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EFFECTS OF A1-BLOCKER ON THE RELEASE OF ATP AND PROSTAGLANDIN E2 FROM THE URETHRAL EPITHELIUM IN BOO RATS

Hypothesis / aims of study

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 (1). 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 α_1-blocker inhibits non-voiding bladder contraction in rats with BOO. These results suggest that α_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 α_1-blocker on the amount of stretch-induced ATP and PGE_2 in rats with BOO.

Study design, materials and methods

Female Sprague-Dawley rats received partial bladder outlet obstructions were used. Four weeks later, the rats were anesthetized with halothane, and the bladder and proximal urethra were exposed through a midline abdominal incision. A catheter infusing Krebs or drug solution was inserted into the proximal urethra through the bladder and fixed at the bladder neck. A second catheter was introduced into the distal urethra and fixed at the external urethra. Urethral perfusion was carried out with 150 μL Krebs solution (baseline), and the solution was collected. Next, 150 μL of Krebs 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.

Results

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. 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 decreased significantly. A similar trend was observed for the PGE_2 release, but not significantly. 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. Intraurethral administration of tamsulosin did not suppress the increase in ATP or PGE_2 release from the urethral epithelium.

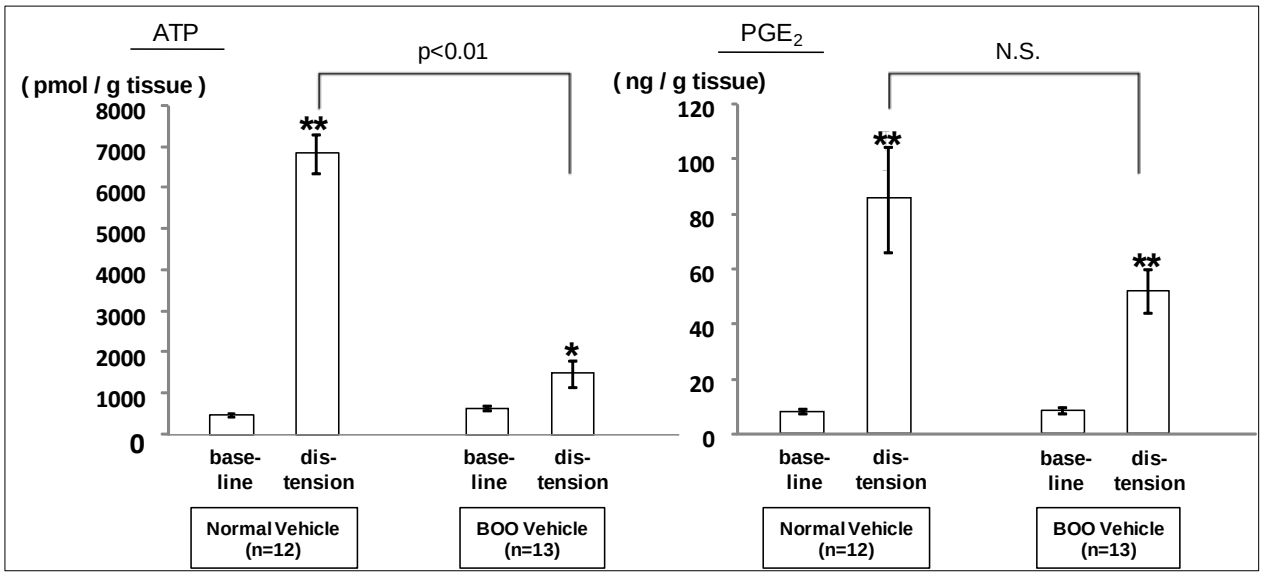

Fig.1 The increases in amounts of ATP and PGE_2 by urethral distension.
(Paired t-test * : $p<0.05$ vs baseline, ** : $p<0.01$ vs baseline)

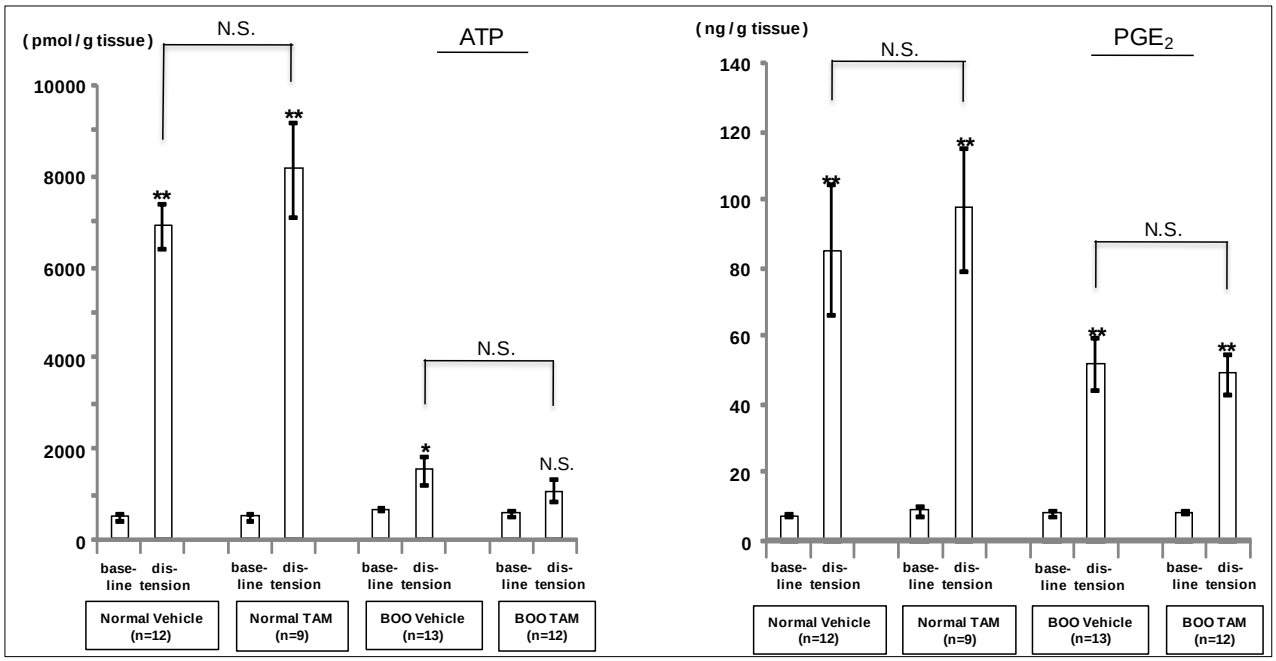

Fig.2 Effects of intraurethral administration of tamsulosin on amounts of ATP and PGE_2.
(Paired t-test * : $p<0.05$ vs baseline, ** : $p<0.01$ vs baseline)

Interpretation of results

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.

α_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 α_1-blocker on interaction between the urethral muscle and C-fiber afferent nerves.

Concluding message

Improvement of storage dysfunction by α_1-blocker does not depend on its inhibitory effects on the release of ATP or PGE_2 from the urethral epithelium in BOO rats.

References

1. J Urol 1994,151:1554
2. J Urol 2007,177:771
3. Neuroscience 1986,18:727

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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**University of Fukui**