IL5: 招請講演 5

Urothelial-Afferent Interaction: A Possible Mechanism inducing Overactive Bladder (OAB)

Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, PA, U.S.A.
Naoki Yoshimura, M.D., Ph.D.

Overactive bladder (OAB) is a symptom complex that includes urinary urgency with or without urge incontinence, urinary frequency and nocturia. Although the precise etiology for OAB is not known, there is increasing evidence showing that bladder urothelial cells can release chemical mediators such as acetylcholine (ACh), adenosine triphosphate (ATP), nitric oxide (NO) and prostaglandins in response to local chemical and mechanical stimuli and that substances released from urothelial cells can alter the excitability of bladder afferent nerves, which are located close to or in the urothelium, acutely and chronically, thereby contributing to OAB symptoms.

Cholinergic mechanism: Evidence suggests that the involvement of the muscarinic ACh receptor in bladder function extends beyond detrusor contractility and into afferent sensory functioning. Muscarinic receptors are located on the urothelium and basal release of ACh from the urothelium is increased with age and stretch. Therefore, there are the possibilities that increased levels of non-neuronal ACh released from the urothelium can induce OAB mediated by enhanced interaction with local muscarinic receptors. Since intravesical application of low dose antimuscarinic agents such as oxybutynin and tolterodine as well as human urine excreted after oral administration of trospium are reportedly effective to suppress detrusor overactivity in a rat model of OAB, suppression of muscarinic receptor–urothelial ACh interactions could be another mechanism for the therapeutic effects on OAB of antimuscarinics in addition to direct inhibition of muscarinic receptors in detrusor smooth muscles.

Local activation of nicotinic ACh receptors located on urothelial cells and afferent nerves can also modulate bladder activity. While intravesical application of low dose nicotine increased bladder capacity, probably due to release of urothelial–derived inhibitory mediators such as NO, intravesical high concentration nicotine can directly stimulate nicotinic receptors located at C-fiber afferent terminals to induce detrusor overactivity in rats. Thus, it is assumed that increased levels of non-neuronal ACh in the bladder could induce OAB mediated by enhanced interaction with afferent nicotinic receptors and that these receptors could be another target for the treatment of OAB.

Purinergic mechanism: ATP released from urothelial cells during stretch or chemical stimuli can activate suburothelial bladder afferents expressing P2X3 receptors to induce signaling changes in bladder activity. Intravesical application of ecto-ATPase inhibitors to increase endogenous ATP levels in the bladder reportedly induced detrusor overactivity in rats. Thus, targeting urothelial ATP release and/or suppression of P2X receptors in afferent pathways could be an effective therapy for OAB.

Nitrergic mechanism: NO can be released by the urothelium via stimulation of various receptors including TRPV1 capsaicin receptors and adrenoceptors. Because suppression of locally released NO by intravesical application of NO synthase inhibitors enhanced capsaicin–induced detrusor overactivity in rats, urothelially released NO seems to act as an inhibitory factor for bladder activity. In addition, intravesical application of NO donors inhibited cyclophosphamide–induced detrusor overactivity in rats. Thus, modulation of local NO levels in the bladder could be a potential modality for the treatment of OAB.

In conclusion, these observations have significant implications for a more complete understanding of the effects of currently used drugs on these sensory mechanisms and for identifying potential targets for pharmacologic intervention in OAB.

Supported by NIH grants (DK57267, DK68557 and P01 HD39768)