Organ cross talk modulates pelvic pain

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Rudick CN, Chen MC, Mongiu AK, Klumpp DJ. Organ cross talk modulates pelvic pain. Am J Physiol Regul Integr Comp Physiol 293: R1191–R1198, 2007. First published July 11, 2007; doi:10.1152/ajpregu.00411.2007.—Interstitial cystitis (IC) is a chronic bladder inflammatory disease of unknown etiology that is often regarded as a neurogenic cystitis. IC is associated with urothelial lesions, voiding dysfunction, and pain in the pelvic/perineal area, and diet can exacerbate IC symptoms. In this study, we used a murine neurogenic cystitis model to investigate the development of pelvic pain behavior. Neurogenic cystitis was induced by the injection of Bartha’s strain of pseudorabies virus (PRV) into the abductor caudalis dorsalis tail base muscle of female C57BL/6J mice. Infectious PRV virions were isolated only from the spinal cord, confirming the centrally mediated nature of this neurogenic cystitis model. Pelvic pain was assessed using von Frey filament stimulation to the pelvic region, and mice infected with PRV developed progressive pelvic pain. Pelvic pain was alleviated by 2% lidocaine instillation into either the bladder or the colon but not following lidocaine instillation into the uterus. The bladders of PRV-infected mice showed markers of inflammation and increased vascular permeability compared with controls. In contrast, colon histology was normal and vascular permeability was unchanged, suggesting that development of pelvic pain was due only to bladder inflammation. Bladder-induced pelvic pain was also exacerbated by colonic administration of a subthreshold dose of capsaicin. These data indicate organ cross talk in pelvic pain and modulation of pain responses by visceral inputs distinct from the inflamed site. Furthermore, these data suggest a mechanism by which dietary modification benefits pelvic pain symptoms.

interstitial cystitis; diet

Interstitial cystitis (IC), also known as painful bladder syndrome, is a chronic bladder inflammatory disease with unknown etiology that afflicts as many as 1 million patients in the United States, with females comprising ~90% of patients (21). Symptoms of IC include pelvic and/or perineal pain, urinary frequency, urgency, and nocturia (17, 20, 32, 39). IC is often regarded as a neurogenic cystitis due to voiding dysfunction and the partial efficacy of sacral nerve stimulation or neuropharmacological therapies in some patients that suggests a neuronal component. Supporting this idea, cats are susceptible to feline IC, a disease that closely mimics human IC and is associated with increased activity in the sympathetic nervous system (40). Since IC symptoms can flare in response to certain foods (e.g., tomatoes), dietary modification is commonly employed by IC patients, although evidence of altered urine properties as the mechanism for dietary effects is lacking.

One model of IC pathogenesis involves a positive feedback loop, whereby substance P-containing peripheral nerves stimulate mast cells, in turn releasing inflammatory mediators that induce urothelial inflammation (15). Furthermore, histamine release by mast cells feeds back onto peripheral nerves to cause sustained release of substance P and mast cell activation. Consistent with this model, patients with IC show elevated mast cell counts in the bladder lamina propria and increased levels of urinary histamine metabolites, and lamina propria mast cells are correlated with IC symptoms (1, 4, 14, 24, 33).

The precise mechanism underlying pelvic pain in IC is unclear, but recent studies suggest cross talk between visceral organs of the pelvis (3). For example, mustard oil administered to the uterine horn or colon in female rats induced vascular permeability in the bladder consistent with inflammation at a site distinct from the inflammatory stimulus (41). This cross talk is at least partially bidirectional, because bladder irritation also sensitized the colon to distension stimuli (28), and this noxious effect can be mediated by either chemical or mechanical stimuli (11, 34, 35). It is not known whether neurogenic cystitis also involves cross talk, but these previous findings suggest that organ cross talk may be exploited for therapeutic approaches to pelvic pain.

To examine organ cross talk in neurogenic cystitis, we characterized pelvic pain in a murine model of virally induced cystitis. Inoculation of the tail base muscle with the Bartha’s strain of pseudorabies virus (PRV) was previously shown to induce a mast cell-associated cystitis in rats that was abrogated by either bladder denervation or lesion of the Barrington’s nucleus of the brain stem, which regulates the micturition reflex (13, 18, 19). PRV also induces mast cell-associated cystitis in mice where bladder pathophysiology is driven by a tumor necrosis factor-α-induced chemokine gradient that mediates bladder mast cell trafficking to the lamina propria (8–10). Since PRV neurogenic cystitis in mice mimics key aspects of IC bladder pathophysiology, we also examined pelvic pain in mice in response to mechanical stimuli. A progressive pain developed following PRV infection that was specific for the pelvic region. This pain response was blocked by local anesthetic administration into either the bladder or colon, although inflammation was restricted to the bladder. Conversely, subthreshold colonic capsaicin increased PRV-induced pelvic pain. These data demonstrate a role for organ cross talk in pelvic pain and suggest a novel mechanism supporting dietary approaches to the clinical management of pelvic pain in IC.

METHODS

Animals. Adult female mice C57BL/6J (10–14 wk old) were purchased from Jackson Laboratory (Bar Harbor, ME). All experiments were performed using protocols approved by Northwestern University. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Animal Care and Use Committee. The mice were housed in containment facilities of the Center for Comparative Medicine and maintained on a regular 12:12-h light-dark cycle with food and water ad libitum.

Induction of neurogenic cystitis. PRV was prepared and titrated as previously reported (6). Neurogenic cystitis was induced by injection of 2.29 × 10^9 plaque-forming units of Bartha’s PRV in the abductor caudalis dorsalis (ACD) muscle with a 26-gauge Hamilton syringe while maintaining the animals under isoflurane anesthesia. Ultraviolet-irradiated/heat-inactivated PRV stocks were employed as negative control inocula in sham-treated mice as previously described (8). Both sham and PRV-infected mice were hydrated daily by subcutaneous injection of 3 ml of saline in the shoulder region, because previous experiments indicated that PRV altered fluid intake (Chen MC and Klump DJ, unpublished observations).

Behavioral testing. Mice were tested before PRV administration (baseline) and postinfection days (PID) 1, 2, 3, and 4 after PRV inoculation. Referred hyperalgesia and tactile allodynia was tested using von Frey filaments applied to the abdomen (22, 23) and the plantar region of the hind paw (7, 16). Mice were tested in individual Plexiglas chambers (6 × 10 × 12 cm) with a stainless steel wire grid floor (mouse acclimation period of 20 min before testing). Frequency of withdrawal responses to the application of von Frey filaments to the abdomen was tested using five individual fibers with forces of 0.04, 0.16, 0.4, 1, and 4 g (Stoelting). Each filament was applied for 1–2 s with an interstimulus interval of 5 s for a total of 10 times, and the hairs were tested in ascending order of force. Stimulation was confined to the lower abdominal area in the general vicinity of the bladder, and care was taken to stimulate different areas within this region to avoid desensitization or “wind up” effects. Three types of behavior were considered as positive responses to filament stimulation: 1) sharp retraction of the abdomen, 2) immediate licking or scratching of the area of filament stimulation, or 3) jumping.

Tactile allodynia was tested on the plantar region of the hind paw by using von Frey filaments with forces of 0.04, 0.16, 0.4, 1, and 4 g. The median 50% withdrawal threshold (7, 16) was assessed using the up-down method, where testing was started with the 0.04-g filament applied perpendicularly to the plantar surface of the hind paw until the filament bent slightly. Filaments were tested in ascending order until a positive response was recorded. A positive response to the filament was defined as either a sharp withdrawal of the paw or licking of the test paw. When a positive response was recorded, the next weaker filament was applied, and if a negative response was observed, then the next stronger filament was applied.

Spontaneous behavior was recorded (Sony VAIO USB camera) for 5 min in a clear plastic open-field chamber (18 × 29 × 12 cm) at 96 h after PRV infection and scored for rearing, grooming, and cage crossing to assess general activity (29).

Lidocaine treatment. Lidocaine drug therapy (50 μl) was administered as a 2% lidocaine solution in distilled water that was instilled into the bladder, colon, or uterus via a Hamilton syringe catheter (P10 tubing 1 cm long for the bladder and uterus; rounded-tip needle 3.8 cm long for the colon) while the mouse was maintained under isoflurane anesthesia. All mice were tested for referred hyperalgesia and tactile allodynia using von Frey filaments before and 45 min after lidocaine treatment.

Capsaicin treatment. Capsaicin (50 μl) was administered as either a 0.03% or 0.3% solution (dissolved in 10% ethanol, 10% Tween 80, and 80% saline) instilled into the colon via a Hamilton syringe catheter (rounded-tip needle 3.8 cm long) while the mouse was maintained under isoflurane anesthesia. All mice were tested for referred hyperalgesia and tactile allodynia using von Frey filaments before and 20 min after capsaicin treatment.

Histology. Following euthanization, mice were perfused with 10% neutral buffered formalin. Bladder and distal colon (4 cm proximal to rectum) tissues were then removed and processed by fixation and sectioning in the Pathology Core Facility, Northwestern University. Hematoxylin- and eosin-stained tissues were assessed by light micros-
copy on a Nikon E800 microscope equipped with a Spot Color RT camera.

Evans blue extravasation. Vascular permeability was assessed by measuring Evans blue dye extravasation. Evans blue (30 mg/kg in phosphate-buffered saline) was administered intravenously via the tail vein and allowed to circulate for 30 min before euthanization. Bladders and colons were harvested, weighed, placed into 1 ml of formamide (Sigma), and incubated for 24 h at 60°C. Extravasation was quantified by measuring absorbance (A620) relative to a standard curve of dye.

PRV plaquing assay. Following infection of mice with PRV, tissues were harvested at PID5 and then homogenized in sterile PBS. Urine from PID5 mice and the homogenates from the lumbar portion of the spinal cord and bladder were plated on confluent cultures of porcine PK15 cells in six-well plates. Wells were then covered with DMEM with sodium bicarbonate containing 2% methylocellulose, 2% fetal bovine serum, and 1% penicillin-streptomycin (5). The plate was incubated at 37°C for 3 days until PRV colony-forming units were observed. Finally, the methylocellulose was aspirated from the plate. The wells were rinsed with PBS and stained with methylene blue to visualize the PRV-induced plaques. The plaques were visualized on a trans-illuminator, and the images were acquired using a Nikon CoolPix digital camera.

Statistical analyses. Results are means ± SE and were analyzed for statistical significance with the use of a single-factor ANOVA. A value of $P < 0.05$ was considered statistically significant. For experiments without pharmacological manipulation (see Fig. 1), statistical comparisons were performed for each filament (e.g., baseline vs. PID3 for the 4.0-g fiber, or baseline vs. PID3). For experiments employing lidocaine or capsaicin (see Figs. 3 and 5), the total events were summed for all filaments for individual animals, and the baseline for the individual was subtracted from the experimental events; the net change in responses for each animal was then averaged across all animals in an experimental group to determine the mean ± SE for that group.

RESULTS

PRV induces pelvic pain. To assess tactile sensitivity, mice were stimulated with von Frey filaments (7, 22). Mechanical stimulation of the pelvic area of sham-treated mice resulted in a response frequency that correlated with the applied force, and this response profile did not change during the 5-day course of the experiment (Fig. 1A). In contrast, although PRV-infected mice exhibited the same baseline response, the response frequency to pelvic stimuli was significantly greater by PID2 (Fig. 1B; $P < 0.05$). The increase in pelvic sensitivity became even more significant at PID4 ($P < 0.01$). To assess the specificity of PRV-induced tactile sensitivity, we also quantified the 50% threshold sensitivity in the paw. PRV induced no changes in tactile sensitivity of the plantar region of the hind paw (Fig. 1C).

To confirm that the effects of PRV were specific to pain behavior, we also quantified normal behaviors during free roaming (Table 1). PRV induced no significant differences in grooming, cage crossing, or rearing, suggesting that pelvic pain is not due to generalized increases in all behaviors. Similarly, the absence of detectable weight change indicates that PRV is not associated with dramatic changes in gross physiology (Table 2). These data suggest that PRV induces a progressive pain in the pelvic area that does not occur in the footpad, indicating pain specific to the pelvic region.

Pelvic pain is neurogenic. To confirm that the effects of PRV are centrally mediated in the mouse, we harvested urine, bladder, and lumbar spinal cord tissues on PID5 from PRV- and inactivated PRV-infected mice. Tissue homogenates were then plated onto porcine PK15 cells to detect infectious virions. No plaques were visible in PK15 cultures exposed to urinary or bladder extracts (Fig. 2). Plaques corresponding to

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No significant difference was observed between control and pseudorabies virus (PRV)-infected mice.
lysed cells (exposed plastic surrounded by cells exhibiting cytopathic effect; see inset) were detected only in PK15 cultures exposed to homogenates of tissue dissected from the lumbosacral portion of the spinal cord in PRV-infected mice (n = 4) but not sham mice (n = 2). These data demonstrate that PRV infection is restricted to neuronal tissues and support the idea that PRV-induced cystitis is neurogenic in the murine model.

*Lidocaine attenuates PRV-induced bladder pain.* One clinical treatment that offers temporary relief of chronic pain in patients with IC is instillation of 2% lidocaine directly into the bladder (27). This treatment modality presumably works by quelling C-fiber activity associated with IC bladder pathophysiology. We used a similar strategy to localize the source of pelvic pain induced by PRV in the murine neurogenic cystitis model by instilling 2% lidocaine into the bladder at PID3. Lidocaine instilled into the bladder significantly reduced the response frequency to mechanical stimulation with von Frey filaments by ~68% (15.4 ± 2.6 vs. 4.8 ± 2.5 responses; P < 0.05), whereas control animals instilled with saline did not exhibit a significant reduction (compare Fig. 3, A and D). The anesthetic effects were specific to pelvic pain, because lidocaine instillation did not alter sensitivity to stimulation of the paw (Table 3).

*Cross talk in pain relief.* There is a growing literature demonstrating “cross talk” between the bladder and the colon at the level of neural signaling (34, 35), and this neuronal cross talk likely also involves the uterus (41). To test the possible role of such cross talk in the development of pelvic pain behavior, we also assessed pelvic sensitivity to mechanical stimuli following instillation of 2% lidocaine into the colon or uterus. Lidocaine instilled in the colon significantly reduced the response frequency to applied von Frey filaments by ~63% (16.0 ± 2.5 vs. 6.0 ± 2.2 responses; P < 0.05), whereas control animals instilled with saline did not exhibit a significant reduction (compare Fig. 3, B and E). However, lidocaine instilled into the uterus did not significantly reduce the pelvic pain response at any point, although overall sensitivity was diminished ~28% (Fig. 3F; 17.2 ± 3.1 vs. 12.5 ± 3.2 responses; P > 0.05). A separate group of animals was instilled with lidocaine in both the bladder and colon, but pain relief was not significantly different from either bladder or colon lidocaine alone (Fig. 3C; 13.9 ± 2.6 vs. 4.0 ± 0.8 responses; P > 0.05). Lidocaine induced no significant changes in tactile

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**Fig. 3.** Bladder or colon lidocaine attenuates PRV-induced pelvic pain. Referred visceral hyperalgesia was measured as responses to mechanical stimulation of the pelvic region with von Frey filaments of 5 intensities. Responsiveness was characterized at baseline, PID3 following PRV infection, and 45 min following administration of saline or 2% lidocaine on PID3. Instilling 50 μl of lidocaine into the bladder (A; n = 10) or colon (B; n = 6) reduced pelvic pain responses (P < 0.05), whereas uterine lidocaine (F; n = 6) had no significant effect. Instilling saline into the bladder (D; n = 4) or colon (E; n = 4) had no effect on pelvic pain. Lidocaine administered to both the bladder and colon (C; n = 8) did not cause greater pelvic pain reduction than treating either site individually (P > 0.05). Data are mean percentages of response frequency (±SE).
sensitivity (50% threshold) of the plantar region of the hind paw when instilled into the colon or uterus (Table 3). These data together suggest that pelvic pain associated with neurogenic cystitis is relieved equally by intervention at either the bladder or colon.

PRV-induced inflammation is specific to the bladder. The involvement of the colon in PRV-induced pelvic pain raises the possibility that gut-associated pain is due to nonspecific actions of PRV that also induce colon inflammation. To assess this possibility, pathology and vascular permeability were characterized in stained tissue sections of the bladder and distal colon. Although many areas appeared histologically normal in bladders of mice infected with PRV, focal areas exhibited dilated blood vessels, leukocytic infiltrate, and signs of edema at PID5 (compare Fig. 4, A and B), consistent with previous characterization of bladder inflammation in the murine neurogenic cystitis model (8). In contrast, colon tissue from PRV-infected mice was indistinguishable from normal tissue and showed no evidence of edema, vascular changes, leukocytic infiltrate, or damage to the epithelium or lamina propria or smooth muscle (compare Fig. 4, C and D). These data suggest that the inflammation induced by Bartha’s PRV in the murine neurogenic cystitis model is specific to the bladder and does not extend to the distal colon.

Edema is a common feature of inflammation that results from increased vascular permeability, yet evaluating subtle signs of edema can be difficult. Vascular permeability associated with pelvic inflammation has been previously characterized by examining extravasation of Evans blue dye from the circulation into tissues (8, 18, 41). We quantified Evans blue dye extravasation in the bladder and colon of PRV-infected mice at PID5. Consistent with previous findings (8), PRV induced significant dye extravasation in the bladders of PRV-infected mice relative to sham-infected controls, demonstrating increased vascular permeability consistent with cystitis (Fig. 4E; P < 0.05). In contrast, dye extravasation in colonic tissue

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<td>Baseline</td>
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<td>Bladder</td>
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<td>Colon</td>
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<td>Bladder and colon</td>
<td>Lidocaine</td>
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<td>Uterus</td>
<td>Lidocaine</td>
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<td>Colon†</td>
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<td>Colon†</td>
<td>Capsaicin (0.3%)</td>
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N/A, not available (mice were not infected with PRV). No significant difference was observed among values at baseline (no treatment), postinfection day (PID) 3 (no treatment), or at PID3 with the treatment indicated.

Fig. 4. PRV-induced inflammation is specific to the bladder. Bladders of PRV-infected mice exhibit inflammation (B) relative to sham-infected mice (A), yet no differences were noted in colon tissues of sham-treated (C) and PRV-infected mice (D) at PID5. Scale bars represent 50 (A and B) or 100 µm (C and D). E: vascular permeability was assessed by measuring Evans blue dye extravasation from bladders and colons in sham- and PRV-infected mice (open and filled bars, respectively). PRV induced significant dye extravasation in the bladder (*P < 0.05), yet no extravasation was induced in the colon (n = 11).
of the same PRV-infected mice was not significantly different from sham-infected controls (Fig. 4E; \( P > 0.05 \)). The absence of colon inflammation is not likely due to failure of PRV to reach gut-specific spinal circuits during the course of our experiments, because studies of Jasmin et al. (18) demonstrated PRV ascending from the ACD to the spinal cord within 48 h. Therefore, these data corroborate the histological findings, supporting the observation that the PRV-induced neurogenic inflammation that mediates pelvic pain is specific to the bladder and does not extend to the colon.

**PRV-induced pain is increased by colonic stimulation.** Since lidocaine instillation into the colon suggested the capacity for negative modulation of bladder-associated pain, we next examined whether the gut could positively modulate pelvic pain. Previous studies demonstrated that colonic 0.03% capsaicin was insufficient to evoke pain behavior or induce inflammation in NMRI mice (22, 23), so we first confirmed that female B6 mice exhibit similar sensitivity to colonic capsaicin. Instillation of 0.3% capsaicin into the colon significantly increased the response frequency to mechanical stimulation with von Frey filaments (\( P < 0.05 \)), whereas animals instilled with 0.03% capsaicin exhibited no change in pelvic sensitivity compared with baseline (Fig. 5, A and B), confirming the subthreshold activity for the lower dose. These effects were also specific to the pelvic region, because colonic capsaicin instillation did not alter sensitivity to stimulation of the paw (Table 3). In contrast to control mice, instillation of 0.03% capsaicin significantly increased pelvic sensitivity in PRV-infected mice at PID3 (Fig. 5C; 11.3 ± 1.2 vs. 17.7 ± 2.2 responses; \( P < 0.05 \)). Although we cannot rule out the possibility that PRV increases the sensitivity of colonic C-fibers to capsaicin (25), these data demonstrate that subthreshold noxious stimuli in the colon can positively modulate pelvic pain associated with bladder inflammation.

**DISCUSSION**

We report that a murine model of neurogenic cystitis induces a progressive pain specific to the pelvic area. This neurogenic cystitis is associated with inflammation and edema specific to the bladder but not the colon. In addition, lidocaine instilled into the bladder, colon, or bladder and colon together significantly attenuated this pelvic pain, whereas lidocaine administered to the uterus did not. These findings have implications for modeling pelvic pain syndromes, understanding mechanisms of organ cross talk, and managing pelvic pain associated with IC.

PRV neurogenic cystitis induces pain behavior specific to the pelvic region, and pelvic pain is also induced in animal models by direct chemical stimulation of visceral organs or by chemical cystitis that follows systemic administration of cyclophosphamide (CYP). Using von Frey filaments, pelvic pain responses were observed following colonic mustard oil or capsaicin, but these treatments also elevated pain in the hind paw (22, 23). CYP-induced cystitis is an important and versatile cystitis model, because CYP can be administered differentially to induce distinct chronic or acute inflammation (12, 16). Consistent with the development of cystitis, CYP also induced pelvic pain behavior. However, CYP-induced pain behavior was not specific to the pelvic region, because hind paw sensitivity also increased (16, 23). Since we observed no increase in paw sensitivity associated with PRV infection, PRV-induced
pain is specific to the pelvic region. This conclusion is bolstered by the finding that spontaneous behaviors (e.g., cage crossings) were not influenced by PRV, suggesting that pelvic specificity of PRV-induced pain is not attributable to general or peripheral neuropathy that may mute paw responses. Therefore, PRV neurogenic cystitis offers the unique advantage of pelvic specificity when modeling referred visceral pain behavior.

Previous studies demonstrate neural cross talk between visceral organs in response to noxious stimuli (28, 34, 35, 41). For example, colonic irritation results in bladder inflammation in rats (28, 34, 35, 41). PRV-induced inflammation appears specific to the bladder, because we observed no changes in colon histology or dye extravasation, suggesting directionality in inflammatory cross talk. This finding is consistent with previous observations of bladder inflammation resulting from colonic administration of mustard but an absence of reciprocal inflammation following bladder mustard oil (41). Collectively, these data suggest that the bladder is more vulnerable to cross-organ inflammation than the colon or uterus. It has been postulated that neuronal cross talk between visceral organs is unidirectional and is only propagated from the colon or uterus to the bladder. This is supported by studies showing that bilateral hypogastric neurectomy reduced Evan’s blue dye extravasation in the inflamed colon and uterus while failing to reduce bladder extravasation. Furthermore, hypogastric neurectomy did not block the small increase in bladder-induced inflammation of the colon, whereas the colon or ureter-induced bladder inflammation was significantly reduced (41). An alternative hypothesis is that neural cross talk is bidirectional, but inflammatory homeostatic mechanisms are greater in the gut. This possibility is consistent with the considerable homeostatic mechanisms necessary to regulate the high density of lymphoid tissues in the gut in the presence of vast inflammatory contents in the gut lumen, whereas the bladder is typically sterile and therefore does not require such robust homeostatic influences. In support of this hypothesis, colitis is observed in mice defective in homeostatic Treg cell responses (reviewed in Ref. 2), but cystitis has not been reported.

Our observations of pelvic pain relief following intravesical lidocaine administration are consistent with clinical findings where patients with severe IC experience temporary relief of pelvic pain by instillation of 2% lidocaine into the bladder (27). In addition, we found that colonic lidocaine relieves pelvic pain associated with neurogenic cystitis, an observation that is reminiscent of irritable bowel patients who experienced relief of both rectal symptoms and abdominal pain from lidocaine administered to the colon (36, 37). This cross talk in pelvic pain relief likely reflects pelvic innervation, and three different mechanisms have been postulated: nerve branching, the dorsal root reflex, and visceral afferent convergence on spinal interneurons. Several studies have reported evidence of single afferent fibers branching to supply both the bladder and colon (34, 35, 41). In addition, visceral organs can interact via the dorsal root reflex, where presynaptic effects at one sacral afferent can act antidiromically via an interneuron to activate other sacral afferents (31). Finally, convergence of bladder and colon primary afferents onto spinal cord interneurons has been reported, with ~30% of lumbosacral spinal neurons receiving convergent inputs from both the bladder and colon in rats and cats (26, 30). By whichever mechanism, the findings of cross talk pain relief suggest a potential model for pelvic pain that has important implications for management of pain symptoms in IC.

Our findings of pelvic pain modulation at a site distinct from inflammation suggest that pelvic pain behavior results from the summation of visceral inputs. For IC patients, this summation model suggests that relatively minor gut stimuli, which otherwise cause no symptoms, would exacerbate established, bladder-driven pelvic pain, because even slight increases of inputs from a second site (i.e., the gut) might lead to a sum of inputs that is considerably elevated above a threshold necessary to induce pain. This possibility is consistent with the documented association of IC with bowel symptoms and the use of dietary alterations for managing the severity of IC symptoms (38). Although dietary management shows efficacy for some IC patients, the precise mechanism by which dietary changes might act on the bladder via urine composition has remained unclear. Our data are consistent with an alternative hypothesis that dietary changes may act at the gut, thereby modulating the sum of visceral inputs that contribute to pelvic pain in IC.

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