysiology of one pelvic organ influences the physiology of another is poorly understood. Here we compared the influence of bladder inflammation and hypogastric neurectomy (HYPX) on uterine contractions and bladder reflexes in urethane-anesthetized rats. Uterine contractions were measured via a latex balloon in one uterine horn. Bladder reflexes were assessed by micturition thresholds (MT) obtained cystometrographically. Whereas bladder inflammation significantly increased bladder reflexes (i.e., reduced MTs), it significantly decreased uterine contraction rate. Whereas HYPX produced small significant decreases in MT, it decreased the rate and significantly increased the amplitude of uterine contractions. These results indicate that bladder pathophysiology can influence uterine contractions and that some of this influence may be via the hypogastric nerve. Such viscero–visceral interactions likely involve spinal cord mechanisms and may have considerable clinical relevance. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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Motility patterns of the urinary, gastrointestinal and reproductive tracts are normally coordinated so that their functions do not conflict. For example, micturition and defecation inhibit each other, and are themselves both inhibited during copulation [10,12]. In animal studies, functional coordination between the colon and bladder [4], and between the bladder and uterine cervix [5] appears to involve spinal input from and output to the organs via the hypogastric and pelvic nerves [3,7,12,20].

The existence of physiological viscero–visceral interactions raises the issue of how pathophysiology in one pelvic organ influences functions of the others. Such influences could be profound. For example, dysmenorrhea, interstitial cystitis, irritable bowel syndrome, and fibromyalgia frequently co-occur in various patterns [2]. More specifically, pain crises evoked by ureteral stones in women with severe dysmenorrhea are increased and their cyclical pattern exaggerated compared with non-dysmenorrheic women [9].

To investigate this issue further, the present study used a rat model of acute bladder inflammation [8,13] to compare the influence of bladder inflammation on spontaneous uterine contractions with its influence on micturition reflexes. Because one major source of afferent and efferent innervation of the rat uterine horn is the hypogastric nerve [3,17], and because information about noxious chemoreceptor activation of the bladder is relayed to the spinal cord via the hypogastric nerve [14], the influence of bilateral hypogastric neurectomy (HYPX) on both bladder reflexes and uterine contractions was also compared. The study was done using metestrous rats, because during that estrous stage uterine contractions are regular and well-defined [6] and serum levels of both progesterone and estrogen are relatively low [18].

Female Sprague–Dawley rats, 200–250 g were used, caged individually, and kept on a 12:12 h light–dark cycle. Estrous stage was evaluated by daily vaginal smears. Only rats exhibiting at least three consecutive 4-day cycles before the experimental day were used. The study was done in compliance with NIH policy and was approved by the university’s Animal Care and Use Committee (protocol #0108).

The rats were anesthetized with urethane (1.5 g/kg, i. p.). Throughout the study, corneal and withdrawal reflexes and breathing rate (visually) were continuously monitored, with supplements given when necessary (rarely). Urethane was chosen because of its well-known stability and use in study-
appropriate point in the experiment, each snare could be 4-0 silk suture was loosely tied around each nerve. At the nerves was gently freed from connective tissue. A snare of manipulation, bladder in Fig. 2. Comparison of changes in micturition threshold after no inflammation, or bilateral hypogastric neurectomy (HYPX). (B) Mean changes in the rate of uterine contractions of the same rats. Significance (P < 0.05): for amplitude, repeated measures ANOVA and Dunnett’s tests; for rate, Friedman and Dunnett’s tests. *different from the first hour of that group; (a) different from the uninflamed group during that hour; (b) different from the inflamed group during that hour.

ing both urinary and reproductive organ functions [5,8,17,20]. A ventral midline incision was made to expose the bladder and left uterine horn. In some rats, the hypogastric nerves were identified as they exit caudally from the inferior mesenteric ganglion, and ~1-cm length of both nerves was gently freed from connective tissue. A snare of 4-0 silk suture was loosely tied around each nerve. At the appropriate point in the experiment, each snare could be pulled through the hypogastric nerves to cut them. Two devices were inserted, one into the left uterine horn to measure uterine contractions, and another into the bladder for delivery of inflammatory agents and measuring contractility. Following a 2-mm incision midway between ovary and uterine body, water-filled catheter with a latex balloon on its end (5 × 1.5 mm) was inserted into the uterine lumen. The bladder was catheterized transurethrally with a 1.1-mm polyethylene catheter, and a suture tied around the skin to secure the catheter and prevent leakage [8]. The incision was covered with a saline-dampened pad, and the rat’s temperature maintained at 37.5°C by heating pad and warming lamp. The two catheters were connected to small-volume pressure transducers. The signals were amplified and relayed to strip chart and videotape recorders and a computer programmed locally to analyze cystometrograms (CMG).

For uterine contractility, the frequency and amplitude of spontaneous uterine contractions were recorded as they passed over the uterine balloon, and measured manually from the strip chart records. For micturition reflexes, two types of measures were made: micturition threshold (MT) and contraction rate [8]. MTs were assessed using CMGs, which measured pressure within the bladder while it was slowly filled (0.055 ml/min) via the transurethral catheter. Before beginning each CMG, the bladder was emptied by gentle pressure and drainage. Saline was then infused until a micturition contraction occurred or to a maximum of 1.0 ml. MT was recorded as either the volume that had been infused when the contraction occurred or 1.0 ml if no contraction occurred (rarely). To examine further the effects of HYPX on bladder reflexes, the rate and amplitude of micturition contractions were counted before and after HYPX in bladders of three rats whose bladder had been partially-filled, i.e., slightly above the rat’s MT (0.6–0.65 ml). A baseline rate was calculated every 5 min for a 1 h-period, then HYPX was performed. Two hours later, the bladder was emptied and partially-filled, and micturition contractions counted for another hour. Average amplitude was also measured during the same periods.

For uterine contractility, at least 1 h of baseline recordings of uterine contractions were made. Then, either no manipulation was performed, the bladder was inflamed, or HYPX was done (n = 6 per group). The bladder was inflamed by instilling into it 0.5 ml of 50% turpentine oil (in olive oil) for 1 h. Uterine contractions were then continuously recorded for 7 h. The rate and mean amplitude of the contractions were calculated for 15-min intervals during the baseline period and for each hour after the manipulation. For bladder contractility, 2 or 3 pre-manipulation control CMGs were carried out. Then, either no manipulation (n = 6), bladder inflammation (n = 21), or HYPX (n = 10) was done. One hour later, a series of CMGs were performed at hourly intervals.

With respect to uterine motility, bladder inflammation produced a significant reduction in the rate of uterine

Fig. 1. (A) Mean changes in the amplitude of contractions over an 8-h period after no manipulation (uninflamed), bladder inflammation (inflamed), or bilateral hypogastric neurectomy (HYPX). (B) Mean changes in the rate of uterine contractions of the same rats. Significance (P < 0.05): for amplitude, repeated measures ANOVA and Dunnett’s tests; for rate, Friedman and Dunnett’s tests. *different from the first hour of that group; (a) different from the uninflamed group during that hour; (b) different from the inflamed group during that hour.

Fig. 2. Comparison of changes in micturition threshold after no manipulation, bladder inflammation, or HYPX. Significance (P < 0.001; repeated measures ANOVA and Dunnett’s post hoc test); *different from baseline value of that group; (a) different from uninflamed group during that hour; (b) different from HYPX group during that hour.
contractions, which began 3 h after inflammation and continued over the next 4–5 h, whereas HYPX only tended to reduce the rate (Fig. 1, bottom). In contrast, HYPX significantly increased the amplitude of uterine contractions beginning about 3–4 h post-HYPX, with continuing increases over the next 4 h, while bladder inflammation had no effect (Fig. 1, top).

With respect to micturition threshold, bladder inflammation and HYPX both decreased MTs, but the time courses differed. MTs after HYPX were significantly smaller than baseline values only at the 1 and 2 h time points (Fig. 2). MTs after bladder inflammation were significantly smaller than baseline values from 2–4 h, and were significantly less than MTs of the uninfamed and HYPX groups at 3 and 4 h. There were no changes in either the rate or amplitude of detrusor contractions of the partly-filled bladder for 2 h after HYPX (not shown).

Stated in another way, bladder reflexes were increased (i.e. MT was decreased) following bladder inflammation, as expected from previous studies [8,13]. In contrast, the rate of uterine contractions was reduced following bladder inflammation, with no change in contraction amplitude. Hypogastric neurectomy briefly decreased micturition threshold, whereas it had long-term effects on uterine contractions, decreasing their rate and increasing their amplitude.

The decrease in uterine contraction rate over the first 2–3 h following intravesical turpentine infusion suggests that uterine motility is influenced by the bladder inflammation that is developing during this period [8,13]. The mechanism underlying this viscero–visceral interaction may be similar to that which is thought to underlie interactions between the healthy bladder and colon. In healthy circumstances, bladder distention inhibits colonic motility in the cat, and these effects involve a process in which input from the bladder to the upper lumbar spinal cord via the hypogastric nerve results in an inhibition of the output to the colon via the sympathetic lumbar colonic nerves [4]. In the present study, the effects may involve a similar process in which input from the inflamed bladder to the upper lumbar spinal cord via the hypogastric nerve results in an inhibition of the output to the uterus via the hypogastric nerves. In support are studies in rat showing that afferent activity from noxious chemostimulation of bladder arises via the hypogastric nerve [14], and that stimulation of the distal end of the cut hypogastric nerve can either evoke [17] or inhibit [11] uterine contractions. The results here showing that HYPX decreased the rate but increased the amplitude of rat uterine contractions are consistent with those findings [11,17]. Mechanisms within the spinal cord by which input from the inflamed bladder can decrease the rate of uterine contractions likely involve some component of the complex mixture of inhibitory and excitatory influences on spinal neurons that result from convergence of input from different pelvic organs. Such influences could involve not only segments that receive direct input from and send output through the hypogastric nerve, i.e. T12–L2 [3,16,19], but also intraspinal interactions with segments that are associated with input from and output through the pelvic nerve, i.e. L6/S1 [3,12,20].

Output to the urinary tract via the hypogastric nerves is thought to play a role in the maintenance of urinary continence by acting on the bladder base and urethral sphincters, as well as on detrusor muscle [7,19]. Thus, it would be expected that hypogastric neurectomy would eliminate some of this maintenance and thereby increase bladder activity. The fact that hypogastric neurectomy here had relatively minor, short-lasting effects on bladder reflexes may reflect the fact that performing cystometrograms via transurethral catheter provides assessments mainly of detrusor, not urethral function, and the predominance of detrusor control is via the pelvic nerves [7,12,19].

The effects of hypogastric neurectomy on uterine contractions supports the conclusion that the hypogastric nerve participates in regulation of uterine contractility. The decrease in rate is consistent with studies showing that hypogastric nerve stimulation evokes uterine contractions [17]. The increase in amplitude may be due in part to removal of the hypogastric nerve’s tonic activation of adrenergic receptors. Blockage of beta- and alpha 2-adrenoceptors has been reported to increase the amplitude of uterine contractions [1], whereas specific activation of beta 2- receptors has been shown to relax uterine muscles [15].

In conclusion, the existence of viscero–visceral convergence within the central nervous system has been known for some time [16], and has been studied to improve understanding of mechanisms involved in the coordination of different visceral functions under healthy conditions [4,12]. That pathophysiology of one pelvic organ, such as the bladder, can influence the physiology of another pelvic organ, such as the uterus, is therefore not unexpected, and may have important implications for clinical diagnosis and therapy [9].

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