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Urinary bladder, cystitis and nerve/urothelial interactions

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ABSTRACT

A hallmark of functional pain syndromes, such as bladder pain syndrome/interstitial cystitis (BPS/IC) is pain in the absence of demonstrable infection or pathology of the viscera or associated nerves. There are no clear definitions of this syndrome, no proven etiologies and no effective treatments able to eradicate the symptoms. 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. Severe cases of this disorder, which affects primarily women, can have considerable impact on the quality of life of patients due to extreme pain and urinary frequency, which are often difficult to treat. In addition, BPS/IC patients may also suffer co-morbid conditions where pain is a common symptom (such as irritable bowel syndrome, fibromyalgia). Theories explaining the pathology of bladder pain syndrome are many and include an altered bladder lining and possible contribution of a bacterial agent.

1. Introduction

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a debilitating chronic disease characterized by suprapubic pain related to bladder filling, coupled with additional symptoms, such as increased day- and night-time urinary frequency, without proven urinary infection or other obvious pathology. Although the symptoms presented may appear similar to those of a urinary tract infection, urine culture reveals no underlying infection and there is no response to antibiotic treatment (Parsons et al., 1993; Hanno et al., 1999; Bladder Research Progress Review Group, 2002). Between 700,000 and 1 million people in the United States have IC, the preponderance of who are women (Bladder Research Progress Review Group, 2002). Moreover, it has been estimated that a 60% increase in the number of cases would be identified by experienced clinicians who apply the strict National Institute of Diabetes, Digestive, and Kidney Diseases definition of BPS/IC (Hanno et al., 1999). While the etiology is unknown, theories explaining the pathology of BPS/IC include altered barrier lining, afferent and/or CNS abnormalities, a possible contribution of inflammatory or bacterial agent and abnormal urothelial signaling.

2. Disease process and relevant animal models

The etiology of BPS/IC is unknown; however, several causes have been postulated, including epithelial dysfunction (i.e., leaky urothelium), infection, autoimmune response, allergic reaction, neurogenic inflammation, and inherited susceptibility (Bladder Research Progress Review Group, 2002; NIH Publication No. 02-3220, 2002).

A number of animal models have been used for the study of BPS/IC, which includes administration of an irritant or immune stimulant (e.g. hydrochloric acid, turpentine, protamine sulfate, mustard oil, lipopolysaccharide and cyclophosphamide). Studies have shown that a deficiency of estrogen receptor-beta in female mice develop a bladder phenotype (including alterations in the urothelium) which may share similarities with human PBS/IC (Imamov et al., 2007). However, a review of such animal models discusses the potential problems in artificially inducing bladder inflammation or injury and thus may not be considered a valid method to model the symptoms of this complex syndrome (Westropp and Buffington, 2002; Buffington, 2008). 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 damaged rodent bladder urothelium to rapidly regenerate post-intravesical insult thus limiting the capacity to establish chronicity in these models reflective of the human condition.

A naturally occurring disease occurring in cats, termed feline interstitial cystitis, reproduces many features of BPS/IC in humans diagnosed with this disorder (Buffington, 2008). In addition, an experimental autoimmune cystitis (EAC) murine model has been shown to exhibit a number of comparable functional and histological alterations to that in human BPS/IC (Lin et al., 2008). Also similar to BPS/IC patients, pseudorabies virus (PRV) injection in mice results in the development of a neurogenic cystitis associated with pelvic pain and accumulation of mast cells (Rudick et al., 2009). Stress has been shown to impair the immune, endocrine and nervous systems and can be an important

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factor in functional gastrointestinal (GI) and genitourinary (GU) disorders such as irritable bowel syndrome (IBS) and BPS/IC. For example, rats exposed to various types of stress (water avoidance, intruder stress) exhibit symptoms of bladder dysfunction including increased micturition frequency as well as anxiety-like behavior (Smith et al., 2008; Wood et al., 2009). Further, an exaggerated acoustic startle response has been demonstrated in both cats diagnosed with feline IC as well as in BPS/IC patients (Westropp et al., 2006; Twiss et al., 2009). This response is a brainstem reflex responding to unexpected loud stimuli and parallels that of autonomic control. Even though the pathophysiology and etiology of most persistent pain syndromes are incompletely understood, it is generally assumed that they involve changes in the target organ as well as alterations in both central and peripheral processing/modulation of nociception and pain. 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 (May, 2008; Mayer and Bushnell, 2009).

Due to the complex nature of BPS/IC it is thus unlikely that a single animal model would be suitable for investigative work and thus a panel of models reflecting the key symptoms and known components

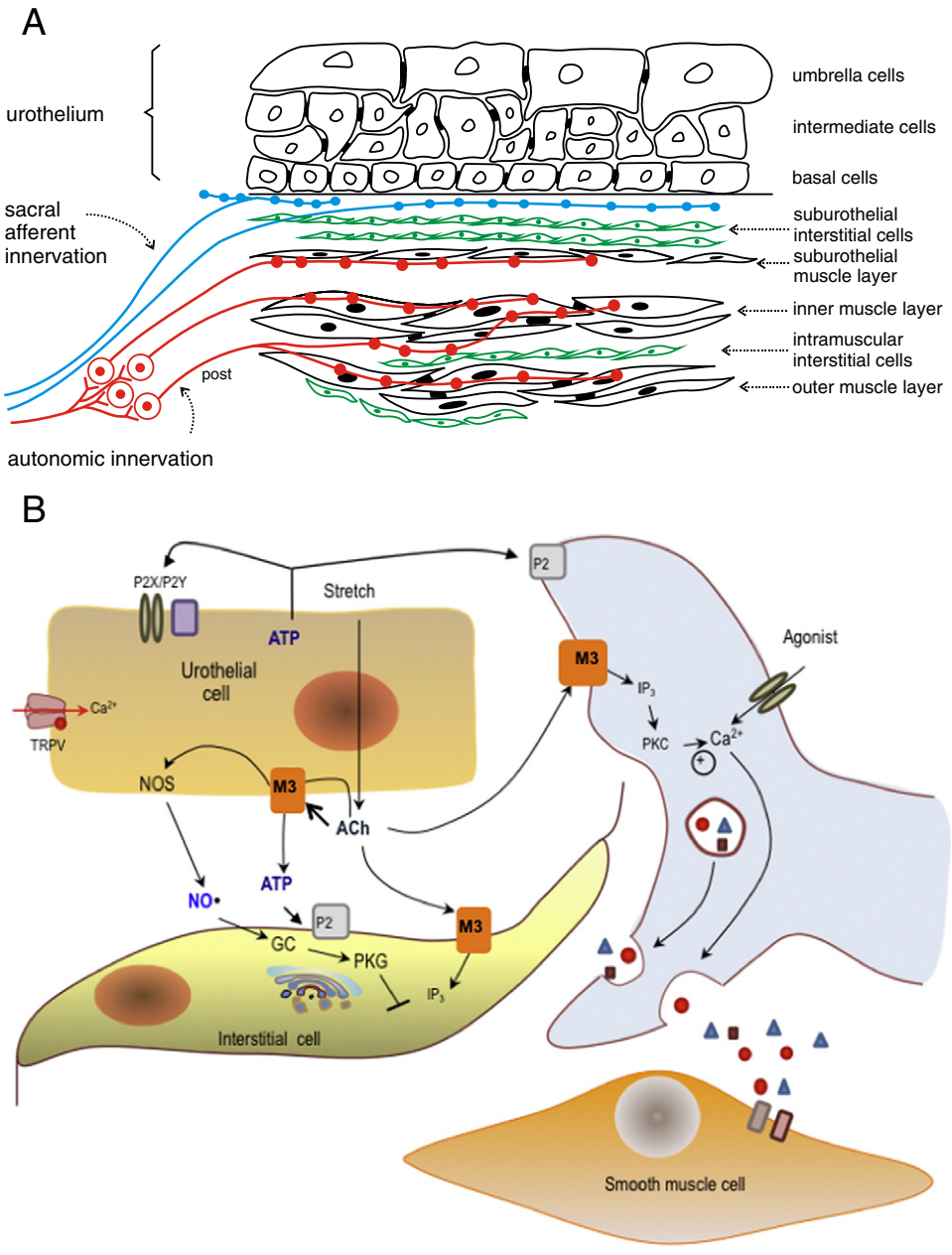

Fig. 1. A) Cartoon depicting various components of the bladder wall. These include subtypes of urothelial cells (with apical or umbrella cells connected via tight junctions), layers of smooth muscle cells; interstitial cells (in green) whose functions have not yet been defined but may play a role in intercellular communication, sacral afferent innervation (blue), and autonomic (parasympathetic and sympathetic) innervation (red). Pre, preganglionic; post, postganglionic. B) Hypothetical model depicting possible interactions between afferent nerve fibers (blue), urothelial cells, smooth muscle and interstitial cells. Urothelial cells can also be targets for transmitters (such as ATP, nitric oxide—NO, acetylcholine—ACh) released from nerves or other cell types. Urothelial cells can be activated by either autocrine (i.e. autoregulation) or paracrine (release from nearby nerves or other cells) mechanisms. For example, mechanical stimuli such as bladder distension can release urothelial-acetylcholine, which then activates urothelial cholinergic (muscarinic) receptor subtypes, resulting in release of additional transmitters. M3-muscarinic subtype receptor; P2R or P2X/P2Y—purinergic subtype receptors; GC—guanylate cyclase; IP3—inositol triphosphate; PKC—protein kinase C; PKG—cGMP-dependent protein kinase; Ca^{2+}-calcium; TRPV—transient receptor potential family of ion channels; NOS—nitric oxide synthase.