EFFECTS OF $\alpha_1$-BLOCKER ON THE RELEASE OF ATP AND PROSTAGLANDIN E$_2$ FROM THE URETHRAL EPITHELIUM IN BOO RATS

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Introduction

The urothelium acts as a sensory receptor that responds to mechanical and chemical stimulation by releasing neurotransmitters, such as acetylcholine, ATP, and prostaglandins (PGs). It has been suggested that detrusor overactivity caused by bladder outlet obstruction (BOO) may be initiated from the bladder outlet region rather than from the bladder itself. Pharmacological activation of urethral afferent nerves by intraurethral PGE$_2$ elicited an excitatory effect on micturition reflex (2). Furthermore, immunohistochemical data have indicated the presence of capsaicin-sensitive primary afferent fibers in the rat proximal urethra (3). Considering these findings, stretch-induced release of some mediators from the urethral epithelium may play an important role in the induction of detrusor overactivity in patients with BOO. We have reported that both of ATP and PGE$_2$ are released from the urethral epithelium by the urethra stretch stimulation; moreover the release was significantly controlled by the COX inhibitors. We have also reported that $\alpha_1$-blocker inhibits non-voiding bladder contraction in rats with BOO. These results suggest that $\alpha_1$-blocker acts on the urethral epithelium and decreasing the release of ATP and PGE$_2$, resulting in inhibiting non-voiding bladder contraction. Therefore, we examined the influence of $\alpha_1$-blocker on the amount of stretch-induced ATP and PGE$_2$ in rats with BOO.

Materials and Methods

- Female Sprague-Dawley rats with partial bladder outlet obstructions (BOO) were used.
- Four weeks after the operation, rats were anesthetized with halothane. The distal or proximal site of the urethra was cannulated as Fig.1.
- After washing the inside of the urethra with 0.5 ml Krebs solution, 1st. urethral perfusion was carried out with 150 $\mu$l Krebs solution (baseline), and the solution was collected.
- 2nd. 150 $\mu$l of Krebs or drug solution was maintained in the urethra for three minutes and then collected.
- ATP and PGE$_2$ amounts were measured with luciferin-luciferase assay and ELISA assay, respectively.

Animal groups

<table>
<thead>
<tr>
<th>Normal-vehicle (n=12)</th>
<th>BOO-Vehicle (n=13)</th>
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<tr>
<td>Normal-Tamsulosin 100μM (n=9)</td>
<td>BOO-Tamsulosin 100μM (n=12)</td>
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Results

There was no change between normal rats and BOO rats in body weight, but urethral weight of BOO rats increased significantly as compared with normal rats (Fig.2). Urethra distension induced the increase in ATP and PGE$_2$ release and reached 14 times and 11 times as much as those at baseline in normal rats, respectively. In BOO rats; the ATP release elicited by urethral distension increased reaching 2 times as much as those at baseline (Fig.3a). The PGE$_2$ release also increased reaching 6 times as much as those at baseline. As compared with the normal rats, the ATP release of BOO rats were significantly decreased. A similar trend was observed for the PGE$_2$ release, but without significance (Fig.3b). Intraurethral administration of tamsulosin did not suppress the increase in ATP or PGE$_2$ release from the urethral epithelium (Fig.4).

Discussion

The urethral epithelium has the ability to synthesize ATP and PGE$_2$ in response to urethral distension in BOO rats. However, the amounts decreased by BOO. $\alpha_1$-blocker has been reported to suppress detrusor overactivity via inhibition of urethral afferent nerves (2), and the underlying mechanism did not depend on mediators from the urethral urothelium. In future experiments, we will evaluate the influence of $\alpha_1$-blocker on interaction between the urethral muscle and C-fiber afferent nerves.

References