
Interstitial Cystitis and Bladder Research Abstracts

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SPEAKER ABSTRACTS

Interstitial Cystitis and Bladder Research

ICBR-1

Interstitial Cystitis: Past and Future

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The diagnosis and management of interstitial cystitis (IC) has had a long and varied history. Leading theories for the pathogenesis of IC include changes in urothelial permeability, increased activity of mast cells, neural-immune mechanisms, plasticity in nervous system, and infectious etiologies. These postulated etiologies have led to a variety of treatment regimens, none of which uniformly eradicate the symptoms of urinary frequency, urgency, nocturia, and/or pain. Treatments for IC have historically ranged from pharmacologic therapies that relax or anesthetize the bladder to antihistamines or drugs that decrease urothelial permeability. Intravesical administration agents such as dimethyl sulfoxide, Clorpactin (sodium

oxychlorosene; Guardian Laboratories, Hauppauge, NY), and bacille Calmette-Guérin have shown some encouraging results in select patients. Pain medications including tricyclic antidepressants have been used with varying success. The surgical history of IC has been dismal for the control of pain. Sacral rhizotomies, augmentation cystoplasties, and cystectomies have failed to relieve symptoms in the majority of patients. More recently, medical devices such as electromagnetic stimulation (Neotonus, Marietta, Ga) or sacral nerve root stimulation (Interstim, Medtronic Corporation, Minneapolis, Minn) have shown some promise. Unfortunately, few of these drugs or devices have been subjected to placebo-controlled randomized trials. Moreover, a consensus on outcome measures is lacking for clinical trials. Thus, the treatment of IC is often not practical, relying on evidence-based medicine.

Recent studies on the natural history of IC have shed insight into potential risk factors, associated conditions, and progression of disease. On the basic science front, there appears to be a surprising convergence of data suggesting common neural mechanisms associated with chronic pain, urgency/frequency symptoms, and nocturia. Regardless of the etiology (infection, inflammatory, neural) for IC, these similar mechanisms may be involved, leading to the limited repertoire of behaviors that bladder can exhibit. Pain and discomfort in IC patients may not be identical, depending on differing etiologies.

Two distinct pathways exist for the initiation and maintenance of chronic pain. One pathway leading to "neuropathic pain" involves sensitization of nociceptive pathways due to nerve growth factor (NGF) with activation of neurons in the central nervous system (CNS) and silent C-fibers in the periphery. Afferents contributing to neuropathic pain exhibit changes in tetrodotoxin (TTX-S) sensitivity to the SCN-3A channel. Another pathway leading to chronic inflammatory pain is associated with activation of silent C-fibers. In contrast, molecular events in response to inflammation cause increased NGF and expression of tetrodotoxin in resistant receptors (TTX-R) as peripheral or central projections. Expression of these 2 distinct isoform Na channels has been linked to spontaneous burst firing of nerves, and a lowering of thresholds for activation. These molecular changes underlie allodynia (nonpainful stimuli causing pain) and hyperesthesia (heightened response to painful stimuli). By analogy, low volume filling of the bladder is painful and nonpainful intravesical contents such as potassium cause discomfort. Changes in primary afferents then lead to plasticity in second-order neurons with the expression of a protein kinase C isoform (Pkc). Elimination of the painful focus may fail to deactivate these neurons in CNS, leading to a behavioral correlate such as phantom pain. Simple blocking or severing a neural pathway is unsuccessful for chronic pain conditions because the abnormal focus of neural activity has been shifted into the CNS. Animal models for chronic cystitis are consistent with this model.

Treatments of neuropathic versus inflammatory conditions differ. Neuropathic pain fails to respond to opiates or prostaglandin inhibitors. Rather, anticonvulsive drugs such as Neurontin (gabapentin capsules; Parke-Davis, Morris Plains, NJ) are of modest benefit. In contrast, inflammatory pain responds to cyclooxygenase-2 (COX-2) inhibitors as well as opiates. It is possible that either or both mechanisms may play a role in the generation of discomfort and even urgency and frequency with IC. Only by understanding the molecular changes associated with the response of bladder to a variety of conditions leading to overactivity can new therapies be developed. The explanation for why certain patients are predisposed to conditions such as IC, prostatodynia, fibromyalgia, and irritable bowel syndrome may be uncovered through genomics. In the absence of identifiable etiologic factors, it is likely that future symptomatic treatments for IC will involve novel approaches relying on turning off activated pain pathways and

targeting specific neurotransmitter receptors or second messenger based on pharmacogenomics.

ICBR-2

Increased Plasma Norepinephrine Concentrations in Cats with Interstitial Cystitis

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The symptoms of interstitial cystitis (IC) seem to be exacerbated by stress, suggesting the involvement of some aspect of the stress effector systems, which include the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. Although previous studies have found abnormal vasomotor tone, and increased bladder sympathetic neuron density and urine norepinephrine (NE) excretion in IC patients, no data concerning plasma catecholamine concentrations or HPA axis function in patients with IC have been reported. To further evaluate the role of the sympathoneural and sympathoadrenal systems and HPA axis in cats with feline IC (FIC), we measured baseline plasma concentrations of catecholamines and their metabolites, and baseline and corticotropin-releasing hormone (CRH)-stimulated plasma adrenocorticotropic hormone (ACTH) and cortisol concentrations to assess the response of the HPA axis to infusion of corticotropin-releasing factor (CRF). A total of 8 healthy cats and 8 cats with FIC were anesthetized and catheters were placed in the external jugular vein. At 6 hours after recovery, samples were obtained for high-performance liquid chromatography analysis of plasma concentrations of NE, dihydroxyphenylglycol (DHPG), epinephrine (E), dihydroxyphenylalanine (DOPA), dopamine (DA), and dihydroxyphenylacetic acid (DOPAC). In 4 cats in each group, 1 μg ovine CRH per kilogram of body weight was infused, and blood samples were collected at intervals for 120 minutes for determination of plasma ACTH and cortisol concentrations. Significant increases in plasma NE and DHPG and a trend toward increased E were found, whereas no effect of FIC on DOPA, DA, DOPAC, ACTH, or cortisol was identified. These results support and extend previous studies identifying an increase in sympathetic activity in cats with FIC. Despite the alterations in sympathetic activity, no effect of FIC on HPA axis function could be identified. In humans, it has been proposed that IC might be a disease within the spectrum of chronic fatigue and pain syndromes that appear to preferentially afflict women. These syndromes are characterized by decreased sympathetic tone and blunted sympathetic and HPA axis responsiveness. The present results, previous studies of sympathetic function in IC patients, and our inability to find abnormalities of HPA axis function suggest that the pathogenesis of IC may be different from other syndromes in the proposed spectrum.

ICBR-3 (See full article on page 32.)

Interstitial Cystitis: A Chronic Visceral Pain Syndrome

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Interstitial cystitis (IC) shares many features with other chronic nonmalignant visceral pain syndromes. In clinical practice, much emphasis has been placed on finding a specific etiology and specific pathological markers for the disease and on identifying specific events that precipitated IC. This focus has influenced clinical treatment approaches for IC, but has not resulted in significant progress in this area so far. An additional approach is suggested, based on 3 hypotheses: (1) a spectrum of different insults can lead to chronic visceral pain in patients suffering from IC; (2) different underlying pathogenic pain mechanisms may require different pain treatment strategies for patients diagnosed with IC; and (3) multiple different pathogenic pain mechanisms may coexist in the same patient, requiring several different pain treatment strategies (perhaps concomitantly) to successfully treat chronic visceral pain associated with IC. This concept is likely to lead to new insights into the pathophysiological mechanisms of IC and to novel treatment avenues for patients with IC as well as—in a broader view—also for patients with other chronic visceral pain syndromes.

ICBR-4

Stimulation of Human Urothelial Cell Proliferation by Estrogen Receptor Activation

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Urothelial cells have been shown to express both estrogen receptor (ER) subtypes, α and β . We examined whether the activation of ER stimulates cell proliferation and whether this effect is mediated by nerve growth factor (NGF). The experiments were performed using human urothelial cells immortalized by human papillomavirus E6 (E6 cells), and cell proliferation was determined using an alamar Blue assay (TREK Diagnostic Systems). The E6 cells were seeded in 96-well plates, incubated with different agents and cell proliferation was determined every 2 hours.

At 8 hours after it was applied, the selective ER- α agonist 16- α -iodo-17 β -estradiol (16 IE2) stimulated cell proliferation by 6.3-fold (10 nmol/L) as compared with a 4.3-fold increase in controls. Similarly, the selective ER- β agonist genistein stimulated cell proliferation by 6.6-fold (100 nmol/L). NGF (100 ng/mL) also stimulated increased cell proliferation (6.5-fold). Cell proliferation was greatly inhibited by specific NGF antiserum. Stimulation of cell proliferation by either 16 IE2 or genistein appeared to be inhibited by specific NGF antiserum. Western blotting and/or immunocytochemistry revealed expression of ER- α and - β , Trk A (high-affinity NGF receptor), p75 (low-affinity NGF receptor), and NGF in E6 cells. Taken together, these results indicate that activation of