Increased Startle Responses in Interstitial Cystitis: Evidence for Central Hyperresponsiveness to Visceral Related Threat

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Purpose: Hypersensitivity to visceral stimuli in interstitial cystitis/painful bladder syndrome may result from enhanced responsiveness of affective circuits (including the amygdala complex) and associated central pain amplification. Potentiation of the eyeblink startle reflex under threat is mediated by output from the amygdala complex and, therefore, represents a noninvasive marker to study group differences in responsiveness in this brain circuit.

Materials and Methods: Acoustic startle responses were examined in female patients with interstitial cystitis/painful bladder syndrome (13) and healthy controls (16) during context threat (application of muscle stimulation electrodes to the lower abdomen overlying the bladder), and cued conditions for safety (no stimulation possible), anticipation and imminent threat of aversive abdominal stimulation over the bladder.

Results: Patients showed significantly greater startle responses during nonimminent threat conditions (baseline, safe and anticipation periods) while both groups showed similar robust startle potentiation during the imminent threat condition. Higher rates of anxiety and depression symptoms in the patient group did not account for the group differences in startle reflex magnitude.

Conclusions: Compared to controls, female patients with interstitial cystitis/painful bladder syndrome showed increased activation of a defensive emotional circuit in the context of a threat of abdominal pain. This pattern is similar to that previously reported in patients with anxiety disorders as well as those with irritable bowel syndrome. Since these circuits have an important role in central pain amplification related to affective and cognitive processes, these results support the hypothesis that the observed abnormality may be involved in the enhanced perception of bladder signals associated with interstitial cystitis/painful bladder syndrome.

Key Words: cystitis, interstitial; sensory gating; startle reaction, reflex

Abbreviations and Acronyms

ASR = acoustic startle reflex

EMG = electromyogram

IBS = irritable bowel syndrome

IC/PBS = interstitial cystitis/painful bladder syndrome

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INTERSTITIAL cystitis/painful bladder syndrome is a debilitating condition characterized by bladder pain and hypersensitivity often accompanied by urinary frequency/urgency, nocturia and dyspareunia. Increased symptoms associated with life stress,[1,2] as well as the presence of bladder (visceral) and somatic hypersensitivity to painful stimuli,[3,4] have led to the hypothesis that central pain amplification may have an important role in the pathophysiology of the pre-

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dominant symptoms in IC/PBS.[5] There is now an extensive literature that supports the concept that increased activity in emotional arousal circuits[6] (with a prominent role of the amygdala complex, and norepinephrine and corticotropin-releasing factor signaling systems) has a key role in mediating stress induced visceral hyperalgesia in patients and in animal models of IBS.[7,8] Thus, the hypothesis that similar heightened reactivity within the emotional arousal circuits may accompany the pain and visceral hypersensitivity of IC/PBS is reasonable. However, to our knowledge this hypothesis has not been investigated in human patients to date.

The acoustic startle reflex is a cross-species defensive response to sudden intense stimuli characterized in mammals by fast, involuntary eyelid closure, and contraction of facial, neck and skeletal muscles. Its magnitude is highly influenced by the presence or absence of aversive states and is mediated via extended amygdala circuits.[9] Startle enhancement has been shown in experiments of conditioned fear as well as the contexts associated with aversive states.[10] Context threat responses are those elicited by the environment in which an aversive stimulus has been received rather than a specific cue that reliably predicts an aversive stimulus onset (as in fear conditioning). In this study we measured ASRs of patients with IC/PBS and healthy controls to standard procedures for eliciting context and cued fear responses germane to visceral pain using the threat of electrical abdominal stimulation. Based on previous findings suggesting hyperresponsiveness of the amygdala complex in patients with IBS, we hypothesized that patients with IC/PBS compared to healthy controls would show 1) greater responsiveness to contextual threat evidenced by enhanced ASRs immediately after placement of the stimulation electrodes over the bladder region, and 2) greater responsiveness to cued threat evidenced by enhanced ASRs when abdominal stimulation was anticipated or imminent relative to safe periods.[11]

METHODS

Subjects

A sample of 14 female patients with IC/PBS and 17 healthy, female controls were recruited through our urology clinic and by advertisement. The diagnosis of IC/PBS was confirmed using symptom criteria during a history and clinical examination by a urologist familiar with diagnosing IC/PBS.[12] Cystoscopy, urinalysis and urine cytology were used to rule out malignancy, calculi or other bladder pathologies. Patients with IC/PBS were taking a variety of medications for urological and pain symptoms but were discouraged from taking opioid or antianxiety medications on the study day (see table). Control subjects were healthy volunteers recruited by advertisement, and screened via medical examination for absence of IC/PBS

Medication use for selected classes of medications for subjects with IC/PBS

	Mean Startle Magnitude in Each Test Phase				Drug Classes Taken							
Subject No.*	Baseline	Safe	Anticipation	Threat	Elmiron®	Antidepressants	Antihistamines	Antimuscarinics	Urinary Analgesics	Narcotic Analgesics	Nonnarcotic Analgesics	Anxiolytics	Anticonvulsants
1	20.14	18.73	20.81	18.66	Yes	Fluoxetine			Urelle®				
2	19.70	17.38	17.34	20.71	No	Fluoxetine		Darifenacin					
3	13.50	14.55	14.90	15.53	No					Hydrocodone, fentanyl	Acetaminophen		
4	12.80	13.04	18.49	14.05	No	Amitriptyline							
5	11.68	11.91	12.44	17.79	Yes		Diphenhydramine		Urised®		Topical lidocaine		
6	12.09	11.50	13.94	13.11	Yes	Escitalopram		Solifenacin	Urelle	Hydrocodone	Ibuprofen, acetaminophen		
7	9.60	10.98	10.44	11.77	Yes	Citalopram	Hydroxyzine	Oxybutynin		Tramadol		Lorazepam	
8	10.27	9.81	9.81	11.96	Yes	Bupropion	Hydroxyzine	Darifenacin		Hydrocodone, tramadol	Acetaminophen		
9	9.18	9.15	7.88	14.02	Yes								
10	10.17	8.91	10.94	10.44	No						Acetaminophen		
11	9.12	7.54	10.14	15.44	Yes	Amitriptyline							Pregabalin
12	6.82	5.37	6.57	7.61	Yes				Urised		Ibuprofen		
13	3.67	4.76	7.06	11.00	Yes		Cetirizine						
14	Nonresponsive	Nonresponsive	Nonresponsive	Nonresponsive	No								
% Subjects taking drug class					64.3	50.0	28.6	28.6	28.6	28.6	42.9	7.1	7.1

* Subject in order by descending size of mean startle response during the safe condition. Subject 14 was the startle nonresponder.