Published in final edited form as:
Neurourol Urodyn. 2011 June ; 30(5): 668–672. doi:10.1002/nau.21109.

Cystitis, Co-morbid Disorders and Associated Epithelial Dysfunction

Lori A. Birder[1,2], **Ann T. Hanna-Mitchell**[1], **Emeran Mayer**[4], and **Charles A. Buffington**[3]

[1] Department of Medicine, University of Pittsburgh, Pittsburgh Pennsylvania

[2] Department of Pharmacology, University of Pittsburgh, Pittsburgh Pennsylvania

[3] Department of Veterinary Clinical Sciences Ohio State University, Columbus Ohio

[4] Center for Neurobiology of Stress, David Geffen School of Medicine at UCLA, Los Angeles, CA

Abstract

Introduction—Interstitial cystitis (painful bladder syndrome / interstitial cystitis; PBS/IC) is a persistent pain syndrome affecting the urinary bladder with symptoms including urinary frequency, bladder pain and nocturia.(1–6) Various animal models have been studied, most of which mimic some aspect of the human condition of interest to the investigator(s). This review will provide examples of various animal models including those incorporating chronic stress, thought to produce features that share similarities to that of PBS/IC patients, whose symptoms are often exacerbated by various stressors. (7–12)

This review also provides evidence that patients with PBS/IC exhibit abnormalities within the bladder epithelium (or urothelium), even though a consistent relationship of such changes with symptom severity has not been demonstrated. These changes include alterations in urothelial integrity, differentiation and/or proliferation as well as changes in 'sensory' function (altered expression or sensitivity of receptors and ion channels).

Establishing a diagnostic 'indicator' with a high degree of correlation in this syndrome would be of value in terms of disease status, diagnosis and treatment. There have been reports of a number of factors/mediators altered in PBS/IC. However, the lack of a validated biomarker and a well-defined etiology for this syndrome introduces a number of complications, including diagnostic confidence, choice of appropriate animal models to study basic mechanism with the goal toward treatment, and rational therapies.

It is also becoming increasingly apparent that patients with PBS/IC often overlap or share symptoms commonly associated with other persistent pain disorders. These include (but are not limited to) irritable bowel syndrome (IBS), non-cardiac chest pain, fibromyalgia and even overactive bladder syndrome (OAB).(13–18) Such types of changes are not limited to the urinary bladder, however, as reports of alterations in epithelial signaling/barrier function have been described in patients diagnosed with a wider variety of syndromes, including functional and inflammatory bowel disorders such as irritable bowel syndrome (IBS), gastrointestinal esophageal reflux disease (GERD) and asthma.(19–21) These and other findings suggest that changes within the epithelium (barrier as well as signaling functions) may be a common occurrence that may contribute to peripheral mechanisms of hypersensitivity in a number of disorders.

Correspondence to: Lori Birder, University of Pittsburgh School of Medicine, A 1207 Scaife Hall, Pittsburgh PA 15261, (tel) 412 383 7368, lbirder@pitt.edu.

Disclosures: None.

Keywords

bladder urothelium; esophageal epithelium; sensor function; hypersensitivity

Cystitis and Animal Models

A hallmark of chronic visceral pain syndromes, including PBS/IC, is pain in the absence of readily demonstrable pathology of the viscera or associated nerves. These disorders are currently defined by symptom criteria in the absence of organic disease. There is no generally agreed upon etiology or pathophysiology for these syndromes, and no effective treatments able to eradicate the symptoms in humans. This condition is characterized by suprapubic pain, associated with bladder filling and can also be accompanied by a persistent strong desire to void, increased frequency of urination and nocturia.(1–6) The presence of non-painful symptoms such as urgency and suprapubic pressure suggests overlap with overactive bladder syndrome (OAB).(14)

A number of animal models have been used for the study of PBS/IC. These have included administration of an irritant or immune stimulant (e.g., hydrochloric acid, turpentine, protamine sulphate, mustard oil, lipopolysaccharide and cyclophosphamide) to healthy rodents.(22) Studies have shown that deficiency of estrogen receptor-β in female mice develop a bladder phenotype (including alterations in the urothelium) that shares some superficial similarities with abnormalities found in the bladder of humans with PBS/IC.(23) However, a review of such animal models has discussed the limitations of artificially inducing bladder inflammation or injury in otherwise healthy animals that greatly limit their face and construct validity, e.g. their ability to model the symptoms of this complex syndrome.(22,24) Furthermore, the degree of bladder hyperreflexia observed in rodents is variable and can resolve within a matter of days. This may be, in part, due to the capacity of the healthy bladder urothelium to rapidly regenerate post-intravesical insult, thus limiting the capacity to establish chronicity reflective of the human condition in these models.

A naturally occurring disease occurring in cats, termed feline interstitial cystitis (FIC), shares nearly all the characteristics of the non-ulcerative form of PBS/IC found in humans. (21,24) As in human beings, cats with FIC also commonly display a variety of systemic abnormalities, which have been found to be responsive to environmental enrichment in both laboratory and clinical studies. (25) Despite the validity of FIC as a model of PBS/IC, its utility is constrained by limited availability of affected animals and reagents validated for use in cats, as well as the relatively superficial knowledge of feline genetics and epigenetics.

In addition, an experimental autoimmune cystitis (EAC) murine model has been shown to exhibit a number of comparable functional and histological bladder alterations that are comparable to those found in humans with PBS/IC. (26) Pseudorabies virus (PRV) injection in mice also results in the development of a neurogenic cystitis associated with pelvic pain and accumulation of mast cells that is somewhat similar to some features of PBS/IC. (27) Evidence using chronic stress models (maternal deprivation, social interactive stress and water avoidance stress) can result in changes in epithelial barrier function, exaggerated stress responses as well as visceral hyperalgesia.(7–10) Various psychosocial stressors have been shown to be associated with the first onset of, and with the exacerbation of chronic symptoms in several persistent pain disorders, including PBS/IC.

Patients with PBS/IC also typically exhibit a number of symptoms that are not part of the current disease classification, but which overlap with symptoms of other persistent pain syndromes, including IBS, endometriosis and fibromyalgia.(28–31) Even though the

mechanisms underlying this overlap are currently incompletely understood, peripheral (e.g. cross sensitization), spinal and supraspinal mechanisms have been proposed.

Studies in animals permit controlled investigation of some dimensions (or endophenotypes) of chronic pain conditions (such as visceral hyperalgesia, stress sensitivity) that are not feasible to perform in humans. However, it is highly unlikely that a complex, symptom based disorder can be modeled closely in rodents. Thus, a panel of models (taking into account variability in both subject sex and strain) reflecting known and well characterized components of the human condition (e.g. endophenotypes) may be useful for target identification and early drug development.

Epithelial Alterations

There is evidence that functional pain syndromes such as PBS/IC are associated with alterations in the urothelium. The urothelium, the epithelial lining of the distal urinary tract is composed of at least three cell layers.(32) These consist of a basal cell layer, an intermediate and a superficial or apical layer composed of cells termed “umbrella” cells, which are interconnected by tight junctions.(33) Though the urothelium maintains a tight barrier to ion and solute flux, a number of local factors (e.g. tissue pH; mechanical, chemical or environmental insult and microbial infection) as well as conditions such as PBS/IC can alter or degrade the barrier function of the urothelium.

Alterations of urothelium at both the molecular and structural levels have been identified in both human patients with PBS/IC, and in cats diagnosed with FIC. Some of the changes within the urothelium reported in PBS/IC include alterations in synthesis of a number of cell adhesion and tight junction proteins. Similar urothelial dysfunction occurs in cats diagnosed with FIC.(34) Changes in the urothelial barrier can permit water, urea and noxious substances present in the urine to pass into the underlying tissue (neural and/or muscle layers), which may acutely result in symptoms of urgency, frequency and pain during bladder filling and voiding, and when present chronically lead to neuroplastic and immune changes in the neuro-immune-epithelial interface.

Disruption of the integrity of the urothelial barrier may be mediated by hormonal and neural mechanisms (such as by substances released by surrounding nerves and other cell types within the bladder wall). For example, nitric oxide (NO) has been found to be elevated in patients with PBS/IC as well as in cats with FIC.(345,36) Excessive NO levels in the urinary bladder can increase permeability to water/urea in addition to producing ultrastructural changes in the apical layer. Although the pathological mechanism(s) remain unknown, these findings appear to be similar to those in other epithelia where excess production of NO has been linked to decreases in epithelial integrity.(37) Disruption of epithelial integrity also may be linked to expression of substances such as antiproliferative factor (APF), which has been characterized as a frizzled-8-related sialoglycopeptide and is detected in the urine of patients with bladder pain syndrome.(5,38) Abnormalities in urothelial growth and proliferation may also be linked to changes in expression of trophic factors such as HB-EGF.(39)

What is the source of pain in PBS/IC?

Painful bladder syndrome has often been described as a disease of the urothelium.(40) The urothelium is likely to play an important role by actively communicating with bladder nerves, urothelial cells, smooth muscle or even cells of the immune and inflammatory systems.(41) The localization of afferent nerves next to the urothelium suggests that urothelial cells could be targets for transmitters released from bladder nerves or that chemicals released by urothelial cells could alter afferent nerve excitability in addition to

influencing other cells. For example, release of an “urothelial derived inhibitory factor” (42) is thought to affect smooth muscle function while urothelial-released mediators including prostaglandins, acetylcholine, ATP, NO and others (41,43–45) may influence bladder afferent nerve activity. The increased afferent nerve excitability in cats with FIC may be affected by changes in release of various transmitters from the urothelium.(46) Augmented release of transmitters, most notably ATP, from the urothelium can lead to painful sensations by excitation of purinergic receptors on sensory fibers both peripherally as well as centrally (47,48). There is speculation that this type of non-cholinergic mechanism could have a role in a number of bladder pathologies including idiopathic detrusor instability and painful bladder syndrome. In this regard, targeting urothelial release mechanisms may prove important in the treatment for a number of bladder dysfunctions. For example, uncontrolled studies have suggested some therapeutic benefit of botulinum toxins (BoNTA) in the treatment of neurogenic and non-neurogenic detrusor overactivity as well as in painful bladder syndrome. (49) Though the effectiveness of BoNTA may be due to a block of transmitters released from bladder nerves, recent evidence suggests that BoNTA also may block release of mediators from non-neuronal cells (including the urothelium). (50)

Even though the pathophysiology and etiology of most persistent pain syndromes is incompletely understood, it is generally assumed that it involves changes in the target organ as well as alterations in both central and peripheral pain processing/modulation. In addition, while alterations in the periphery may alter nociceptive input to the CNS, pain remains an emergent property of the brain. A number of recent studies have identified structural and functional changes in the brain of patients with chronic pain syndromes that may influence the perception of sensory input. (51–54)

Can PBS/IC be correlated with a validated ‘biomarker’?

Though not currently available, reliable diagnostic markers would be very helpful in the diagnosis of PBS/IC. Antiproliferative Factor (APF), heparin-binding epidermal growth factor-like growth factor (HP-EGF), epidermal growth factor (EGF), insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP3) have been shown to be correlated to PBS/IC. Of these, urine levels of APF, HB-EGF and EGF have been reported to discriminate between patients with PBS/IC and asymptomatic controls. (55,56) However studies also have shown weak associations between urine markers and bladder biopsy findings, which may reflect in part variations in biopsies taken from different regions of the bladder. (57)

Increased nerve growth factor (NGF) in urine and tissue have been linked with bladder pathologies including idiopathic sensory urgency, patients with overactivity as well as PBS/IC.(58) We have previously reported increased NGF in bladder urothelium in cats diagnosed with FIC as compared to urothelium from healthy, unaffected cats.(59) Studies have shown that a major source of NGF comes from urinary bladder smooth muscle as well as the urothelium, which may contribute to increased neural excitability and emergence of bladder pain in PBS/IC. (60) Thus, NGF has been proposed as a potential ‘biomarker’ for a number of bladder disorders due to a suggested link between elevated NGF levels to overactivity and painful inflammatory conditions as compared to unaffected controls.(61)

Additionally, Rubio-diaz et al., (62) recently evaluated the feasibility of diagnosing PBS/IC in blood from humans and domestic cats using principle components analysis of the spectral patterns in the blood obtained using infrared microspectroscopy. The classification models successfully classified spectra based on condition (control/affected), and a different set of masked spectra correctly predicted the condition of 100% of the subjects in both species. Classification required information from the 1500–1800 cm^{-1} spectral region to

discriminate between subjects with IC, other disorders, and healthy subjects. Analysis of cat samples using liquid chromatography-mass spectroscopy revealed differences in the concentration of tryptophan and its metabolities between healthy and affected cats. (62,63) These results demonstrate the potential utility of infrared microspectroscopy to diagnose PBS/IC in both humans and cats.

Co morbid disorders

Patients with PBS/IC often report a variety of co-morbid disorders, which can include other pelvic pain problems such as IBS, vulvodynia and endometriosis or fibromyalgia. (11–18) Individuals with these conditions typically exhibit diffuse hyperalgesia and/or allodynia, suggesting a generalized dysfunction in pain or sensory processing or central modulation. For example, functional brain-imaging techniques (which can visualize structures linked with sensory processing) have revealed a hyperactivity of the insula region (associated with pain processing) in patients with fibromyalgia (64) and with IBS (65).

Though the etiology is unknown, several factors have been proposed to contribute to the pathophysiology of some of these disorders which can include changes in epithelial sensor/barrier function, neurogenic inflammation and even autoimmune involvement.(5,66,67) In addition, the overlap of symptoms thought to originate from different pelvic organs may be due in part to organ cross-talk between pelvic viscera. (29,31,68) Although such organ cross talk cannot readily explain the presence of co-morbid disorders outside the pelvic cavity, or the observation that the ‘cross-talk’ may not extend to other conditions wherein epithelial damage is a prominent feature, such as ulcerative colitis or chronic urinary tract infections. It has also been suggested that PBS/IC may be part of the spectrum of persistent pain disorders, sharing mechanisms of central pain amplification or augmentation (51). Such central pain mechanisms are thought to play a primary role in persistent pain conditions in which few or no peripheral abnormalities can be identified, including common pain disorders of the gastrointestinal tract such as IBS, functional dyspepsia and functional heartburn. The latter refers to patients who report symptoms of heartburn, but no not have evidence for gastroesophageal reflex of acid or bile, or evidence for mucosal erosions (69).

Though mechanistic differences are certain to exist, a number of these visceral disorders also share increased stress responsiveness, as a pathophysiological factor.(70,71) Reports of abnormalities in vasomotor tone and increases in bladder sympathetic neuron density and urine norepinephrine secretion in both humans with IC and FIC cats are consistent with altered noradrenergic function, including increased stress responsiveness. (72) Moreover, environmental enrichment has been shown to reduce lower urinary tract and co-morbid symptoms in cats with FIC in both laboratory and clinical studies, further supporting a role for abnormalities of the stress response system playing a role in the pathophysiology of PBS/IC. (73,74) Studies in animals with experimentally induced disease also have documented that stress-sensitization is associated with hyperalgesic states similar to that exhibited by many persistent pain syndromes.(75) In addition, stress has been linked to disturbances of the epithelial barrier in a number of tissues. Reports in both healthy human volunteers and animals show that excessive exposure to stress results in an abnormal epithelial response to stimuli and can impair the barrier function. (76,77) Thus, defects in epithelial response to stimuli in a number of tissues including the urinary bladder may lead to the development of a persistent mucosal dysfunction and increased susceptibility for symptom flares.

Alterations in esophageal epithelium: Is there a common link in PBS/IC?

Changes in epithelial signaling/barrier function are not unique to the urinary bladder. For example, airway epithelia in asthmatic patients as well as keratinocytes in certain types of

skin disease also exhibit a number of similar abnormalities and compromised repair processes. (77,78) In addition, it has also been shown that patients with GERD exhibit alterations of esophageal epithelial structure and function. (79–81) This dilation of intercellular spaces (or DIS) signifies a break in the epithelial barrier. Similar to events reported as a consequence of urothelial barrier dysfunction in PBS/IC, loss of esophageal epithelial integrity may allow access of (refluxed) luminal acid and other agents to underlying lamina propria cells, enteric neurons and afferent nerve terminals, which in turn may result in peripheral and central sensitization, associated with esophageal pain. It is not known if such loss of epithelial integrity also plays a role in functional heartburn.

TRPV1 is a plausible candidate for mediating the symptoms of heartburn and esophageal pain. Similar to reported findings in the urinary bladder, TRPV1-immunoreactive nerves have been localized within esophageal mucosa in humans and animals. (82–84) Patients with symptoms of esophagitis exhibit increased expression of TRPV1-positive nerve fibers as compared to healthy subjects.(83,84) In association with increased TRPV1 expression, studies of patients with esophagitis also demonstrated elevated levels of NGF, which can sensitize and alter expression of TRPV1 in various tissues.(85) Thus, inflammatory mediators including NGF can indirectly sensitize TRPV1, which may be an integral component of pathways contributing to pain and hypersensitivity.

Release of proinflammatory mediators such as plate-activating factor (PAF) has been linked to esophageal damage as well as amplifying the response of inflammatory and immune cells. Evidence supports an important role for esophageal epithelial cells as the initiating cell type in esophageal inflammation. It has been shown that stimulation of TRPV1 from cat esophageal epithelial cells releases PAF. (86) Thus, activation of esophageal-epithelial TRPV1 may lead to release of a number of factors that could contribute to alterations in the epithelium as well as excitability of underlying afferent nerves. This is consistent with findings in mice lacking TRPV1, which have been shown to be less likely to develop esophagitis as compared to wild-type mice when exposed to acid (87).

Summary

A variety of chronic pain syndromes share alterations in epithelial barrier or signaling functions. These epithelial cells can respond to a number of challenges, including environmental inputs and mediators released from nerves or nearby inflammatory cells, which can result in altered expression and/or sensitivity of various receptor/channels as well as changes in release of mediators, all of which could impact normal function.

Patients with PBS/IC exhibit increased association with certain chronic diseases and pain syndromes. It has been described that gastrointestinal disorders are common in relation to PBS/IC and many PBS/IC patients also describe symptoms of heartburn. One may speculate that shared disease mechanisms (“endophenotypes”), such as increased epithelial permeability and/or increased responsiveness of epithelial cells to mechanical and/or chemical stimuli exist in these disorders. In this regard, it has long been reported that augmented release of epithelial-derived ATP from ‘tubes and sacs” (88) (such as the urinary bladder, ureter, gastrointestinal tract and esophagus) may play a significant role in primary afferent sensitization in a number of pain-related diseases. Taken together, modification of the epithelium and/or loss of epithelial integrity in a number of pathological conditions can result in passage of irritating substances and/or release of neuroactive substances from the epithelium. These can lead to changes in the properties of sensory nerves and sensory symptoms.

Acknowledgments

This work was supported by NIH grants R37 DK54824 and R01 DK57284 (LAB), P50 DK64539 (EM, LAB, CAB) and K01 DK080184 (AHM).

References

1. Martinez-Bianchi V, Halstater BH. Urologic chronic pelvic pain syndrome. Prim Care. 2010; 37:527–46. [PubMed: 20705197]
2. Butrick CW, Howard FM, Sand PK. Diagnosis and treatment of interstitial cystitis/painful bladder syndrome: a review. J Womens Health. 2010; 19:1185–93.
3. Buffington CA. A watershed year for interstitial cystitis. 2010; 183:854–5.
4. Hanno P, Lin A, Nordling J, et al. Bladder pain syndrome committee of the international consultation on incontinence. Neurourol Urodyn. 2010; 29:191–8. [PubMed: 20025029]
5. Chai TC, Keay S. New theories in interstitial cystitis. Nat Clin Pract Urol. 2004; 1:85–9. [PubMed: 16474520]
6. Hanno, PM. Painful Bladder Syndrome/Interstitial Cystitis and Related Diseases. In: Wein, AJ.; Kavoussi, LR.; Novick, AC.; Partin, AW.; Peters, CA., editors. Campbell-Walsh Urology. Philadelphia: W.B Saunders Company; 2007. p. 330-370.
7. Robbins MT, DeBerry J, Ness TJ. Chronic psychological stress enhances nociceptive processing in the urinary bladder in high-anxiety rats. Physiol Behav. 2007; 91:544–50. [PubMed: 17521683]
8. O'Mahony SM, Hyland NP, Dinan TG, et al. Maternal separation as a model of brain-gut axis dysfunction. Psychopharmacology. 2010
9. Bradesi S, Schwetz I, Ennes HS, et al. Repeated exposure to water avoidance stress in rats: a new model for sustained visceral hyperalgesia. AJP Gastro Liver Physiol. 2005; 289:G42–53.
10. Vicario M, Guilarte M, Alonso C, Yang P, Martinez C, Ramos L, Lobo B, Gonzalez A, Guila M, Pigrau M, Saperas E, Azpiroz F, Santos J. Chronological assessment of mast cell-mediated gut dysfunction and mucosal inflammation in a rat model of chronic psychosocial stress. Brain Behav Immun. 2010; 24:1166–75. [PubMed: 20600818]
11. Peters KM, Carrico DJ, Diokno AC. Characterization of a clinical cohort of 87 women with interstitial cystitis/painful bladder syndrome. Urology. 2008; 71:634–640. [PubMed: 18387392]
12. Rodriguez MAB, Buchwald BAD, Afari N. Psychological distress in twins with urological symptoms. General Hospital Psychiatry. 2010; 32:262–267. [PubMed: 20430229]
13. Nickel JC, Tripp DA, Pontari M, et al. Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome. J Urol. 2010; 184:1358–63. [PubMed: 20719340]
14. MacDiarmid SA, Sand PK. Diagnosis of interstitial cystitis/painful bladder syndrome in patients with overactive bladder symptoms. Rev Urol. 2007; 9:9–16. [PubMed: 17396167]
15. Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: Overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation. 1997; 4:134–153. [PubMed: 9500148]
16. Clauw DJ, Schmidt M, Singer A, et al. The relationship between fibromyalgia and interstitial cystitis. J Psych Res. 1997; 31:125–131.
17. Clemens JQ, Meenan RT, O'Keeffe Rosetti MC, et al. Case-control study of medical comorbidities in women with interstitial cystitis. J Urol. 2008; 179:2222–2225. [PubMed: 18423759]
18. Erickson DR, Morgan KC, Ordille S, et al. Nonbladder related symptoms in patients with interstitial cystitis. J Urol. 2001; 166:557–562. [PubMed: 11458068]
19. Bosse Y, Pare PD, Seow CY. Airway wall remodeling in asthma: from the epithelial layer to the adventitia. Curr Allergy Asthma Rep. 2008; 8:357–66. [PubMed: 18606090]
20. Bove M, Vieth M, Dombrowski F, et al. Acid challenge to the human esophageal mucosa: effects on epithelial architecture in health and disease. Dig Dis Sci. 2005; 50:1488–96. [PubMed: 16110841]

21. Piche T, Barbara G, Aubert P, et al. Impaired intestinal barrier integrity in the colon of patients with irritable bowel syndrome: involvement of soluble mediators. Gut. 2009; 58:196–201. [PubMed: 18824556]
22. Westropp JL, Buffington CA. In vivo models of interstitial cystitis. J Urol. 2002; 167:694–702. [PubMed: 11792956]
23. Imamov O, Yakimchuk K, Morani A, et al. Estrogen receptor beta-deficient female mice develop a bladder phenotype resembling human interstitial cystitis. Proc Natl Acad Sci. 2007; 104:9806–9. [PubMed: 17522255]
24. Buffington, CAT. Bladder Pain Syndrome/Interstitial Cystitis. In: Baranowski, AP.; Abrams, P.; Fall, M., editors. Urogenital Pain in Clinical Practice. New York: Informa Healthcare, USA; 2008. p. 169-183.
25. Stella JL, Lord LK, Buffington CAT. Sickness behaviors in response to unusual external events in healthy cats and cats with feline interstitial cystitis. J Amer Vet Med Assoc. 2011; 238(1):67–73. [PubMed: 21194324]
26. Lin YH, Liu G, Kavran M, et al. Lower urinary tract phenotype of experimental autoimmune cystitis in mouse: a potential animal model for interstitial cystitis. BJU Int. 2008; 102:1724–30. [PubMed: 18710451]
27. Rudick CN, Schaeffer AJ, Klumpp DJ. Pharmacologic attenuation of pelvic pain in a murine model of interstitial cystitis. BMC Urol. 2009; 12:9–16.
28. Buffington CAT. Comorbidity of interstitial cystitis with other unexplained clinical conditions. J Urol. 2004; 172:1242–48. [PubMed: 15371816]
29. Pezzone MA, Liang R, Fraser MO. A model of neural cross-talk and irritation in the pelvis: implications for the overlap of chronic pelvic pain disorders. Gastroenterology. 2005; 128:1953–64. [PubMed: 15940629]
30. Zabbarova I, Birder L, Roppolo J, et al. Bladder-colon cross-sensitization induced bladder overactivity. Neurourol Urodynamics. 2009:267–68.
31. Winnard KP, Dmitrieva N, Berkley KJ. Cross-organ interactions between reproductive, gastrointestinal, and urinary tract tracts: modulation by estrous stage and involvement of the hypogastric nerve. Am J Physiol Regul Integr Comp Physiol. 2006; 291:R1592–601. [PubMed: 16946082]
32. Khandelwal P, Abraham SN, Apodaca G. Cell biology and physiology of the uroepithelium. AJP. 2009; 297:F1477–501.
33. Acharya P, Beckel JM, Ruiz WG, et al. Distribution of the tight junction proteins ZO1, occluding, and claudin-4, -8, and -12 in bladder epithelium. AJP. 2004; 287:F305–318.
34. Lavelle JP, Meyers SA, Ruiz WG, et al. Urothelial pathophysiological changes in feline interstitial cystitis: a human model. AJP. 2000; 278:F540–53.
35. Koskela LR, Thiel T, Ehren I, et al. Localization and expression of inducible nitric oxide synthase in biopsies from patients with interstitial cystitis. J Urol. 2008; 180:737–41. [PubMed: 18554637]
36. Birder LA, Wolf-Johnston A, Buffington CA, et al. Altered inducible nitric oxide synthase expression and nitric oxide production in the bladder of cats with feline interstitial cystitis. J Urol. 2005; 173:625–9. [PubMed: 15643277]
37. Han X, Fink MP, Yang R, et al. Increased iNOS activity is essential for intestinal epithelial tight junction dysfunction in endotoxemic mice. Shock. 2004; 21:261–70. [PubMed: 14770040]
38. Keay SK, Szekely Z, Conrads TP, et al. An antiproliferative factor from interstitial cystitis patients is a frizzled 8 protein-related sialoglycopeptide. Proc Natl Acad Sci. 2004; 101:11803–808. [PubMed: 15282374]
39. Chai TC, Zhang CO, Shoenfelt JL, et al. Bladder stretch alters urinary heparin-binding epidermal growth factor and antiproliferative factor in patients with interstitial cystitis. J Urol. 2000; 163:1440–44. [PubMed: 10751853]
40. Graham E, Chai TC. Dysfunction of bladder urothelium and bladder urothelial cells in interstitial cystitis. Curr Urol Rep. 2006; 7:440–46. [PubMed: 17052438]
41. Birder LA, de Groat WC. Mechanisms of disease: involvement of the urothelium in bladder dysfunction. Nat Clin Prac. 2007; 4:46–54.

42. Templeman L, Chapple CR, Chess-Williams R. Urothelium derived inhibitory factor and cross-talk among receptors in the trigone of the bladder of the pig. 2002; 167:472–45.
43. Sun YN, Chai TC. Augmented extracellular ATP signaling in bladder urothelial cells from patients with interstitial cystitis. AJP. 2006; 290:C27–34.
44. Hanna-Mitchell AT, Beckel JM, Barbadora S, et al. Non-neuronal acetylcholine and urinary bladder urothelium. Life Sci. 2007; 80:2298–2302. [PubMed: 17363007]
45. Rastogi P, Rickard A, Dorokhov N, et al. Loss of prostaglandin E2 release from immortalized urothelial cells obtained from interstitial cystitis patient bladders. AJP. 2008; 294:F1129–35.
46. Sculptoreanu A, de Groat WC, Buffington CA, et al. Abnormal excitability in capsaicin-responsive DRG neurons from cats with feline interstitial cystitis. Exp Neurol. 2005; 193:437–43. [PubMed: 15869946]
47. Burnstock G. Purinergic mechanosensory transduction and visceral pain. Mol Pain. 2009; 30:5–69.
48. Kaan TK, Yip PK, Grist J, et al. Endogenous purinergic control of bladder activity via presynaptic P2X3 and P2X2/3 receptors in the spinal cord. J Neurosci. 2010; 30:4503–7. [PubMed: 20335487]
49. Chancellor MB, Fowler CJ, Apostolidis A, et al. Drug insight: biological effects of botulinum toxin A in the lower urinary tract. Nat Clin Pract Urol. 2008; 5:319–28. [PubMed: 18461049]
50. Smith CP, Gangitano DA, Munoz A, et al. Botulinum toxin type A normalizes alterations in urothelial ATP and NO release induced by chronic spinal cord injury. Neurochem Int. 2007; 52:1068–75. [PubMed: 18187233]
51. Mayer, Emeran A.; Catherine Bushnell, M. Functional pain disorders: time for a paradigm shift?. Mayer, EA.; Bushnell, MC., editors. Vol. 251. Seattle: IASP press; 2009. p. 531-5.
52. May A. Chronic pain may change the structure of the brain. Pain. 2008; 137:7–15. [PubMed: 18410991]
53. Brooks J, Tracey I. From nociception to pain perception: imaging the spinal and supraspinal pathways. 2005; 207:19–33.
54. Seminowicz DA, Labus JS, Bueller JA, Tillisch K, Naliboff BD, Bushnell MC, Mayer EA. Regional gray matter density changes in brains of patients with irritable bowel syndrome. Gastroenterology. 2010; 139:48–57. e2. [PubMed: 20347816]
55. Zhang CO, Li ZL, Kong CZ. APF, HB-EGF and EGF biomarkers in patients with ulcerative vs. non-ulcerative interstitial cystitis. BMC Urol. 2005; 29:5–7.
56. Keay SK, Zhang CO, Shoenfelt J, et al. Sensitivity and specificity of antiproliferative factor, heparin-binding epidermal growth factor-like growth factor, and epidermal growth factor as urine markers for interstitial cystitis. Urology. 2001; 57:9–14. [PubMed: 11378043]
57. Erickson DR, Tomaszewski JE, Kunselman AR, et al. Urine markers do not predict biopsy findings or presence of bladder ulcers in interstitial cystitis/painful bladder syndrome. J Urol. 2008; 179:1850–6. [PubMed: 18353383]
58. Liu HT, Kuo HC. Intravesical botulinum toxin A injections plus hydrodistension can reduce nerve growth factor production and control bladder pain in interstitial cystitis. Urology. 2007; 70:463–8. [PubMed: 17905097]
59. Birder LA, Wolf-Johnston AS, Chib MK, et al. Beyond neurons: involvement of urothelial and glial cells in bladder function. Neurourol Urodyn. 2010; 29:88–96. [PubMed: 20025015]
60. Micera A, Lambiase A, Stampachiacchiere B, et al. Nerve growth factor and tissue repair remodeling: trkA (NGFR) and p75 (NTR), two receptors one fate. Cytokine Growth Factor Rev. 2007; 18:245–6. [PubMed: 17531524]
61. Kuo HC, Liu HT, Chancellor MB. Can urinary nerve growth factor be a biomarker for overactive bladder? Rev Urol. 2010; 12:e69–77. [PubMed: 20811555]
62. Rubio-Diaz DE, Pozza ME, Dimitrakov J, Gilleran JP, Giusti MM, Stella JL, Rodriguez-Saona LE, Buffington CA. A candidate serum biomarker for bladder pain syndrome/interstitial cystitis. Analyst. 2009; 134:1133–7. [PubMed: 19475139]
63. Gilleran J, Pozza M, Dimitrakov J, Stella J, Rodriguez-Saona L, Buffington T. Differential diagnosis of painful bladder syndrome/interstitial cystitis using infrared microspectroscopy. Neurourology and Urodynamics. 2009; 28:265. [PubMed: 19034954]

64. Cook DB, Lange G, Ciccone DS, et al. Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol. 2004; 31:364–378. [PubMed: 14760810]
65. Tillisch K, Mayer EA, Labus JS. Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome. Gastoenterology. 2010 in press. PMID: 20696168.
66. Hendrix S. Neuroimmune communication in skin: far from peripheral. J Invest Derm. 2008; 128:260–261. [PubMed: 18195741]
67. Van de Merwe J. Interstitial cystitis and systemic autoimmune diseases. Nat Clin Pract Urol. 2007; 4:8.
68. Rudick CN, Chen MC, Mongiu AK, et al. Organ cross talk modulates pelvic pain. Am J Physiol. 2007; 293:R1191–98.
69. Herschcovici T, Fass R. GERD: are functional heartburn and functional dyspepsia one disorder? Nat Rev Gasteroentrol. 2010; 7:71–2.
70. Bunnett NW. The stressed gut: contributions of intestinal stress peptides to inflammation and motility. Proc Natl Acad Sci USA. 2005; 102:7409–7410. [PubMed: 15899972]
71. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. Brain Behav Immun. 2007; 21:993–999. [PubMed: 17493786]
72. Westropp JL, Kass PH, Buffington CA. Evaluation of the effects of stress in cats with idiopathic cystitis. Am J Vet Res. 2006; 67:731–6. [PubMed: 16579769]
73. Buffington CAT, Westropp JL, Chew DJ, Bolus RR. Clinical evaluation of multimodal environmental modification (MEMO) in the management of cats with idiopathic cystitis. Journal of Feline Medicine and Surgery. 2006; 8:261–268. [PubMed: 16616567]
74. Westropp JL, Kass PH, Buffington CA. In vivo evaluation of alpha(2)-adrenoceptors in cats with idiopathic cystitis. Am J Vet Res. 2007; 68:203–7. [PubMed: 17269887]
75. Khasar SG, Burkham J, Dina OA, et al. Stress induces a switch of intracellular signaling in sensory neurons in a model of generalized pain. J Neurosci. 2008; 28:5721–30. [PubMed: 18509033]
76. Alonso C, Guilarte M, Vicario M, et al. Maladaptive intestinal epithelial responses to life stress may predispose healthy women to gut mucosal inflammation. Gastroenterology. 2008; 135:163–72. [PubMed: 18455999]
77. Slominski A. A nervous breakdown in the skin: stress and the epidermal barrier. J Clin Invest. 2007; 117:3166–69. [PubMed: 17975659]
78. Bosse Y, Pare PD, Seow CY. Airway wall remodeling in asthma: from the epithelial layer to the adventitia. Curr Allergy Asthma Rep. 2008; 8:357–66. [PubMed: 18606090]
79. Zhang DH, Zhou LY, Dong XY, et al. Factors influencing intercellular spaces in the rat esophageal epithelium. World J Gastro. 2010; 16:1063–9.
80. Caviglia R, Ribolsi M, Maggiano N, et al. Dilated intercellular spaces of esophageal epithelium in nonerosive reflex disease patients with physiological esophageal acid exposure. Am J Gastro. 2005; 100:543–8.
81. Orlando LA, Orlando RC. Dilated intercellular spaces as a marker of GERD. Curr Gastro Rep. 2009; 11:190–4.
82. Banerjee B, Meda BK, Lazarova Z, et al. Effect of reflex-induced inflammation on transient receptor potential vanilloid one (TRPV1) expression in primary sensory neurons innervating the oesophagus of rats. Neurogastroenterol Motil. 2007; 19:681–91. [PubMed: 17640184]
83. Matthews PJ, Aziz Q, Facer P, et al. Increased capsaicin receptor TRPV1 nerve fibres in the inflamed human oesophagus. Eur J Gastroenterol Hepatol. 2004; 16:897–902. [PubMed: 15316415]
84. Guarino MP, Cheng L, Ma J, et al. Increased TRPV1 gene expression in esophageal mucosa of patients with non-erosive and erosive reflex disease. Neurogastroenterol Motil. 2010; 22:746–51. [PubMed: 20456759]
85. Shieh KR, Yi CH, Liu TT, et al. Evidence for neurotrophic factors associating with TRPV1 gene expression in the inflamed human esophagus. Neurogastroenterol Motil. 2010; 22:971–7. [PubMed: 20518854]

86. Bieldfeldt K, Davis BM. Differential effects of ASIC3 and TRPV1 deletion on gastroesophageal sensation in mice. Am J Physiol Gastrointest Liver Physiol. 2008; 294:G130–8. [PubMed: 17975130]

87. Cheng L, de la Monte S, Ma J, et al. HCl-activated neural and epithelial vanilloid receptors (TRPV1) in cat esophageal mucosa. Am J Physiol Gastrointest Liver Physiol. 2009; 297:G135–43. [PubMed: 19389802]

88. Burnstock G. Physiology and pathophysiology of purinergic neurotransmission. Physiol Rev. 2007; 87:659–797. [PubMed: 17429044]