Urethral Sensations are Related to the Development of Detrusor Overactivity

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Urgency is the core symptom of the overactive bladder symptom complex, but the underlying mechanisms are not fully understood. Clinical findings have led to the assumption that bladder outlet obstruction (BOO) caused by benign prostatic enlargement (BPE) induces storage symptoms and detrusor overactivity. Presumably, BOO by BPE accounts for urgency; however, urgency is not always caused by BOO. Sensory nerves in the wall of the urethra fire in response to urethral fluid flow, and this activity initiates bladder contractions in the quiescent bladder and augments ongoing contractions in the active bladder. In humans, prostatic urethral anesthesia results in significant increases in bladder capacity among BPH patients without neurological diseases, therefore sensory stimuli from an anatomically altered prostatic urethra has the possibility to induce urgency and detrusor overactivity. Studies in animals demonstrate the basis for an excitatory urethra to bladder reflex. Urethral stimulation by prostaglandin E2 induces an excitatory effect on micturition reflex by activation of C-fiber afferent nerves. α1A-adrenoceptor blocker has an inhibitory effect on the micturition reflex, suggesting excitatory urethra to bladder reflex is mediated by α1A-adrenoceptor. Even if there is no obstruction, increase in urethral sensory due to BPE may induce the development of the detrusor overactivity.

Key words detrusor overactivity, prostatic hyperplasia, sensory, urethra, urinary bladder

1. INTRODUCTION

The lower urinary tract consists of the urinary bladder and urethra. Two principal functions of the urinary bladder are urine storage and voiding. The urethra maintains urinary continence by relaxing during the voiding phase and contracting during the urine storage phase. The storage or voiding function of the urinary bladder and urethra sometimes is destroyed under some pathological conditions, resulting in the development of lower urinary tract symptoms (LUTS). Male LUTS guidelines have been published by the Neurogenic Bladder Society in Japan.1 The causes of LUTS in middle-aged and older men are diverse, and include diseases of the lower urinary tract, prostate, and nervous system, as well as systemic diseases and other pathological conditions. The most common causes are benign prostatic hyperplasia (BPH), overactive bladder and underactive bladder. BPH is an age-related increase in prostate volume, which leads to voiding and storage dysfunction regardless of the presence of bladder outlet obstruction (BOO).2–4 BPH is highly prevalent in elderly men and is associated with various combinations of voiding and storage symptoms.5 Presumably, BOO by the enlarged prostate accounts for LUTS in BPH; however, the severity of LUTS is not necessarily correlated with the degree of BOO or prostate volume.6 Among storage symptoms, only urgency has been reported to correlate to the prostate volume.7,8

Barrington’s second reflex, the urethral detrusor facilitative reflex, is believed to exist in cats, but its existence in humans is uncertain.9 Chalfin and Bradley postulated that this reflex might exist in humans and might even become a significant force in various states of proximal urethral disease, that is, BPH resulting in an anatomically altered proximal urethra.10 They speculated that sensory stimuli from the altered urethra induced detrusor instability, which was eliminated by transperineal prosthetic block with lidocaine. If this is true, there is a possibility that urgency depends on the urethral sensation in patients with an enlarged prostate. We therefore discussed the possible mechanisms underlying the pathogenesis of urgency, focusing on urethral sensations.

2. SENSORY INNERVATION OF THE URETHRA

Sensory innervation of the urethra is conveyed to the spinal cord mainly via the pelvic nerve and dorsal root

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ganglia and to some extent via the hypogastric nerve. The sensory nerves innervating the rhabdosphincter run through the pudendal nerve to the sacral spinal cord region. Immunohistochemical data indicate the presence of capsaicin-sensitive primary afferent C-fibers in the rat proximal urethra. Afferent C-fibers are suggested to be specific sensory nerves related to pain perception (nociception) and they have also been shown to initiate a usually inactive, non-voluntary, spinal micturition reflex.

3. URETHRA TO BLADDER REFLEX

Reflexes between the urethra and bladder play an integral role in the neural control of the lower urinary tract. Various reflex pathways have been identified that are activated by bladder or urethral afferents and which can facilitate or inhibit voiding. Sensory nerves in the wall of the urethra fire in response to urethral fluid flow, and this activity initiates bladder contractions in the quiescent bladder and augments ongoing contractions in the active bladder. Urethra to bladder reflexes are mediated by afferent inputs traveling through the pudendal nerve to the sacral spinal cord and brain. In cats, urethral perfusion triggers spontaneous bladder contraction of such intensity and frequency that bladder filling is not possible. Pharmacological activation of the urethral afferent nerves by intraurethral capsaicin elicits a biphasic change in the micturition reflex, initially decreasing the bladder contraction interval within minutes, followed 15–30 min later by complete micturition reflex blockage. Furthermore, intraurethral administration of prostaglandin E2 produces an excitatory effect on the micturition reflex by stimulation of C-fiber afferent nerves via prostaglandin E receptor 1 (Fig. 1). Studies in animals have demonstrated the basis for an excitatory urethra to bladder reflex; however, whether such a reflex is present in humans is unclear.

4. DETRUSOR OVERACTIVITY AND URETHRAL SENSATIONS

It is widely believed that more than 50% of patients with obstruction secondary to BPH have involuntary detrusor contractions, defined as detrusor overactivity, and that in approximately 40% of these patients the overactivity persists after relief of the obstruction. However, the pathophysiology of the detrusor overactivity in infravesical obstruction is not clearly understood. Various theories have been proposed, including increased sensory stimulation from the prostatic urethra and trigone of the bladder. Chalfin et al. revealed that a transperineal prostatic block with lidocaine eliminated involuntary detrusor contractions in 10 of 11 patients but had no effect in the four patients with a normal cystometrogram. They contended that sensory stimuli from an anatomically altered prostatic urethra induced involuntary detrusor contraction. We previously reported that prostatic urethral anesthesia resulted in significant increases in first sensation volume and maximum cystometric capacity in BPH patients without neurological diseases (Fig. 2). In patients without BPH but with obvious neurological diseases, no significant differences were found in first sensation volume or maximum cystometric capacity between before and after prostatic urethral anesthesia. These results indicate that the bladder might be augmented more effectively in BPH patients than in patients who have neurological disease affecting micturition. By measurement of trigonal sensitivity using a balloon catheter traction technique, Klein suggested that the pressure-sensitive receptors in the mucosa or submucosa of the bladder base and posterior urethra had a role in micturition. Mahony et al. reported that the most potent facilitative receptors for the micturition reflex
reflex were in the posterior urethra. Of note, the first procedure during transurethral resection of the prostate is to remove the urothelium lining the prostate, which may be of greater relevance in the relief of detrusor overactivity and associated storage symptoms. The evidence in support of this theory is limited but includes reports of the potency of botulinum toxin injections into the prostate in relieving lower urinary tract symptoms. Injection of botulinum toxin into the bladder neck and urethra has been shown to improve LUTS and increase bladder capacity in men with a small prostate. Therefore, the bladder neck and urethra may play a role in the development of storage symptoms even in men without BPH.

5. DETRUSOR OVERACTIVITY AND α-ADRENOCEPTOR BLOCKERS

Recently, involvement of the detrusor α1D-adrenoceptor (α1D-AR) in storage symptoms was indicated by experimental findings in rats and humans. Among these findings, it was shown that α1D-AR messenger ribonucleic acid (mRNA) is present in the human detrusor, that the ratio of α1D-AR mRNA to all α1-AR subtype mRNAs is higher than that of α1A-AR mRNA, and also that the α1D-AR subtype is closely related to storage symptoms in patients with BPH. Therefore, α1-AR blockers with significant affinity for the α1D-AR subtype are thought likely to be able to improve storage symptoms related to BOO. However, subtype analysis carried out in humans indicated that the α1A- and α1D-AR mRNAs in the detrusor were expressed at equally low densities, while normal and obstructed human bladders did not differ in their α1-AR subtype mRNA expressions and functions, suggesting that the detrusor overactivity involving α1D-AR could be mediated by receptors located outside the bladder. One of the postulated mechanisms by which α1-AR blockers might improve storage symptoms involves effects on α1A-AR within the sacral spinal cord.

Noradrenalin produced contractions through α1A-AR in the prostate of wild type, α1b-AR, and α1d-AR gene-knockout mice, but the contractions were abolished or markedly abolished in α1d-AR-knockout mice. Therefore, α1A-AR, not but α1D-AR, has an important role in the contraction of the prostate. Intra-arterial administration of an α1A-AR blocker, silodosin, has an inhibitory effect on the intraurethral prostaglandin E2–stimulated micturition reflex (Fig. 3). Excitatory effects of prostaglandin E2 on the micturition reflex were not seen in resiniferatoxin-treated (C-fiber-desensitized) rats. Therefore, silodosin may exert an inhibitory effect on C-fiber afferent nerves via the α1A-AR situated predominantly within the urethra. In a receptor-binding study, the affinity for the human α1A-AR subtype shown by silodosin was at least 100-fold higher than that of an α1D-AR blocker, naftopidil, while the affinities of these drugs for the human α1D-AR subtype were approximately equal to each other. In fact, in a recent clinical trial, silodosin improved storage symptoms as well as voiding symptoms, confirming the effectiveness of the α1A-AR blocker on storage symptoms.

Further research is needed, however, on the mechanism underlying the interaction between C-fiber urethral afferents and α1A-AR.

6. DETRUSOR OVERACTIVITY AND BLADDER SENSATIONS

Bors et al. examined the effects of urethral and vesical anesthesia on the cystometry of patients with spinal cord injuries. The bladder capacity increased less frequently following urethral anesthesia than following vesical anesthesia in these patients. These reports suggested that detrusor overactivity caused by neurological disorders cannot be restrained by prostatic urethral anesthesia. Because intravesical lidocaine had an inhibitory effect on detrusor overactivity caused by spinal lesions, we suggested that lidocaine was useful to determine whether detrusor overactivity was due to spinal lesions (Fig. 4). Furthermore, among patients with overactive bladder caused by brain lesions, spinal lesions, or BPH, as well as those with idiopathic overactive bladder, the percentage increase in bladder capacity was the smallest (29%) in those with overactive bladder due to BPH. Intravesical administration of lidocaine increased bladder capacity more effectively in patients with spinal lesions or cord injuries than in those with other lesions. Considering that smaller unmyelinated C-fibers are blocked more readily than large myelinated afferents (Adelta) and that tissue penetration of intravesical lidocaine is poor, lidocaine is thought to exert its effects by initially blocking the submucosal afferent nerves (C fibers). Therefore, the effect of lidocaine on the bladder probably depends on the disease, with C-fiber bladder afferents contributing to the micturition reflex. Intravesical lidocaine increased bladder capacity by only 29%, suggesting that the distribution of C-fibers in relation to detrusor overactivity is less important in patients with BPH.

7. CONCLUSIONS

We hypothesized that the onset of the micturition reflex was triggered by detrusor contractions induced by increased sensory input from the prostatic urethra in patients with BPH. Accordingly, it was believed that
might be related to the initiation of detrusor contraction. The existing evidence, sensory input from the urethra enlargement of bladder capacity. Furthermore, based on the easy irritability of the anatomically altered prostatic Detrusor overactivity is believed to be a manifestation of urethral anesthesia and an

decomposition of the present paper.

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