What We Know about Overactive Bladder in 2009 - Editorial

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Overactive bladder (OAB) is a highly prevalent disorder which affects the quality of life in both genders [1]. About 70% of patients with OAB can be successfully treated with antimuscarinics, however, OAB symptoms may recur from time to time [2]. OAB can be involuntary detrusor contractions (detrusor overactivity, DO) occurring during the bladder filling phase or before bladder capacity is reached. Recent research on animal and human bladders has demonstrated that DO occurring in the filling phase is likely to be caused by abnormal activation of sensory nerves through excitability of sensory receptors such as the transient receptor potential vanilloid subfamily 1 (TRPV1), purinergic receptor $P2X_3$, and muscarinic receptors on the suburothelial fibers [3-6]. Abnormally increased production of acetylcholine (ACh) or adenosine triphosphate (ATP) could be another source in response to urothelial dysfunction or stretching [7].

Immunohistochemistry studies of the bladder wall of patients with OAB have revealed increases of sensory receptors in the suburothelium [8]. Nerve growth factor (NGF) production has been found to increase in the bladder wall of patients with OAB [9]. Although the NGF levels in bladder tissue are not correlated with urine NGF levels [10], urinary NGF concentrations have been consistently found to increase in patients with OAB, especially in those with the symptom of urgency incontinence (OAB wet) [11]. Urinary NGF levels were found to decrease in OAB responders to antimuscarinics [12] and in those treated with intravesical botulinum toxin injections [13]. Moreover, urinary NGF levels were found to increase not only in idiopathic DO, but also in patients with neurogenic DO due to spinal cord injury or cerebrovascular accident [14,15]. These results provide evidence that OAB could be partially a sensory disorder.

NGF has been implicated as a chemical mediator of pathology-induced changes in C-fiber afferent nerve excitability and reflex bladder activity [16,17]. NGF has attracted considerable attention as a key player in the link between inflammation and altered pain signaling. It is expressed widely in various cells including urothelial cells, smooth muscle cells and mast cells and can activate mast cells to degranulate and proliferate. In patients with interstitial cystitis/painful bladder syndrome (IC/PBS), neurotrophins, including NGF, neurotrophin-3 and glial cell derived neurotrophic factor have been detected in the urine [18]. Increased expression of NGF is also present in bladder biopsies from women with IC/PBS [9]. NGF- activated mechanisms might be a potential target for the treatment of painful symptoms in IC/PBS.

Much research has demonstrated that OAB and IC/PBS might have a common pathophysiological pathway. OAB has been considered a disorder of bladder hypersensitivity [19]. This hypothesis could be true in patients with OAB without urgency incontinence or urodynamic DO (OAB dry), but might not be completely true in those with OAB wet. Patients with OAB dry present with urgency and frequency, and some also present with lower abdominal discomfort at full bladder. These symptoms are quite similar to those in patients with IC/PBS. In an analysis of urinary NGF and prostaglandin E2 in patients with OAB dry, OAB wet and IC/PBS, we found that urinary NGF levels were significantly elevated in patients with OAB wet as well as IC/PBS, but only mildly elevated in those with OAB dry [20]. In a recent study investigating urinary cytokines and chemikines, the mean urine cytokine/chemokine levels were higher in OAB wet than OAB dry, suggesting a linear relationship between symptom severity and cytokine levels. Using proteomics, urinary chemokines such as monocyte chemoattractant protein 1, IP-10, and platelet derived growth factor were also found to increase in OAB dry, OAB wet and IC/PBS in comparison with that in controls [21]. The increased urinary chemokines reflect the inflammatory condition in the bladder wall in OAB and IC/PBS. Although correlations of these urinary chemokines with the clinical presentation of OAB and IC/PBS at baseline and after treatment should be further evaluated, these two bladder disorders could be caused by inflammatory conditions.

Bladder inflammation caused by intravesical irritants or that in patients with IC/PBS leads to acute afferent nerve activity and to long-term plasticity that lowers the threshold for nociceptive and mechanoceptive afferent fibers [22-24]. Chronic sensitization of afferent fibers might involve both peripheral and central mechanisms. A rise in bladder NGF in the muscle or urothelium initiates signals that are transported along the afferent nerves of the bladder to the dorsal root ganglia or spinal cord [25,26]. A previous study using intravesical injection of botulinum toxin A (BoNT-A) in treatment of refractory IC/PBS has shown that BoNT-A injections reduce bladder pain in IC/PBS patients [27]. NGF levels in the bladder tissue are significantly increased in patients with IC/PBS and decreased to the normal range after BoNT-A treatment [28].

The actual pathophysiologies of OAB and IC/PBS have not yet been elucidated. Recent investigations have focused the pathophysiology of OAB and IC/PBS on sensory disorders. Chronic inflammation activated either locally or systemically could be the very beginning. Activation of sensory nerves (A δ or C-fibers) by mechanical or chemical stimuli plays a key role in this condition by transmitting signals to the central nervous system to induce painful sensations and by releasing chemicals such as tachykinins that induce or enhance inflammatory mechanisms in the periphery. Understanding the pathophysiology of OAB and IC/PBS would aid in the selection of appropriate medication for an adequate period of treatment and increase the chance of a cure for these chronic bladder disorders.

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