201

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ALPHA ADRENOCEPTOR ANTAGONISTS INHIBIT THE SENSORY AFFERENT ACTIVATION DURING THE STORAGE PHASE IN RAT URINARY BLADDER.

Hypothesis / aims of study

Currently the predominant medical therapy used for lower urinary tract symptom (LUTS) in patients with benign prostatic hyperplasia (BPH) is □□adrenoceptor (AR) antagonist, which can improve voiding and storage symptoms. □□AR antagonists are also known to relieve LUTS in women. These clinical findings suggest that norepinephrine and □□AR involve in LUTS. The therapeutic effect of □□AR antagonists on the voiding symptom is due to relaxation of prostatic or urethral smooth muscle, but the mechanism of action of these drugs in the treatment of the storage symptom is still unclear. Recent studies have shown that c-Fos expression in L6 spinal cord is able to use as a marker for afferent neuronal input from an irritated bladder in the rat. The present study was designed to determine whether □□or □□AR antagonist inhibits the afferent activation resulting from continuous infusion of saline into the bladder, and whether reduction of afferent activation alters the storage or voiding function of the bladder. In addition, the spontaneously hypertensive rat (SHR) of which there exist a generalized increase in norepinephrine contents in the peripheral vasculature was used to investigate whether endogenous norepinephrine stimulates the afferent pathway. We compared the number of c-Fos-positive cells at L6 in the spinal cord and the cystometric parameters of rats given the drugs, of control rats and of SHRs.

Study design, materials and methods

At 12 weeks of age 40 female Wistar-Kyoto(WKY) rats were treated with □□AR antagonist prazosin (0.12 mg/kg/day),□□□□□□□AR antagonist phentolamine(0.15 mg/kg/day), □□AR antagonist yohimbine(0.1 mg/kg/day), or vehicle (control) for 4weeks using osmotic pumps. At 12 weeks of age 10 female SHRs were treated with vehicle. Continuous cystometry with saline was performed without anesthesia or restraint 4 weeks after drug administration until the number of micturition became the same (30 times) in each rat. Cystometric capacity, micturition interval and micturition pressure were measured. After cystometry, each rat received cardiac perfusion with 10% formalin fixative. Spinal cord was excised for c−Fos immunostaining. The L6 spinal cord was cut into sections 20 μm thickness with a cryostat microtome. C-Fos protein was immunoreacted with primary antibody (Ab2, Calbiochem, USA) diluted at 1: 2000. All values are expressed as means ± SE. The data were statistically analyzed by one-way ANOVA with the Bonferroni post-test, and a probability value of $p < 0.05$ was considered significant.

Results

Chronic treatment of drugs significantly lengthened the micturition interval and increased cystometric capacity (Table). The micturition interval and cystometric capacity was significantly decreased in SHRs. There were no differences in micturition pressure among all groups (Table).

Microscopic evaluation of c-Fos staining revealed the clear differences among all groups (Figure). Prazosin and phentolamine resulted in approximately a 25% decrease in the number of c-Fos-positive cells (13 ± 1.1, 15 ± 1.6 cell/section), whereas yohimbine did not change the number of c-Fos-positive cells compared to control group (54 ± 3.2 cells/section) (Figure). In the SHRs there was an approximately 50% increase in the number of c-Fos-positive cells compared to control group. (95 ± 3.5 cells/section)

Interpretation of results

Prazosin and phentolamine acted on the lower afferent pathway than the L6 spinal cord because they inhibited c-Fos expression at the L6 spinal cord. And these reductions of the afferent input resulted in the increased cystometric capacity and extended micturition interval without affecting voiding contractions. On the other hand, yohimbine acted on the upper afferent pathway than the L6 spinal cord, because it did not inhibit c-Fos expression at the L6 spinal cord but it increased micturition interval and cystometric capacity without affecting voiding contractions. Since in SHRs c-Fos expression increased, and micturition interval and cystometric capacity decreased with no change in voiding contractions, we believe that the peripheral afferent pathway of the lower urinary tract is activated by norepinephrine during the storage phase.

Concluding message

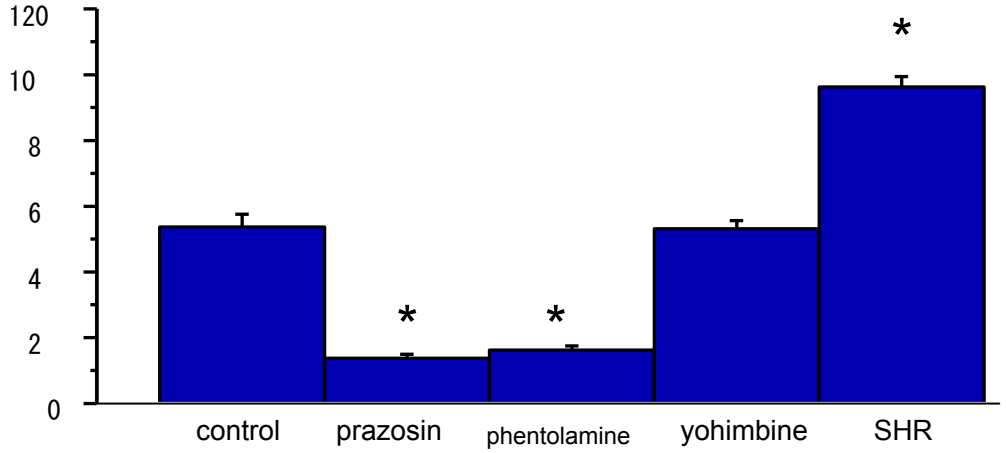
This study provides evidence that □□AR antagonist inhibits the afferent activation by acting on the peripheral afferent pathway, whereas □□AR antagonist inhibits the afferent activation by acting on the central afferent pathway of the lower urinary tract. There reductions of afferent activation alter storage function, not voiding. In addition, this study suggests that, at least in the bladder under non-nociceptive stimulation, norepinephrine plays an important role in afferent pathway excitability during the storage phase.

Table
Cystometrical parameters in control, prazosin, edrophonium, and SHR groups.

	Control	prazosin	phentolamine	yohimbine	SHR
Micturition pressure (cmH2O)	42± 3	54 ± 3	59± 5	62± 11	50±10
Cystometric capacity (ml)	0.72 ± 0.22	1.06 ± 0.03*	1.20 ± 0.14*	1.30 ±0.15	0.22 ± 0.06*
Micturition interval (minute)	4.33 ± 0.13	6.38 ± 0.18*	7.20 ± 0.86*	7.80 ± 0.9	2.16 ± 0.96*

* indicates p=0.01 versus control group.

Figure Total number of c-Fos-positive cells / section



Error bars indicate SE. * indicates < 0.0001 versus control group.

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