Recent Research Advances in the Pathophysiology of Overactive Bladder

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INTRODUCTION

Overactive bladder syndrome (OAB) is a widespread medical condition with significant impact on the quality of life. It is characterized by urinary frequency and urgency with or without incontinence [1]. In the early 2000s, it had an overall prevalence of 16% in western Europe [2] as well as in the United States [3]. It occurs more frequently in women than in men, and its incidence increases with age [4,5]. Although many basic and clinical studies have been performed, the cause of OAB is still to be established [6]. The mainstay of current pharmacological treatment involves the use of muscarinic antagonists, but their therapeutic effectiveness is limited by a combination of limited efficacy and troublesome side effects [7,8]. Therefore, finding the true cause of OAB is currently the most important issue for developing effective treatments for OAB. This review aims to provide insight into recent research advances in the pathophysiology of OAB.

MAIN THEORIES SURROUNDING OAB

Three main theories have been proposed regarding the cause of OAB, the myogenic, neurogenic and autonomous bladder theories.

The myogenic theory was first stated by Brading in 1997 [9]. It suggests that alterations in the properties of the detrusor myocytes are a necessary prerequisite for the production of an involuntary detrusor contraction which in turn causes an unstable increase in intravesical pressure. It has recently been reported that events leading to enhanced intravesical pressure during voiding may result in periodic ischemia of the bladder resulting in damage to some intrinsic neurons in the bladder wall and secondary changes in the smooth muscle properties over time [10,11]. These changes may then increase excitability and electrical coupling between cells. A local contraction occurring in any part of the detrusor will then spread throughout the bladder wall, resulting in a coordinated myogenic contraction of the entire bladder [9,12,13]. In addition, partial denervation of the detrusor may cause supersensitivity of the detrusor to neurotransmitters, which consequently augments the response to stimulation [14].

The neurogenic theory suggests that damage to central inhibitory pathways in the brain and spinal cord or sensitization of peripheral afferent terminals in the bladder can unmask primitive voiding reflexes that trigger detrusor overactivity. This can result from damage to the brain, which can induce detrusor overactivity by suppressing suprapontine inhibition; damage to axonal pathways in the spinal cord leads to the emergence of primitive spinal bladder reflexes triggered by C-fiber bladder afferent neurons [15]. Neurogenic causes may therefore be seen in patients who have multiple sclerosis, cerebrovascular events and Parkinson's disease. Kessler et al [16] reported that thalamic deep brain stimulation resulted in an earlier desire to void and decreased bladder capacity, suggesting a regulatory role of the thalamus in lower urinary tract function. Recent brain imaging studies have also demonstrated that bladder control depends on an extensive network of brain regions. Dysfunction in various parts may contribute to urge incontinence, suggesting that there are different phenotypes requiring different treatments [17]. Abnormality in non-adrenergic non-cholinergic (NANC) neurotransmission may also cause OAB. O'Reilly et al [18] were unable to detect a purinergic component of nerve-mediated contractions in control (normal) human bladder preparations but found a significant component in overactive bladder specimens, where the purinergic component was around 50%. They concluded that this abnormal purinergic transmission in the bladder might explain symptoms in these patients.

The autonomous bladder theory, which has recently been developed, suggests that the detrusor muscle is arranged into modules, which are circumscribed areas of muscle active during the filling phase of the micturition cycle. These modules might be controlled by a peripheral myovesical plexus, consisting of intramural ganglia and interstitial cells (ICs). There can be synchronization of activity between modules, which could propagate through the intramural nerve or interstitial cell networks, or by direct communication between muscle cells. Researchers propose that detrusor overactivity results from exaggerated symptomatic expression of peripheral autonomous activity, resulting from a shift in the balance of excitation and inhibition in smooth muscle modules [19,20]. Although this theory also applies within the myogenic model, it is less specific with respect to the mechanism.

AFFERENT BLADDER SIGNALING

Afferent innervations locating within the suburothelial layer of the bladder wall have recently attracted much research interest. Numerous stimulatory and inhibitory mediators and neurotransmitters may be released from the urothelium and interact with a variety of specialized receptors and participate in signal transduction leading to wider neuroactivation. Dysregulation of bladder afferent activity leads to altered micturition signaling within bladder efferent pathways and consequently causes impaired detrusor function [21]. Oxidative stress induced by H_2O_2 has recently been demonstrated to activate capsaicin-sensitive C-fiber afferent pathways, thereby inducing detrusor overactivity. Yamagushi et al [22] hypothesized that OAB may be more accurately defined as a hypersensitivity disorder than a syndrome characterized primarily by urgency. Therefore, research is focusing on developing afferent nerve blockers as a potential treatment for OAB. A novel

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positive modulator of calcium-activated K^+ channels of small and intermediate conductance, 4,5-dichloro-1,3-diethyl-1,3-dihydrobenzoimidazol-2- one (NS4591), which activates small conductance K^+ channels in acutely dissociated bladder primary afferent neurons, has been demonstrated as an effective compound in animal models of bladder overactivity [23].

UROTHELIUM

Increasing evidence has suggested that the urothelium is not just a passive barrier, but is also a responsive structure capable of detecting thermal, mechanical and chemical stimuli. The factors that release from the urothelium may alter the excitability of afferent nerves and affect detrusor muscle contractility [24,25]. Absence of the urothelium may cause an increase in the spontaneous activity of the detrusor [26]. Shioyama et al [27] reported that chronic urotherial injury leads to an increase in urinary frequency and a decrease in voiding volume. Thus the urothelium is an important participant in the pathophysiology of OAB.

Urothelial cells express ion channels similar to the stretch activated (mechanosensitive) channels in nervous tissue and these channels may play a role in mechanotransduction in the lower urinary tract. The epithelial sodium channel (ENaC) has been implicated in several processes including transduction of mechanical and nociceptive stimuli [28]. The transient receptor potential vanilloid 1 (TRPV1), a Ca^{2+}-permeable, non-selective cation channel which has a prominent role in nociception, is present in urothelial cells and underlies their sensitivity to vanilloid compounds. Exogenous application of capsaicin or resiniferatoxin increases intracellular calcium and evokes transmitter (NO, ATP) release in cultured urothelial cells. These responses were eliminated in TRPV1 null mice [29,30], indicating that TRPV1 is essential in mediating the responses of the urothelium in intravesical chemical stimulation. Although only TRPV1 has been extensively studied so far, the role of TRP channels is an interesting new target of research [31].

A recent study has demonstrated that the urothelium synthesizes and releases acetylcholine (Ach) which differs widely from that of neurons with respect to the molecular components of the ACh synthesis and release machinery. Thus, these two systems might be differentially targeted by pharmacologic approaches to OAB [32].

INTERSTITIAL CELLS

The importance of a further component of the bladder wall, interstitial cells (ICs), is currently evoking much interest, although their exact function is still to be established. Hashitani et al [33] demonstrated that unlike the interstitial cells of Cajal in the gastrointestinal tract, ICs in the detrusor layer may modulate the transmission of Ca^{2+} transients originating from smooth muscle cells rather than acting as the pacemaker of spontaneous activity in detrusor smooth muscle. Suburothelial ICs which form a network by gap junctions have been suggested to play a role in amplifying the sensory response to bladder-wall stretch through physical interaction with their neighbors [34]. Guinea pig bladder detrusor ICs, both as isolated cells and within whole tissue preparations, respond to cholinergic stimulation by firing Ca^{2+} transients [35]. Furthermore, a c-Kit antagonist, imatinib mesylate (Gleevec®, Novartis Pharma AG, Basel, Switzerland), has the ability to affect the spontaneous electrical activity of detrusor at concentrations that do not change the shape of the action potential [36], and it also inhibits the spontaneous activity and evoked smooth muscle contraction in human overactive detrusor [37]. Therefore, it is not surprising that enhanced activity of ICs may cause bladder overactivity. Increased gap junction formation in the suburothelium has recently been demonstrated in biopsies from humans with detrusor overactivity (DO) [38]. It is hypothesised that this change could have a significant role in the pathogenesis of detrusor abnormality.

CONCLUSION

In summary, the pathophysiology of OAB includes damage to intrinsic neurons resulting in altered properties of smooth muscle cells, decreased suppression of suprapontine inhibition, abnormal peripheral NANC neurotransmission, increased afferent activity, changes in urothelial signaling and enhanced activity of ICs. The true cause of OAB and detrusor overactivity may be different in different individuals, and may include one or more of the above and possibly other mechanisms that are yet to be described.

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