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PRAZOSIN IMPROVES DETRUSOR OVERACTIVITY SECONDARY TO BLADDER OUTLET OBSTRUCTION THROUGH THE INHIBITION OF THE AFFERENT ACTIVATION IN THE RAT.

Hypothesis / aims of study
Alpha1-blockers improve the storage symptoms as well as the voiding symptoms associated with benign prostatic hyperplasia(BPH), but the mechanism of action of the agents for improvement of the storage symptoms is still unclear. Recently there has been increasing evidence suggesting that the activation of afferent pathway of the bladder results in the storage symptoms in overactive bladder patients. Previous reports have shown that c-Fos immunoreactivity in the L6 spinal cord is commonly used as an indicator of afferent neuronal input from an irritated bladder in the rat. The present study was designed to determine whether bladder outlet obstruction (BOO) increases the afferent activation resulting from a continuous saline infusion into the bladder and the α1-blocker prazosin inhibits increases in that afferent activation resulting from a continuous saline into the bladder and the α1-blocker prazosin inhibits increases in that afferent activation. We also investigated whether changes in the afferent activation alter the storage or voiding function of the bladder.

Study design, materials and methods
At 12 weeks of age 30 male Sprague-Dawley rats received partial urethral obstruction (n=22) or sham surgery (n=8). Four weeks following surgery, continuous cystometry with saline was performed without anesthesia or restraint until the number of micturition became 30 times in each rat (first cystometry). The cystometric parameters were used to evaluate micturition interval and micturition pressure. At the end of cystometry, residual urine was measured and bladder capacity was calculated as the amount of saline infused into the bladder between voids, plus the amount of residual urine. And then 22 BOO-rats were administered subcutaneously either prazosin at a rate of 0.12mg/kg/day (prazosin group) or vehicle (BOO group) for 2 weeks by means of osmotic pumps. Six weeks following surgery, continuous cystometry was performed again as the above description (second cystometry). After cystometry, each rat received cardiac perfusion with 10% formalin and L6 spinal cord was removed for c-Fos immunostaining. Using anti c-Fos antibody (Ab2, Calbiochem), section of the L6 spinal cord were immunostained. All value are expressed as means $\pm$SE. The data were statistically analyses by one-way ANOVA with the Bonferroni post-test, and a probability value of $p<0.05$ was considered significant.

Results
The first cystometry showed that micturition interval significantly shortened in BOO-rats compared with sham-rats. This shortening interval was similar between the first cystometry and the second cystometry in BOO group, whereas prazosin lengthened micturition interval in BOO-rats (Figure). The number of c-Fos-positive cells significantly increased in BOO-rats compared to sham-rats, whereas prazosin significantly decreased the number of c-Fos-positive cells in BOO-rats (Table). There were no differences in micturition pressure between the prazosin group and BOO group. Prazosin increased bladder capacity and residual urine in BOO-rats, but that increase of residual urine was not statistically significant (Table).

Interpretation of results
The afferent activation in this rat model of BOO would be due to increases in afferent input from the obstructed bladder, not prostate. Consequently, effects of parazosin on the afferent activation also would be due to pharmacological effects on α-adrenergic systems outside those present in the prostate. Prazosin results in the significant increase in residual urine compared to sham-rats, because the agent decreased the afferent input and this model continued mechanical obstruction.

Concluding message
Our results demonstrated that in BOO-rats the afferent input increased and micturition interval shortened, and prazosin inhibited that afferent activation and lengthened micturition interval without affecting voiding contraction.

Figure Cystometry before and after treatment with prazosin or vehicle in BOO-rats

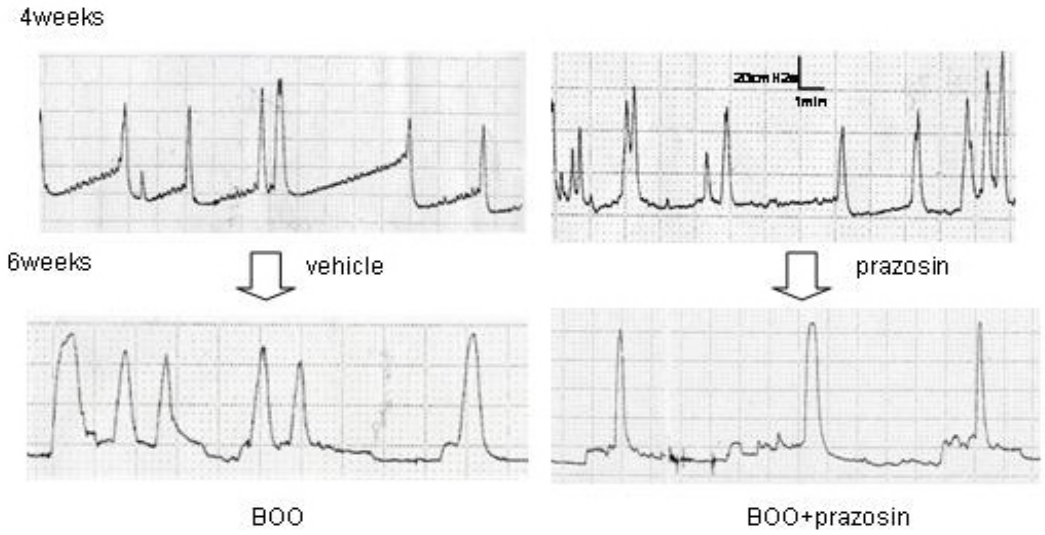

Table The results of cystometric parameters and the number of cFos-positive cells in the 3 groups

	Sham	BOO	BOO+prazosin
Bladder weight(mg)	0.137±0.021	0.61±0.068*	0.793±0.203*
Micturition intervals(min)	4.386±0.109	2.313±0.403*	6.403±0.555*†
Micturition pressure(cmH2O)	43.780±4.015	83.396±9.981*	81.52±15.348*
Bladder capacity(ml)	0.720±0.018	0.985±0.338	3.430±1.687*†
Residual urine(ml)	0.007±0.003	0.620±0.418	2.367±1.757*
cFos-positive cells	40.690±2.227	63.646±1.495*	30.121±1.325*†

*indicates P<0.05 versus Sham
†indicatesP<0.05 versus BOO

References

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