

ALPHA-1 ANTAGONISTS INHIBIT THE PRIMARY AFFERENT ACTIVITY FROM THE IRRITATIVE BLADDER OF THE RAT.**Hypothesis / aims of study**

Many reports show alpha-1 effects in the efferent systems to the urinary bladder. Alpha-1 facilitation for micturition reflex has been reported in the preganglionic neurons of spinal cord, in the pelvic ganglia and in the detrusor smooth muscle. Recently, a theory is coming out that alpha-1 antagonists inhibit the afferent limb in the lumbosacral cord (1). Then, we interested whether or not alpha-1 antagonist effects in the afferent systems. Many clinical data indicate alpha-1 antagonists tend to improve the irritative symptoms as well as obstructive symptoms. These data also suggest alpha-1 antagonist might act on the primary afferent systems, not only on the spinal cord. Since alpha-1 receptors were not identified at the primary afferent neurons, alpha-1 agonist and/or antagonist might act on the uroepithelium and nearby structures. Anyway, we examined the effects of alpha-1 antagonist on single unit-recording from the bladder afferent fibers in vivo.

Study design, materials and methods

We used Wistar female rats for these experiments (n=28). Rats were anesthetized by 0.9-1.0 mg/kg (i.p.) urethane. Double lumen catheter was inserted into the urinary bladder from external urethral orifice for infusion and recording the vesical pressure. Then, L3-L6 vertebrae were exposed and we selected very fine filament of the L6 dorsal root for recording the afferent activity from the pelvic viscera. We used alpha-1 antagonists, naftopidil (0.75-1.66 mg/kg) and tamsulosin (0.0001-0.01 mg/kg) for these experiments. Drugs were administered intravenously into the external jugular vein. Unit-recording was digitalized with AD converter and recorded in Power Lab System (version 5.0). The numbers of spikes/sec were counted with window discriminator.

Results

Naftopidil (1 mg/kg, i.v.) inhibited the rhythmic bladder contraction in constant volume condition. The effect was appeared at 5-10 minutes and complete inhibition was observed for 20-50 minutes. When recovery appeared, frequency of contraction (22 ± 4.2 /h) and maximum contraction pressure (32 ± 2.4 cmH₂O) was same as control. Naftopidil (1.0 mg/kg, i.v.) increased the latency of bladder contraction for 180 ± 12 % in single cystometrogram (CMG, n=3). Intercontraction interval was prolonged to 210 ± 15 % when we used continuous CMG (n=4).

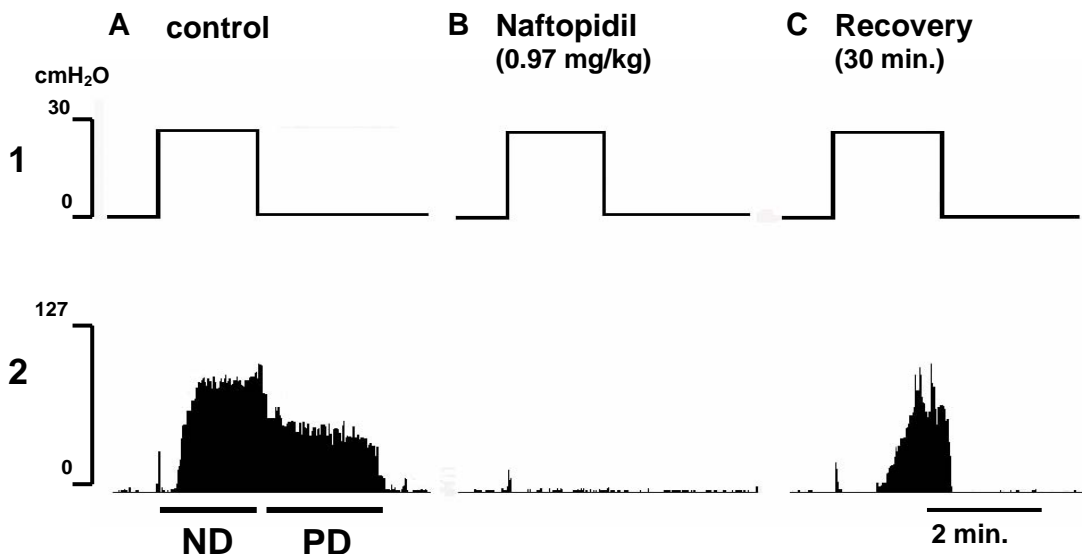


Figure: Naftopidil inhibited the neural discharge (ND) and post discharge (PD). 1: vesical pressure, 2: rate meter recording of the neural discharge (spikes/sec)

In single unit-recording, pressure stimulation of urinary bladder using the saline injection produced the neural discharge (ND). ND detected at 20-30 cmH₂O increased as vesical pressure increased (128-235 spikes/sec). ND immediately disappeared when vesical pressure returned to 0 cmH₂O from the 30 cmH₂O. When over use of the pressure stimulation, discharge was remained after decreasing the vesical pressure (post-discharge; PD). PD was not observed in control. Naftopidil (1.5 mg/kg i.v.) reduced or diminished the ND and recovery was observed in 30-60 minutes. It also inhibited the PD. Naftopidil (1.0 mg/kg) did not alter the carotid arterial pressure (120±7 mmHg).

In addition, we tried acetic acid (0.1%, AA) infusion into the urinary bladder as the interstitial cystitis model (n=3). AA infusion shortened the latency of micturition reflex (LMR, 7.2 to 5.1 minutes) resulted from increasing the afferent activity (320±20 %). Naftopidil reversed the AA effects to the control (89% and 102%, LMR and ND respectively). AA infusion unmasked PD which abolished by naftopidil.

Tamsulosin (0.0001 and 0.001 mg/kg i.v.) diminished the ND (0-7.1 %) and recovery was observed in 25-45 minutes. When recovery appeared, frequency of contraction and maximum contraction pressure was same as control. Unexpectedly, tamsulosin did not inhibit the PD. Larger dose of tamsulosin (0.01mg/kg i.v.) reduced the ND partially (78±2.5 %). Obvious recovery was not observed. When tamsulosin (0.01 mg/kg) did not act on the micturition-related discharge, naftopidil (1.5 mg/kg) completely inhibited these discharge and recovery was observed in 82±10 minutes (n=3). These data indicated larger dose of tamsulosin might have another effects.

Interpretation of results

Alpha-1 receptor antagonists inhibit the pressure-dependent ND of the vesical afferent. PD was inhibited with naftopidil but not with tamsulosin. Previous studies indicated naftopidil has selective affinity for alpha-1D adrenoceptor and tamsulosin has for alpha-1A adrenoceptor. Since PD was observed with inflammation of the uroepithelium and nearby structure, alpha-1D receptors might activate during the pathological condition.

Concluding message

Alpha-1D antagonist might be useful to treat the irritative symptoms in overactive bladder.

References

1. Sugaya, K., Nishijima, S., Miyazato, M., Ashitomi, K., Hatano, T., Ogawa, Y.: Effects of intrathecal injection of tamsulosin and naftopidil, alpha-1A and alpha-1D adrenergic receptor antagonists, on bladder activity in rats. *Neuroscience Letters* 2002, 328: 74-76