The Role of Urothelial Dysfunction in Pathogenesis of Overactive Bladder

Yao-Chi Chuang, M.D.

Department of Urology, Chang Gung Memorial Hospital, Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan

ABSTRACT

Several recent studies have provided new insight into the mechanisms of overactive bladder (OAB) and the pharmacological therapies to control them. The urothelium is comprised of three cell layers, a basal cell layer, an intermediate cell layer, and a layer of large polyhedral umbrella cells. Bladder urothelium cells have neurosensory-like functions, which is beyond the scope of barrier function.

The cross talk between the urothelium and nervous system has expanded our understanding of OAB. Evidence has shown that urothelium cells have muscarinic receptors, purinergic receptors, and TRPV1 receptors (transient receptor potential TRP) channels that are commonly attributed to neurons. Therefore, the functions of the urothelium, that is the barrier function and sensory function, have a close relationship with the nervous system. Malfunction of the urothelium might link to the development of OAB.

The identification of chemical dialogue between the urothelium and the suburothelial nerve plexus provides additional targets for the treatment of OAB. Muscarinic receptors are widespread in the urothelium as well as in detrusor muscle. The role of antimuscarinic agents in the treatment of OAB may be focused largely at the bladder urothelium. Injection of botulinum toxin, which not only targets both the sensory and motor arms, but also normalizes urothelial chemical transmission, provides an alternative for those refractory to conventional therapy.

Keywords: overactive bladder, muscarinic receptors, purinergic receptors

INTRODUCTION

Several recent studies on the sensory mechanisms of the urothelium and application of botulinum toxin for the treatment of overactive bladder (OAB) have provided new insight into the mechanisms of OAB and the pharmacological therapies to control them. The current article is a brief summary from the review papers of Birder et al [1], Apostolidis et al [2], and Hsu et al [3]

THE ANATOMY AND BARRIER FUNCTION OF THE UROTHELIUM

The luminal surface of the bladder is covered by the urothelium, which functions as a highly efficient barrier to the movement of water, ionized substances, and toxic solutes across the bladder wall. Urothelium is composed of at least three layers, a basal cell layer attached to a basement membrane, an intermediate layer, and a superficial or apical layer composed of large hexagonal cells (diameters of 25-250 μm) known as 'umbrella cells'. Normally the urothelium has a turnover rate of about 3 to 6 months. However, the turnover can be markedly increased by injury or pathological conditions.

The primary urine-plasma barrier is the layer of superficial umbrella cells. The umbrella cells are interconnected by tight junctions and are covered on their apical surface by crystalline proteins called uroplakins which assemble into hexagonal plaques. The barrier function of the urothelium depends on several features of the umbrella cell layer, namely (1) tight-junction complexes that reduce the movement of ions and solutes between cells, (2) specialized lipid molecules and uroplakin proteins in the apical membrane, which reduce the permeability of the cells to small molecules (e.g. water, urea, protons), and (3) the sulfated polysaccharide glycosaminoglycan layer at the apical surface of the urothelium that is thought to act as a nonspecific antiadherence factor and as a defense mechanism against infection.

INJURED UROTHELIUM

When the umbrella cell layer was selectively damaged by protamine sulfate, it was shown that the urothelium rapidly undergoes both functional and structural changes to restore the barrier. The initiation of urothelial proliferation is thought to involve upregulation of growth factors, such as fibroblast growth factor and nerve growth factor. A number of local factors (e.g. tissue pH, mechanical or chemical trauma, and bacterial infection) and pathological conditions, such as interstitial cystitis or spinal cord injury, can modulate the barrier function of the urothelium. When the barrier function is compromised, water, urea and toxic substances can pass into the underlying tissue (neural and/or muscle layers), which results in symptoms of urgency, frequency and pain during bladder filling and voiding. In addition, disruption of the urothelial barrier has been associated with ultra structural changes and alterations in the levels of chemical mediators such as nitric oxide (NO) and adenosine triphosphate (ATP), which can alter epithelial function and/or integrity.

INNERVATION OF THE UROTHELIUM

Both afferent and autonomic efferent nerves are located in close proximity to the urothelium. Peptide-immunoreactive and TRPV1-immunoreactive nerve fibers (two types of afferent nerves) are localized throughout the urinary bladder musculature and in a plexus that lies beneath, and extends into, the urothelium. Markers for cholinergic and adrenergic nerves have also been detected in these same regions.

Received: February 10, 2009 Accepted: March 2, 2009
Address correspondence to: Dr. Yao-Chi Chuang, Department of Urology, Chang Gung Memorial Hospital, Kaohsiung Medical Center, 123, Ta-Pei Road, Niao Song Hsiang, Kaohsiung, Taiwan
E-mail: chuang82@ms26.hinet.net

Human bladders have shown mRNA expression in both human detrusor and urothelium for β1, β2 and β3-adrenoceptors and M1 to M5 muscarinic receptors. There is a slightly higher level of beta adrenoceptor mRNA expression in the urothelium than the detrusor muscle. The functional implicaton of urothelial beta adreneoreceptors is intriguing and remains to be explored.

There is an anatomic substrate for bidirectional urothelial-neural communication in the urinary bladder. Myofibroblasts have been detected in the suburothelial space of the bladder in both humans and animals. These cells are in close contact with nerves and can release and be activated by ATP. The myofibroblast is regarded as an intermediary in urothelium-afferent nerve interactions.

SENSORY ROLES OF THE UROTHELIUM: TRANSDUCER AND SIGNALING

The urothelium has been increasingly recognized as a responsive structure that is capable of detecting physiological and chemical stimuli, and of releasing a number of signaling molecules, including ATP, NO, calcitonin gene related peptide, substance P, acetylcholine, adenosine, antiproliferative factor, cytokines, prostanoids and various trophic factors, following physical and chemical stimulation. Thus, urothelial cells display a number of properties similar to those of sensory neurons such as nociceptors and mechanoreceptors, which can detect physiological stimuli.

Some neuronal 'sensor molecules' (i.e. receptors and ion channels) have been identified in the urothelium, including receptors for bradykinin, nerve growth factor (Trk-A and p75), purines (P2X and P2Y), norepinephrine (α and β), acetylcholine (nicotinic and muscarinic receptors), and a number of transient receptor potential (TRP) channels (TRPV1, TRPV2, TRPV4, TRPM8).

INVOLVEMENT OF ATP IN BLADDER DYSFUNCTION

Augmented ATP release from the urothelium can cause pain by excitation of purinergic (P2X) receptors on sensory fibers. There is speculation that this type of noncholinergic mechanism could have a role in a number of bladder pathologies (e.g. idiopathic detrusor instability, interstitial cystitis and bladder outflow obstruction), as well as in the aging bladder

NERVE GROWTH FACTOR (NGF) AND BLADDER DISORDERS

NGF is produced by bladder urothelium and smooth muscle. NGF is involved in regulation of neural function, inflammation and pain. It has been shown that NGF levels are elevated in the bladders of patients with benign prostatic hyperplasia, interstitial cystitis, and idiopathic OAB.

UROTHELIAL ACETYLCHOLINE AND MUSCARINIC RECEPTORS IN OAB

In OAB, the release of acetylcholine from the urothelium during the storage phase of micturition can activate the muscarinic receptors in the urothelium, which trigger the release of urothelium ATP and NO and lead to activation of afferent pathways. Thus, blocking the urothelial muscarinic receptors could act indirectly to reduce afferent nerve activation and therefore decrease OAB symptoms. Patients with overactive bladder are typically treated with antimuscarinic agents. Traditionally, they are thought to prevent the stimulation of postjunctional muscarinic receptors by acetylcholine released from bladder efferent nerves and result in increased bladder capacity. Recently, evidence has shown that the urothelium expresses the full complement of muscarinic receptors (M1-M5), which has sparked an interest in finding out more about the role of the urothelium in the overactive bladder. Since antimuscarinic agents effectively enhance the storage phase of micturition, when parasympathetic nerves are silent, it is postulated that the release of acetylcholine from the urothelium might play a major role in OAB. In addition, release of acetylcholine from nearby bladder efferent nerves could activate urothelial muscarinic receptors. This activation, in turn, could lead to the release of mediators such as ATP that alter bladder sensation by stimulating nearby sensory afferent nerves. Therefore, targeting muscarinic receptors activated by acetylcholine released from the urothelium and/or other urothelial-release mechanisms may prove to be an effective therapy.

BOTULINUM TOXIN AND BLADDER UROTHELIUM

Bladder urothelium plays an important role in the sensory transduction mechanisms modulating micturition, particularly in conditions of increased sensory nerve transmission following chronic inflammation and spinal cord injury. Botulinum toxin A (BoNT-A) was shown to normalize ATP and NO release from the urothelium in spinal cord injured rat bladders. BoNT-A's effects are not limited solely to inhibiting neurotransmitter release. For example, studies have shown that TRPV1 (i.e. capsaicin-sensitive) receptors are released by SNARE-dependent processes and can be inhibited by BoNT-A treatment during laboratory studies. In addition, decreased sensory receptors $P2X_3$ and TRPV1 in suburothelial nerve fibers associated with a decrease in urgency following intradetrusor injections of BoNT-A have been found in human detrusor overactivity. Giannantoni reported that intravesical BoNT-A injection reduces the NGF content in the bladder tissue of patients with neurogenic detrusor overactivity. The reduction of NGF content leads to decreases in the hyperexcitability of C-fiber bladder afferents, thereby reducing neurogenic detrusor overactivity. Thus, the inhibitory effects of BoNT-A on sensory function may relieve somatic and visceral irritative symptoms. In this regard, the use of botulinum toxin has been investigated for treating a number of bladder disorders including neurogenic detrusor overactivity, and detrusor-sphincter dyssynergia, as well as interstitial cystitis.

REFERENCES

1. Birder LA, de Groat WC: Mechanisms of disease: Involvement of the urothelium in bladder dysfunction. Nat Clin Pract Urol 2007; **4**: 46-54.
2. Apostolidis A, Dasgupta P, Fowler CJ: Proposed mechanism for the efficacy of injected Botulinum toxin in the treatment of human detrusor overactivity. Eur Urol 2006; **49**:644-650.
3. Hsu CC, Chuang YC: Mechanisms of action of botulinum toxin a on lower urinary tract. JTUA 2008; **19**:77-82.