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Segmental Hyperalgesia to Mechanical Stimulus in Interstitial Cystitis/Bladder Pain Syndrome: Evidence of Central Sensitization

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Abstract

Purpose—We investigate if subjects with interstitial cystitis/bladder pain syndrome demonstrate mechanical or thermal hyperalgesia, and whether the hyperalgesia is segmental or generalized (global).

Materials and Methods—Ten female subjects with interstitial cystitis/bladder pain syndrome and 10 age matched female controls without comorbid fibromyalgia or narcotic use were recruited for quantitative sensory testing. Using the method of limits, pressure pain and heat pain thresholds were measured. Using the method of fixed stimulus, the visual analog scale pain experienced was recorded when a fixed pressure/temperature was applied.

Results—The visual analog scale pain rated by female subjects with interstitial cystitis/bladder pain syndrome was significantly higher than that rated by female control subjects when a fixed mechanical pressure (2 or 4 kg) was applied to the suprapubic (T11) area ($p = 0.028$). There was an up shift of the stimulus-response curve, which corresponded to the presence of mechanical hyperalgesia in the suprapubic area in interstitial cystitis/bladder pain syndrome. However, the visual analog scale pain rated by subjects with interstitial cystitis/bladder pain syndrome was not different from that rated by controls when a fixed pressure was applied at the other body sites (T1 arm, L4 leg, S2-3 sacral). No difference in visual analog scale pain rating was noted when a fixed heat stimulus (35C or 37C) was applied to any of the body sites tested (T1, T11, L4, S2). There was no difference in pressure pain thresholds or thermal pain thresholds between subjects with interstitial cystitis/bladder pain syndrome and controls.

Conclusions—Female subjects with interstitial cystitis/bladder pain syndrome showed segmental hyperalgesia to mechanical pressure stimulation in the suprapubic area (T10-T12). This segmental hyperalgesia may be explained in part by spinal central sensitization.

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Keywords

cystitis, interstitial; hyperalgesia; central nervous system sensitization; pain measurement

INTERSTITIAL cystitis/bladder pain syndrome is characterized by hypersensitivity to bladder distention. At any given volume of bladder filling, subjects with IC/BPS reported significantly higher rating of bladder pain on a visual analog scale compared to control subjects without IC/BPS.¹ Although bladder hyperalgesia is a hallmark feature of IC/BPS, it is unclear if patients with IC/BPS have generalized hyperalgesia outside of the pelvis. Previous studies have examined pain thresholds in mixed populations of subjects with IC/BPS and did not account for the presence of other comorbid syndromes^{2,3} or other variables such as narcotic use. These studies revealed lower pressure pain thresholds compared to controls in sites distant from the bladder⁴ and less tolerance to ischemic stimuli but no difference in thermal pain measures.^{4,5} Fitzgerald et al showed that the perception thresholds to nonpainful electric current on the skin in subjects with IC/BPS were no different than those in controls in the C5, T6, T10, T12 and S3 dermatomes, and no global differences were present in the warmth perception threshold or vibration perception threshold in the IC/BPS group compared to controls.¹ However, subjects with IC/BPS did report more intense sensations in the T12 and S3 dermatomes when subjected to a sustained suprathreshold thermal stimulus.⁶ Overall the reported literature is conflicting with respect to the presence of hyperalgesia in IC/BPS.

Therefore, in this study we investigate 1) if subjects with IC/BPS demonstrate mechanical or thermal hyperalgesia, and 2) whether the hyperalgesia is segmental (more pronounced in T10-T12 or S2-S4) or global (also involving the extremities). To avoid factors known to alter sensory processing, a sample of subjects with IC/BPS was enrolled which was free from the comorbidity of fibromyalgia or from daily narcotic use.

MATERIALS AND METHODS

Subjects

A total of 10 female subjects with a clinical diagnosis of IC/BPS and 10 age matched female healthy volunteers (controls) were recruited for QST. Subjects with IC/BPS had pain, pressure or discomfort perceived to be related to the bladder and/or pelvis in the last 6 months, with associated urinary symptoms such as frequency or urgency.⁷ All subjects with IC/BPS underwent a urological evaluation including history and physical examination, and completed questionnaires including the ICSI and ICPI (IC Symptom Index and IC Problem Index),⁸ PUF (Pelvic Pain and Urgency/Frequency questionnaire)⁹ and GUPI (Genitourinary Pain Index questionnaire).¹⁰ Subjects with a diagnosis of fibromyalgia or those who used narcotic pain medication were specifically excluded from the study. All participants signed an informed consent and were reimbursed for their effort. The study was approved by the institutional review board of Washington University. Subject demographics are listed in the table.

Mechanical Pain Threshold Determination

A handheld pressure algometer with a 1 cm² flat probe was used to deliver a steadily increasing and quantifiable pressure to underlying muscle/deep tissues (Algomed, Medoc Ltd, Minneapolis, Minnesota). The method of ascending limits was used.¹¹ Subjects were instructed to press a button when the first sensation of pressure pain occurred (pressure pain threshold). Subjects underwent a training session before testing. Each body site was stimulated 3 times and the average was calculated. The sites were 1) T1: upper extremity—ulnar surface of the forearm, halfway between the wrist and elbow; 2) T11: suprapubic—midline between the umbilicus and pubic symphysis; 3) L4: lower extremity—medial surface of the leg, halfway between the knee and ankle; 4) S2: sacral dermatome—posterior medial surface of upper thigh and 5) S3: perineum—midline perineum behind the scrotum and anterior to anus in males, behind posterior introitus and anterior to anus in females.

Heat Pain Threshold Determination

A 9 cm² Peltier thermode with a flat contact surface (Pathway ATS, Medoc Ltd) was used to deliver increasing heat to the skin (an increase of 1C per second) after the skin was initially habituated at a baseline temperature of 32C. Subjects were given the instruction to “push the button the moment you begin to feel pain” (heat pain threshold). The thermode rapidly returned to the baseline temperature. Each body site was stimulated 3 times and the average was calculated. The same 4 sites previously described were tested. Due to concern of genital burn the perineum site (S3) was not heated.

VAS Pain Rating During Fixed Intensity Stimulus Testing

Since the anticipation of a predictable stimulus of increasing intensity (method of ascending limits) may bias the pain threshold reporting in some subjects with IC/BPS (eg those with anxiety, hypervigilance or catastrophizing),¹² we also applied a random sequence of fixed intensity stimulus (2 or 4 kg, 35C or 37C) to the body sites (method of constant stimulus). Immediately after the stimulus was applied the subjects were asked to rate the pain severity on a sliding ruler with a VAS from 0—no pain to 10—worst pain. The averages of 3 VAS ratings were used.

Statistics

Pressure pain thresholds and heat pain thresholds (dependent variables in figure 1) were compared independently using 2-tailed t-tests at each of the body sites to look for patient group effects (factor was IC/BPS vs controls). Post hoc Mann-Whitney tests were performed. VAS pain ratings (dependent variables in figure 2) at each of the body sites were compared using 2-factor ANOVA. The 2 factors were patient groups (IC/BPS vs controls) and stimulus intensity (2 vs 4 kg, or 35C vs 37C). Interactions

RESULTS

Pressure Pain Threshold and Heat Pain Threshold

The pressure pain thresholds of female subjects with IC/BPS were not statistically different from those of female control subjects at any of the body sites tested in T1 (arm), T11

(suprapubic), L4 (leg) and S2-3 (sacral) (fig. 1, A, 2-tailed t-test). Although the T11 pressure pain thresholds of subjects with IC/BPS appeared to be lower than those of controls (mean \pm SEM 201.5 ± 21.8 vs 260.2 ± 30.9 kPa), the difference was not statistically significant ($p = 0.14$). A post hoc analysis using the Mann-Whitney test did not reveal any statistical difference at T11 ($p = 0.28$) or any of the other sites. The heat pain thresholds of female subjects with IC/BPS were not different from those of female control subjects (fig. 1, B, 2-tailed t-test with Mann-Whitney test).

Pain Rating with Fixed Mechanical or Thermal Stimuli

The VAS pain rated by female subjects with IC/BPS was significantly higher than the VAS pain rated by female control subjects when a fixed mechanical pressure (2 or 4 kg) was applied to the suprapubic (T11) area (fig. 2, A, 2-factor ANOVA, significant group difference between IC/BPS and controls with $p = 0.028$, significant difference between stimulus intensity with $p = 0.0005$, no interaction between the 2 factors with $p = 0.93$). There was an up shift of the stimulus-response curve which corresponded to the presence of mechanical hyperalgesia in the suprapubic area in the IC/BPS group.

In contrast, the VAS pain rated by subjects with IC/BPS was not different from that rated by controls when a fixed pressure was applied at the other body sites (eg the sacral S2 and leg L4 areas, fig. 2, B and C). The VAS pain rated by subjects with IC/BPS was also not significantly different from that rated by controls when a fixed heat stimulus (35C or 37C) was applied to any of the body sites tested including the suprapubic (T11) area (fig. 2, D-F).

DISCUSSION

This study demonstrated that IC/BPS is characterized by psychophysical evidence of hypersensitivity to mechanical pressure applied to the suprapubic area. Mechanical hyperalgesia was demonstrated in the suprapubic area (T10-T12) but not in the sacral area (S2-S4) or in the upper and lower extremities. Thermal heat hyperalgesia was not observed in any of the body sites. These findings do not support generalized (global) hyperalgesia in IC/BPS in those modalities.

Segmental hyperalgesia was noted in the T10-T12 area, which corresponds to the most common site of pain referral reported by patients and during experimental bladder filling (in 83% and 80% of patients with IC/BPS, respectively).^{1,13} This segmental hyperalgesia may be explained in part by the development of central sensitization of the viscerosomatic convergent neurons in the T10-T12 dorsal horn, which receive afferent signals from the bladder (viscera) and T10-T12 somatic structures. Chronic nociceptive signals from the bladder to the central nervous system could lead to increased excitability of T10-T12 spinal convergent neurons (central sensitization) and, thus, augment the gain of spinal transmission of somatic signals. This is manifested clinically as the development of secondary mechanical hyperalgesia to the area of referred pain (T10-T12) in a topographically organized segmental pattern (fig. 3).^{14,15}

Viscerosomatic hypersensitivity has previously been demonstrated in humans. For example, exposure of the lower esophagus to acid stimulation induces central sensitization, leading to

viscerovisceral (pain hypersensitivity in the upper esophagus) and viscerosomatic hypersensitivity (allodynia of the chest wall).¹⁶ Yang et al demonstrated segmental hyperalgesia in S2-S3 (perineum) but not in L2-L3 (lower extremity) in subjects with chronic prostatitis.¹⁷ The authors attributed this segmental hyperalgesia to central sensitization of sacral DH neurons. Although the findings in this study are more consistent with localized processes such as spinal central sensitization, involvement of global mechanisms such as alteration of descending modulation of the spinal gate, or convergence/sensitization at supraspinal levels cannot be completely ruled out.^{18,19} S2-S4 convergent neurons presumably also receive afferent signals from the bladder and sacral structures. However, we did not observe secondary hyperalgesia in the S2-S4 referral area. We do not know whether the observed difference between T10-T12 and S2-S4 represents a biological difference. Of note, our findings are consistent with those of Lowenstein et al, who also found a difference in the T12 dermatome but not in S3.⁶

Another potential explanation of the hypersensitivity was that the pressure applied in the suprapubic region could have been pushing onto the bladder itself (primary bladder hypersensitivity). However, this seems unlikely as subjects were asked to empty the bladder before testing and none complained of increased urgency or pressure to urinate when the algometer was applied to the suprapubic area. Patients with IC/BPS commonly reported that tight clothing worsened their pain, which suggested that there is at least some cutaneous hypersensitivity.^{20,21}

Our pressure pain testing results were different from those of Ness et al, who found significantly lower pressure pain thresholds in the trapezius, masseter and ulnar muscle sites compared to controls.⁴ The reason for this discrepancy was not clear, but possible explanations include 1) differences in symptom severity, 2) absence vs presence of comorbid fibromyalgia and 3) shorter duration of symptoms.

Subjects in our study had lower ICSI (11.2 ± 1.5 vs 14.3 ± 0.8) and ICPI (8.9 ± 1.2 vs 11.4 ± 0.5) scores than in the study by Ness et al. Our cohort had moderate symptoms while that of Ness et al had more severe symptoms. In addition, we specifically excluded patients with comorbid fibromyalgia while Ness et al did not. Fibromyalgia is characterized by widespread tenderness to touch and tender points throughout the body, and there is high degree of comorbidity between IC/BPS and fibromyalgia.^{2,3} Therefore, we believe the expected decrease in pressure pain thresholds might skew the results of pressure pain testing. It was unknown how many patients in the study by Ness et al had fibromyalgia since that factor was not assessed. If their cohort was enriched with these patients, it might explain the difference in pressure pain thresholds.

There is evidence in the literature that fibromyalgia can influence QST results. Chang et al showed that subjects with irritable bowel syndrome with comorbid fibromyalgia have generalized hyperalgesia, whereas subjects with irritable bowel syndrome without fibromyalgia have somatic hypoalgesia compared to controls.²² In addition, only 1 of our subjects had IC/BPS symptoms for more than 3 years (12.85 years). In fact, 2 of our subjects had IC/BPS symptoms for less than 12 months but more than 6 months. Most of our cohort can be considered relatively early cases of IC/BPS, which may also explain why there is

evidence to suggest spinal central sensitization (segmental hypersensitivity) but not yet global hypersensitivity.

There were apparently different results presented in part A of figure 1 (no difference in pressure pain thresholds at T11) and of figure 2 (difference in VAS pain ratings at T11) from the same patients. This finding should not be considered a contradiction or a lack of results. In fact, it illustrates an observation in quantitative sensory testing of some patients with chronic pain that measurements of pain threshold values (the bare first perception of pain) may not distinguish IC/BPS from controls, but measurements of pain tolerance (ability to tolerate pain as long as one can possibly do, not done here) and measurements of pain ratings on a VAS with a suprathreshold stimulus may distinguish IC/BPS from controls, as observed in this cohort.

In addition to providing novel insights on the mechanism of sensitization of IC/BPS, quantitative sensory study may be used to 1) provide clinicians a means to test indirectly for visceral/pelvic hypersensitivity without needing to catheterize the urethra or distend the bladder, which is extremely painful in patients with IC/BPS; 2) identify a phenotypic subgroup of patients with IC/BPS who have physiological evidence of spinal central sensitization and associated secondary hyperalgesia; and 3) provide a measurable and more objective outcome to monitor response to therapy. QST may be used to supplement patient reported outcome measurements in clinical trials.

Quantification of human painful sensory experience using QST is an essential step in the bidirectional translation of knowledge between animal nociceptive testing and human pain testing. Many of the methods used in nociceptive testing of rodent models (eg using von Frey filaments to quantify referred mechanical hyperalgesia²³ or using visceromotor response to quantify distention evoked bladder nociception²⁴) have parallel QST methodologies in humans (eg VAS rating using pressure algometer or urodynamics filling). In this study we demonstrated secondary mechanical hyperalgesia to the suprapubic area in IC/BPS. This observation provided face validity to some rodent models of pelvic pain (eg cyclophosphamide cystitis) that also demonstrated hypersensitivity to von Frey filaments in the suprapubic area.²⁵

A limitation of this study is the small number of subjects. The study was more difficult to recruit than we originally anticipated since many patients declined to participate in a noninterventional study that evoked repeated pain to different parts of the body including the perineum. This may potentially lead to a bias because patients with greater hypersensitivity may disproportionately decline to participate. Our exclusion criteria of no narcotic use also made many potential participants ineligible. Overall our sample size of 20 was similar to that of other published QST studies for IC/BPS (17, 21 and 26 subjects).^{1,4,6} On the other hand, a strength of the study was that we measured not only pain thresholds or pain tolerance, which tend to quantify the extreme ends of pain perception, but we also measured suprathreshold pain perception using fixed intensity stimuli. In addition, we used 0 to 10 VAS pain ratings to report the severity of pain that was experienced.

CONCLUSIONS

Female subjects with IC/BPS showed segmental hyperalgesia to mechanical pressure stimulation in the suprapubic area (T10-T12). This segmental hyperalgesia may be explained in part by spinal central sensitization.

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Abbreviations and Acronyms

BPS	bladder pain syndrome
DH	dorsal horn
IC	interstitial cystitis
QST	quantitative sensory testing
VAS	visual analog scale

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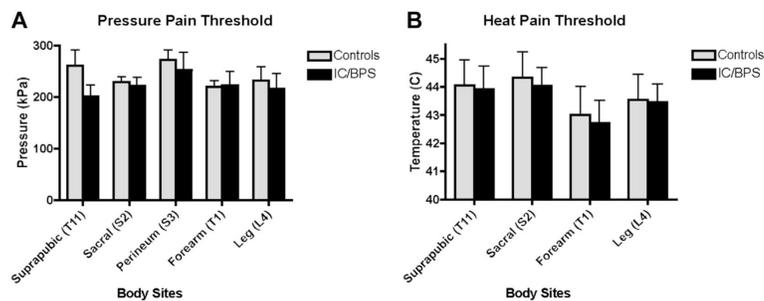


Figure 1.

No difference was found in pressure pain thresholds between female IC/BPS (10) and controls (10) in body sites tested (A). However, trend toward lower pressure pain threshold was noted in IC/BPS in suprapubic (T11) area (mean \pm SEM 201.5 \pm 21.8 vs 260 \pm 30.9 kPa, 2-tailed t-test $p = 0.14$). In addition, no difference was found in heat pain thresholds between female IC/BPS and controls (B).

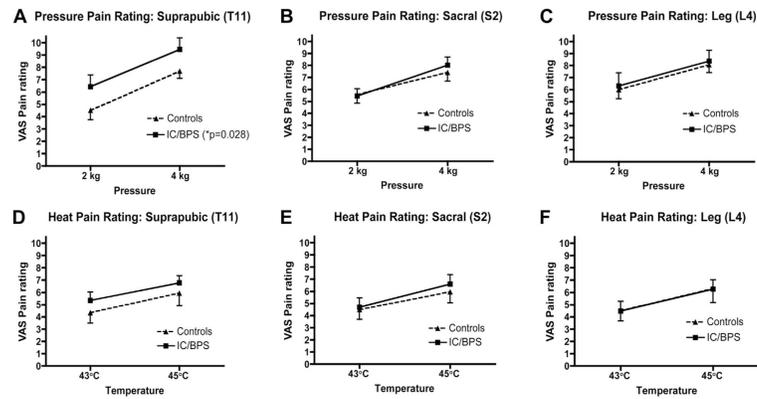


Figure 2.

VAS pain rated by female subjects with IC/BPS (10) was significantly higher than VAS pain rated by controls (10) when fixed mechanical pressure (2 or 4 kg) was applied to suprapubic (T11) area (A, 2-factor ANOVA, significant group difference between IC/BPS and controls with $p = 0.028$, significant difference between stimulus intensity with $p = 0.0005$, no interaction between 2 factors with $p = 0.93$). In contrast, there was no difference when fixed pressure was applied to other body sites (B, C) or when fixed heat stimulus (35C or 37C) was applied to any of body sites tested including suprapubic (T11) area (D-F). IC/BPS vs controls $p = 0.73$, stimulus intensity $p = 0.003$, interaction $p = 0.61$ (B); IC/BPS vs controls $p = 0.72$, stimulus intensity $p = 0.025$, interaction $p = 1.00$ (C); IC/BPS vs controls $p = 0.26$, stimulus intensity $p = 0.07$, interaction $p = 0.91$ (D); IC/BPS vs controls $p = 0.62$, stimulus intensity $p = 0.046$, interaction $p = 0.79$ (E); IC/BPS vs controls $p = 0.97$, stimulus intensity $p = 0.05$, interaction $p = 1.00$ (F).

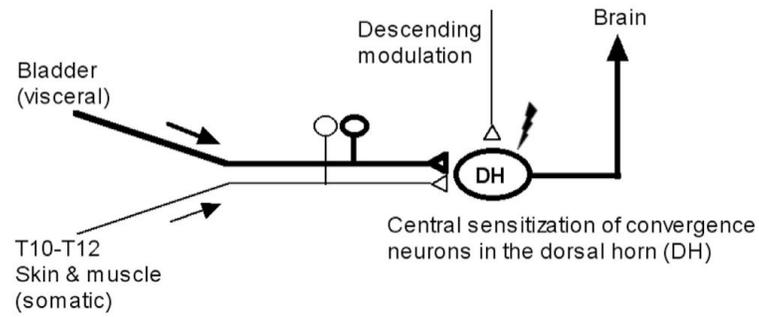


Figure 3. Model of convergent inputs onto spinal DH neurons. Hyperexcitability of DH neurons (spinal central sensitization) might explain segmental hyperalgesia and expansion of pain receptive field to referral areas.

Subject demographics

	Mean ± SEM IC/BPS (range)	Mean ± SEM Controls (range)	p Value
Age	41.4 ± 5.1 (21–68)	39.7 ± 4.6 (22–64)	0.80
ICSI	11.2 ± 1.5 (6–19)	2.9 ± 0.8 (1–9)	0.0001
ICPI	8.9 ± 1.2 (3–14)	1.4 ± 0.7 (0–6)	<0.0001
PUF	17.5 ± 1.8 (6–26)	3.2 ± 0.7 (1–7)	<0.0001
GUPI	22.4 ± 3.0 (4–36)	1.9 ± 0.7 (0–5)	<0.0001