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A SELECTIVE A1A-ADRENOCEPTOR ANTAGONIST IMPROVES DETRUSOR OVERACTIVITY SECONDARY TO BLADDER OUTLET OBSTRUCTION THROUGH THE INHIBITION OF THE AFFERENT ACTIVATION IN THE RAT

Hypothesis / aims of study

Recently, the importance of the α1-adrenoceptor (α1-AR) subtypes in the pathophysiology of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia has been discussed. Considerable interest has been focused on the α1D-AR of extra-prostatic sites and storage symptoms. A distinct selectivity for α1A-AR antagonists, however are needed to study the functional role of α1A-AR. Silodosin (KMD-3213), which is a highly selective α1A -AR antagonist, also has clinically good effects on both voiding and storage symptoms. Therefore, we investigated the effect of silodosin on afferent nerve activity in an experimental model of partial urethral ligation in the rat. Previous reports have shown that c-Fos immunoreactivity in the L6 spinal cord is commonly used as an indicator of afferent neuronal input from the bladder in the rat. The present study was designed to determine whether bladder outlet obstruction (BOO) increases the bladder afferent activity and, whether the α1A -AR antagonist silodosin inhibits the increased afferent activation, regarding to the alteration of storage or voiding function derived from conscious metabolic voiding measurement and cystomety.

Study design, materials and methods

Study1: At 12 weeks of age 18 male Sprague-Dawley rats received partial bladder outlet obstruction (n=12) or sham surgery (sham group; n=6) were used. Four weeks following surgery, voiding behavior was observed in a metabolic cage. Twelve BOO-rats were administered subcutaneously either silodosin at a rate 0.1 mg/kg/day (silodosin group; n=6) or vehicle (BOO group; n=6) for 2 weeks with osmotic pumps. Six weeks following surgery, voiding behavior was observed in a metabolic cage again. Then, 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.

Study2: The rats were divided into 3 groups with the same treatment as described above. Four weeks and six weeks following surgery, continuous cystometry with saline was performed without anesthesia or restraint. The cystometric parameters were used to evaluate the storage and voiding function of the bladder. At the end of cystometry, residual urine was also measured

All value are expressed as means $\pm$SE. The data were statistically analysed by one-way ANOVA with the Bonferroni post-test, and a probability value of $p<0.05$ was considered significant.

Results

Between the BOO and Silodosin groups, no significant differences is detected in the pre-drug treatment (Table 1, 3). BOO caused a significant increase in voiding frequency or micturition pressure, and a significant decrease in the mean voided volume or cystometric capacity (Table 1, 3). Silodosin significantly decreased voiding frequency, and increased cystometric capacity or micturition interval (Table 2, 4). The increase in bladder weight, that is an approximately 3.5-fold increase versus that in sham-rats, was observed in each BOO-rat. There were no significant differences in bladder weight between the BOO and silodosin groups (Table 2, 4). Residual urine in the BOO group was significantly increased and silodosin did not change that in the BOO-rats (Table 4). BOO caused a significant increase in the number of c-Fos positive cells, whereas silodosin significantly decreased that in the BOO-rats (Table 2).

Interpretation of results

Our cystometric findings show that the present BOO-rats keep the bladder contractile function. The number of c-Fos positive cells shows that BOO increases afferent activity and α1A-AR antagonist inhibits it. The results of voiding behavior suggest that BOO reduces the storage function and α1A-AR antagonist improves it. Therefore, α1A-AR also plays a role in the storage symptoms secondary to outflow obstruction via the activation of afferent pathway. We consider that increased afferent activities are mainly due to inputs from the obstructed bladder, but we can not exclude the possibility of the ligated urethra because partial urethral ligation is not relieved in this study.

Concluding message

Our results suggest that BOO enhances voiding frequency through the afferent activation on lower urinary tract and α1A-AR antagonist inhibits the afferent activity independently of reducing prostatic urethral resistance, thereby improving storage function.

Table1

Water intake and voiding characteristics at 4 weeks after surgery (pre-drug treatment) in the 3 groups

	Sham	BOO	BOO(silodosin)
24-hr water consumption(ml)	19±1.91	25.19±4.1	25.5±3.74
24-hr frequency	17.5±1.10	28.2±1.74*	28.4±1.52*
Mean voided volume(ml)	0.98±0.04	0.76±0.06*	0.60±0.06*
Maximum voided volume(ml)	2.4±0.13	2.0±0.25	1.95±0.30
c-Fos positive cells / section	1.5±0.11	20.6±1.61*	15.6±1.72*†

* indicates P<0.05versus Sham

Table2
Water intake, voiding characteristics, bladder weight and c-Fos positive cells at 6 weeks after surgery (post-drug treatment) in the 3 groups

	Sham	BOO	BOO+silodosin
24-hr water consumption(ml)	21.1±2.45	29.8±1.93*	29.8±1.86*
24-hr frequency	20.0±1.24	30.2±1.78 *	24.2±1.42†
Mean voided volume(ml)	0.97±0.06	0.73±0.06	0.93±0.11
Maximum voided volume(ml)	2.6±0.18	2.23±0.32	2.64±0.40
Bladder weight(mg)	0.13±0.01	0.46±0.05 *	0.45±0.03*
c-Fos positive cells / section	1.5±0.11	20.6±1.61*	15.6±1.72*†

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

Table3
Cystometric parameters at 4 weeks after surgery (pre-drug treatment) in the 3 groups

	Sham	BOO	BOO(silodosin)
Micturition intervals(min)	4.0±0.58	2.14±0.47*	1.83±0.51*
Micturition pressure(cmH2O)	51.2±2.55	84.1±4.46*	85.1±8.31*
cystometric capacity(ml)	0.67±009	0.35±0.79*	0.30±0.08*

* indicates P<0.05versus Sham

Table4
Cystometric parameters and bladder weight at 6 weeks after surgery (post-drug treatment) in the 3 groups

	Sham	BOO	BOO+silodosin
Micturition intervals(min)	4.3±0.13	2.29±0.45	4.95±0.91†
Micturition pressure(cmH2O)	50.4±5.38	89.0±6.34*	85.3±13.04*
cystometric capacity(ml)	0.72±0.22	0.38±0.75	0.82±0.15†
Residual urine(ml)	0.02±0.002	0.94±0.37*	0.90±0.38*
Bladder weight(mg)	0.20±0.01	0.67±0.11*	0.75±0.12*

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

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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	**the Animal Ethics Committee of Fukushima Medical University.**