Pathophysiology of the urothelium detrusor

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Pathophysiology of the urothelium and detrusor

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Abstract

Conventional wisdom now agrees that symptoms of overactive bladder (OAB) seem to emanate from an aberration in the voiding reflex, leading to involuntary detrusor contractions of either neurogenic or myogenic origin. Furthermore, emerging evidence also encourages us to adopt a new paradigm, in which bladder urothelium is not just a simple barrier but an active contributor to bladder function. In this paradigm, aberration in sensory mechanisms emanating from the urothelium can also contribute to OAB symptoms through altered excitability of afferents in the bladder leading to increased bladder sensation. The high density of muscarinic receptors expressed on urothelium can not only mediate release of urothelium-derived inhibitory factor, but can also be seen as an alternative site of action for antimuscarinic drugs. Urothelium also expresses a host of other receptors such as TRPV1 and TRPM8, whose functional role is yet to be confirmed.

Overactive bladder (OAB) is characterized by painless but bothersome lower urinary tract symptoms of unknown etiology. Current understanding of the pathophysiology of these bothersome symptoms indicates that there is a contribution from both neurogenic and myogenic sources. In addition, it is now thought that the urothelium plays a more active role in bladder function than simply being a barrier. Figure 1 is a simplified diagram of these potential contributing mechanisms. This short review focuses on the local pathophysiology. Further information on the neurogenic mechanisms of OAB with particular emphasis on the central nervous system, is provided in this publication by Dr. Christopher Chapple.

The physiology of voiding

The normal micturition cycle is mostly comprised of the storage phase, with only a small minority of the time spent in actual voiding. The storage phase is governed by the sympathetic nerve, which causes the relaxation of the detrusor through beta-3 receptor mediated relaxation. Contraction of the sphincter, which is also essential during the storage phase, is mediated by the sympathetic nerve and the pudendal nerve. For voiding, sphincter relaxation and detrusor contraction are required.

It is understood that voiding in healthy situations is triggered by acetylcholine (ACh) released from parasympathetic nerves activating the postjunctional muscarinic receptors in the detrusor. The neural control for the voiding reflexes is mediated by a spinobulbospinal pathway passing through a coordination centre (the pontine micturition centre) located in the brainstem, whereas urine storage reflexes are organized in the spinal cord, involving a host of neurotransmitters including norepinephrine, dopamine, serotonin, excitatory and inhibitory amino acids, adenosine triphosphate (ATP), nitric oxide and neuropeptides.

Conventional wisdom now agrees that OAB symptoms seem to emanate from an aberration in the voiding reflex leading to involuntary detrusor contractions of either neurogenic or myogenic origin.

The complex pathophysiology of overactive bladder

Neurogenic OAB seems to arise from either increased afferent input from the bladder, abnormal central processing of afferent input leading to reduced suprapontine inhibition or physical damage to the axonal paths integral to micturition reflex organized in spinal cord. Locally, there is a shift from the Adelta fibres that dominate during the normal voiding to abnormal C-fiber activity in the pathologic state. The ability of the nervous system to change transmitters, reflexes, or synaptic transmission with disease, injury or changes in the environment involves neural plasticity.

While plasticity may shift the balance towards voiding, co-existent conditions such as periodic ischemia in bladder during voiding may injure nerves so that sensation is lost, or that damage to smooth muscle leads to impaired contractility. In myogenic OAB, the theory postulates that unstable increase in intravesical pressure during involuntary

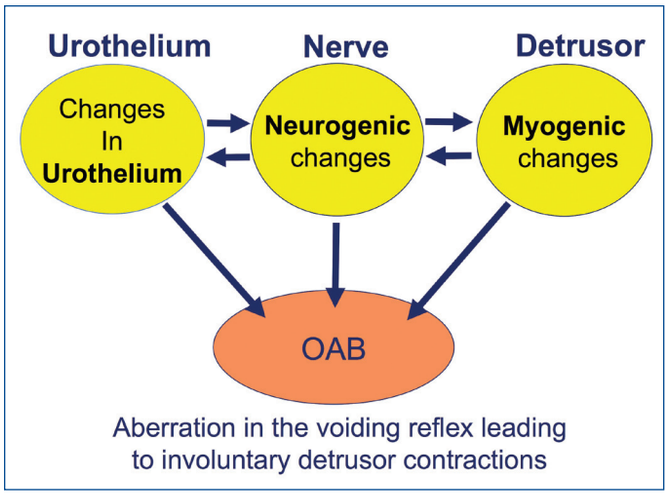

Fig. 1. Mechanisms underlying overactive bladder.

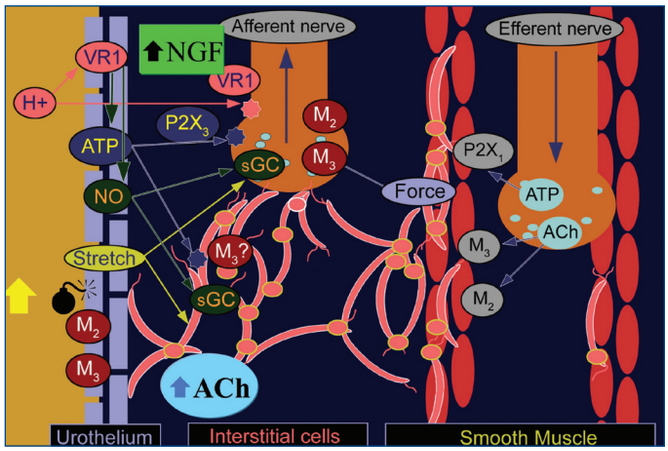

Fig. 2. Urothelial pathways and detrusor overactivity.

detrusor contraction may result in periodic ischemia of bladder, resulting in damage to some intrinsic neurons in the bladder wall and secondary changes in the smooth muscle properties. Detrusor smooth muscle cells in myogenic OAB have been shown to develop extensive coupling and supersenstivity to muscarinic stimulation of bladder. Myogenic mechanisms usually exist in healthy state at the peripheral level to ensure that an inadvertent neural impulse does not trigger a detrusor contraction.[1]

The pathology becomes further confounding with the coexistence of both neurogenic and myogenic causes in OAB patients who suffer from urine leakage into the proximal urethra, which can then lead to either physical or chemical stimulation of urethral afferents mediated by the static presence of urine in urethra.[2-5]

The role of the urothelium in overactive bladder

Evidence has encouraged us to adopt a new paradigm in which bladder urothelium is not just a simple barrier but an active contributor to bladder function, and wherein aberration in sensory mechanisms emanating from the urothelium can contribute to OAB symptoms.[6] The urothelium is believed to serve a role of "sensor transducer" in voiding by its ability to release many substances in response to stretch during filling, including ATP, prostaglandins, nitric oxide, and ACh that can affect nerve, smooth muscle, interstitial and immune cells. As the bladder fills, it exerts pressure on the endothelium, which results in heightened release of these substances from the urothelium. Figure 2 shows the various substances and receptors potentially involved. This, in turn, can alter excitability of afferents in the bladder leading to increased bladder sensation and OAB symptoms.[7,8] One theory is that there is an increased amount of ACh released from the urothelium during bladder filling, above and beyond the typical basal ACh release.[9,10] Additionally, there may also be an increased expression of muscarinic M2 and M3 receptors in the pathologic state.[11,12] The high density of muscarinic receptors expressed on urothelium can not only mediate release of urothelium-derived inhibitory factor, but these receptors, along with the innate mechanism of non-neuronal ACh release operating at the urothelium, can become an alternative site of action for antimuscarinic drugs.

An increase in expression of urothelial neural growth factor (NGF) can also increased sensitivity of suburothelial afferents, leading to neuronal hyperinnervation, pelvic sensitivity, and detrusor overactivity.[13-15]

Higher expression of ornithine decarboxylase is responsible for upregulated polyamine signalling in OAB patients, which can affect detrusor contractility through blockade of calcium-activated large-conductance potassium channels.[16]

Urothelium also expresses a host of other metabotropic and ionotropic receptors such as TRPV1 and TRPM8, whose functional role is yet to be confirmed.

Conclusion

Physiological voiding and OAB may involve different mechanisms. Urothelium, afferent nerves, CNS processing, efferent mechanisms and unstable bladder contribute to overactivity but the relative roles remain unclear. Our current understanding of the mechanisms underlying OAB offers many possible targets for pharmacologic intervention.

Competing interests: Dr. Tyagi has received honoraria and speaker fees from Astellas.

This paper has been peer-reviewed.

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