Could Overactive Bladder be a Chronic Inflammatory Disorder?

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INTRODUCTION

Overactive bladder syndrome (OAB) typically includes the lower urinary tract symptoms of frequency, urgency, and varying severities of urgency urinary incontinence. It has been defined by the International Continence Society as a "symptom syndrome suggestive of lower urinary tract dysfunction". It is specifically defined as "urgency, with or without urge incontinence, usually with frequency and nocturia". The prevalence in men has been estimated to be around 17% and OAB negatively impacts the quality of life [1]. Although the cause has been divided into neurogenic and non-neurogenic pathophysiologies [2], there has been investigation into the role of inflammation in the development of detrusor overactivity in patients with overactive bladder. Galvin et al [3] demonstrated that stretching of human bladder smooth muscle cells, as seen in OAB, is associated with a decrease in proapoptotic cytokine transforming growth factor-β1 at the mRNA and protein levels. These findings support the hypothesis that an inflammatory process has a role in the pathophysiology of OAB. This article reviews published reports consisting of basic research and clinical studies on the pathophysiology of OAB to evaluate whether inflammation could explain some of the causative and propagating features of overactive bladder.

PATHOPHYSIOLOGY

Myogenic hypothesis

The myogenic theory as summarized by Brading et al [4] is based on the findings of common macroscopic structural changes of detrusor muscles in overactive bladder. These morphologic features are caused by reduced excitatory impulses to the bladder, which result in alterations in bladder smooth muscle and an increase in the sensitivity and coupling of the smooth muscle cells of the bladder. Histological examination of bladder smooth muscle in patients with overactive bladder shows increased myogenic activity, enhanced coupling and fused tetanic contractions [5]. In addition, increased connective tissue infiltration in smooth muscle bundles, with patchy denervation of the detrusor muscle has been seen in human bladder tissue of those with detrusor overactivity [6,7]. The reduction in normal neuronal excitatory input causes detrusor muscle supersensitivity to acetylcholine, the most important neurotransmitter, resulting in detrusor contractions [8]. Thus, the smooth muscle cells of the overactive bladder are more susceptible to contraction and smooth muscle bundles are better coupled. It has been postulated that the structural changes and increased coupling in overactive bladder allow this local activity to spread to the rest of the detrusor and make it more susceptible to spontaneous contractions [4]. However, the myogenic hypothesis does not seem to explain any role of inflammation in the pathophysiology of overactive bladder.

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Peripheral autonomous hypothesis

Drake et al [9] proposed that the bladder is modular, that increased bladder sensation results from exaggerated localized modular contraction, and that detrusor overactivity is due to enhanced coordination of modular activity through the intramural ganglia and interstitial cells. An imbalance of excitation and inhibition increases in peripheral autonomous activity, resulting in increased bladder sensation as well as detrusor overactivity. These synchronized activated localized modules and subsequent propagation of contraction could be the cause of overactive bladder. We cannot yet interpret any relationship between inflammation and the mechanism of overactive bladder based on this hypothesis.

Afferent mechanism

C-fibers are generally quiescent during normal voiding, but they may be critical for symptom generation in pathologic conditions. In a cat model, some mechano-insensitive units started to respond to increases in intravesical pressure [10]. Several authors have concluded that these normally insensitive C-fibers are recruited to form a new afferent pathway and establish the mechanism of bladder pain and detrusor overactivity [11,12]. Following neurologic or inflammatory pathology, C-fibers become the important afferent pathway carrying impulses involved in the micturition reflex to the spinal cord [13]. In an animal model of partial bladder outlet obstruction, significantly enlarged postganglionic neurons of the urinary bladder were identified to confirm the development of neural plasticity in bladder afferent pathways [14]. Bladder outlet obstruction- induced hypertrophied bladder tissue contains higher NGF levels; blockade of NGF could lead to a significant decrease in the mean area of pelvic ganglion neurons from unobstructed animals [15]. In addition, Rong et al [16] suggested that $P2X_3$ receptor-mediated mechanisms also contribute to mechanosensory transduction in the bladder. Smet et al [17] demonstrated that nerves containing calcitonin gene-related peptide (CGRP) and tackykinins are typically present within the suburothelium. They also examined bladder biopsies from patients with idiopathic detrusor overactivity, and found that the inmmunoreactive nerves of CGRP and substance P in the suburothelium were increased significantly. The urothelium has been postulated to be a mechanosensor, with various inhibitory and excitatory mediators involved in the control and modula-

tion of afferent nerve firing and thresholds for bladder activity [18]. In the afferent mechanism, it is of note that several neuropeptides (nerve growth factor, substance P, tachykinins), which might be released from the urothelium through the activation of inflammatory insults, are associated with the pathophysiology of overactive bladder.

Neurogenic hypothesis and neurogenic inflammation

The neurogenic theory suggests that detrusor overactivity arises from generalized, nerve-mediated excitation of the detrusor muscle. Several studies have demonstrated that damage to central inhibitory pathways or sensitization of bladder peripheral afferents can induce detrusor overactivity by unmasking primitive micturition reflexes. Neurogenic detrusor overactivity includes various neurological disorders such as Parkinson's disease, multiple sclerosis, stroke spinal cord injury and pelvic nerve neuropathy [19]. When suprapontine lesions involving the micturition centers are disturbed, the normal inhibitory signal to the bladder is reduced, and detrusor overactivity occurs [20]. In an animal spinal cord injury model [12], the afferent micturition reflex consists of C-fibers; the pathways from the brain to spinal cord are interrupted, and reorganization of spinal reflexes develops, causing initiation of automatic micturition. The main trigger for changes in afferent transmission in the central nervous system may be nerve growth factor (NGF). NGF is elevated in the bladders of some models of OAB [21,22]. In animal models of bladder outlet obstruction, chemical cystitis, and spinal cord injury, blockade of NGF by antibodies against NGF prevents urinary frequency, detrusor contractions, micturition reflex activity, and hypertrophy of dorsal root ganglion neurons. Based on these findings, NGF plays a critical role in the pathophysiology of OAB [5].

The concept of neurogenic inflammation has recently been described. Neurogenic inflammation is associated with overactivity of the bladder, which is triggered by the release of substance P and CGRP from sensory nerve terminals [23]. There is neurogenic inflammatory processing- induced overexpression of transient receptor potential vanilloid 1 (TRPV1) receptors in the suburothelium and c-fos protein in the dorsal root ganglia in animal models of OAB [24]. In addition, similar findings were identified in biopsies of human bladders [25]. Taken together, these observations suggest that inflammation might involve the pathophysiology of neuronal events resulting in OAB.

EVIDENCE OF INFLAMMATION ASSOCIATED WITH OAB

Bladder outlet obstruction (BOO) is the most common etiology of OAB and benign prostatic hyperplasia (BPH) is the main cause of BOO in men. Investigators found expression of cytokines and growth factors in BPH stromal tissue [26], which implicates inflammation in BPH and OAB. A large-scale population-based cohort study demonstrated that non-steroidal inflammatory drug use may prevent or delay development of benign prostatic hyperplasia [27]. Another short-term study also indicated that adding a cyclooxygenase-2 (COX-2) inhibitor anti-inflammatory agent (Refecoxib) improved lower urinary tract symptoms (LUTS) in subjects with BPH [28]. The serum C-reactive protein concentration, an indicator of intraprostatic inflammation, might correlate with lower urinary symptoms in men [29]. Data from the REDUCE trial, a 4-yr, phase 3, placebo-controlled study, also provided evidence of a relationship between the degree of LUTS and the degree of chronic inflammation [30]. In a rodent model of overactive bladder, Jang et al demonstrated that intravesical instillation of COX-2 inhibitors can alter the expression of inflammatory modulators and cytokines in bladder tissue, and improve the parameters of detrusor contraction [31]. In an experimental model of cystitis, treatment with RDP58, a synthetic peptide that inhibits early signal transduction pathways for the expression of inflammatory cytokines, reduced inflammation and neurotrophic factors such as NGF and substance P in vivo. Consequently, by decreasing the production of inflammatory and neurotrophic factors, RDP58 modulates the neuroplastic response to inflammation to improve symptoms of OAB [32].

CONCLUSIONS

OAB has various etiologic mechanisms from which we hope to identify the relationship between detrusor overactivity and chronic inflammation. An association among inflammatory disorders, cytokines, and the peripheral and central nervous system may be responsible for the pathogenesis of overactive bladder. Many published reports have also demonstrated that anti-inflammatory drugs aid in the treatment of OAB symptoms by modulating inflammatory responses. In summary, OAB syndrome could be a chronic inflammatory disorder.

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