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**Title:** THE ACTION OF PREJUNCTIONAL ALPHA-ADRENERGIC RECEPTORS FOR NOREPINEPHRINE RELEASED IN THE HUMAN URETHRA

### **Aims of Study**

The sympathetic nervous system plays an important role on function of lower urinary tract. A major neurotransmitter for physiological urethral contraction is norepinephrine released from prejunctional site of sympathetic nerve endings. There are reports that prejunctional adrenergic receptors contribute to the sympathetic neurotransmitter in several tissues (1,2). In the present study, we have evaluated the regulation mechanism of prejunctional alpha adrenergic receptors in human urethral smooth muscles, using muscle bath technique and microdialysis procedure. Furthermore, the effects of pretreatment with alpha-1 and alpha-2 antagonists on norepinephrine release and the contractile response induced by electrical field stimulation were evaluated.

### **Methods**

The muscle strips were prepared from human urethra resected by cystoprostatectomy due to bladder malignancy (n=11, mean age  $\pm$  S.E.M.  $66.5 \pm 6.7$  years). These were suspended in 20 ml muscle baths filled with Krebs-Heinseleit solution and isometric tension developments were recorded. The microdialysis probe (O-P-100-10; Eicom, Kyoto, Japan) was inserted into the strip, and the inlet cannula of the probe was connected to a microinfusion syringe pump. Ringer's solution was continuously perfused at a rate of  $2\mu\text{l} / \text{min}$  into the probe. Electrical field stimulation (supramaximum voltage, pulse duration 0.5 msec, frequency 5 -80 Hz, train of pulse 2 sec, main interval 60 sec) was applied to urethral preparation in the presence of  $1\mu\text{M}$  atropine and  $1\mu\text{M}$  indomethacin. The dialysate during electrical field stimulation was collected for 10 min ( $20\mu\text{l}$ ), and the amount of norepinephrine release in the dialysate was measured by high performance liquid chromatography. The effects of pretreatment with alpha-1 and alpha-2 antagonists (prazosin and yohimbine) on norepinephrine release and the contractile response induced by electrical field stimulation were evaluated.

### **Results**

Electrical field stimulation caused frequency-dependent increases in the amounts of norepinephrine release and the contractile response. Pretreatment with tetrodotoxin ( $10\mu\text{M}$ ) completely inhibited both contractile response and norepinephrine release. Pretreatment with prazosin ( $0.01-1\mu\text{M}$ ) significantly reduced the contractile responses and norepinephrine release induced by electrical field stimulation. In contrast, pretreatment with yohimbine ( $0.1-10\mu\text{M}$ ) did not cause significant changes in the contractile responses and norepinephrine releases induced by electrical field stimulation.

### **Conclusions**

The present data demonstrated that there are prejunctional alpha-1 adrenergic receptors in the adrenergic nerve endings, and norepinephrine released from the adrenergic nerve endings in human urethral smooth muscles. The mechanism may contribute to the regulation of urethral tone.

### **References**

1. J. Urol., 157, 2356-2360, 1997.
2. Eur. J. Pharmacol., 400, 271-278, 2000.