#372 An alpha 1-blocker inhibits non-voiding contractions and decreases the level of intravesical prostaglandin E_2 in rats with partial bladder outlet obstruction

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Introduction

The mechanisms of action for how α_1-blockers improve storage symptoms have not been elucidated thoroughly. The aims of this study, in an experimental animal model of bladder outlet obstruction (BOO), is to determine the mechanisms of action of naftopidil, an α_1-blocker, by investigating a possible association between bladder functions and intravesically released PGE_2 or ATP, and a possible association between the effects of naftopidil and resiniferatoxin (RTX)-sensitive C fibers or TRPV1, which is the site of action of RTX.

Methods

Thirty-five rats were randomly divided into the sham or BOO groups, and rats in each group were given vehicle or RTX (0.3 mg/kg) subcutaneously 3 days before cystometry. Incomplete urethral ligation was applied to the BOO group, and the other group underwent sham surgery. Filling cystometry was performed in the conscious condition 5 weeks after the operation. Cystometry was repeated at least three times and determine the BC. Levels of ATP and PGE_2 were measured in the instilled perfusate that was collected at 30% and 80% bladder capacity (BC) (Fig. 1). The bladders were then removed and weighed.

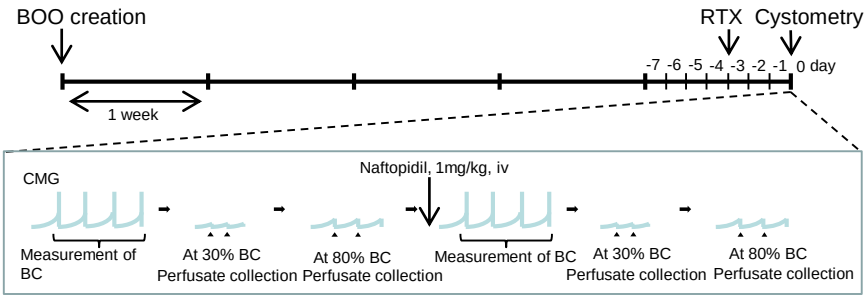

Fig. 1 The experimental design

Results

- ✓ NVCs and BC were markedly increased in BOO rats compared to sham rats without the RTX treatment, and RTX further increased the frequency of NVCs (Table) and BC in BOO rats as well as in sham rats.
- ✓ The intravesical levels of PGE_2 and ATP were higher in BOO rats compared to sham rats but not changed by the RTX treatment.
- ✓ Naftopidil inhibited NVCs in BOO rats irrespective of the RTX treatment (Table) and enlarged BC in BOO rats without the RTX treatment. Naftopidil did not enlarge BC in BOO rats with the RTX treatment. The intravesical levels of PGE_2 and ATP were decreased by naftopidil in BOO rats without the RTX treatment. In BOO rats with the RTX treatment, naftopidil decreased the intravesical level of PGE_2 but not that of ATP (Fig. 2).

Table. The comparison of the frequency and amplitude of NVCs between BOO groups with and without RTX and the effect of naftopidil on NVCs at 80% BC

Naftopidil	BOO		
	(-) RTX, n = 10	(+) RTX, n = 8	P^a
	frequency of NVCs, events/min		
before	1.4 [1.1, 2.0]	2.5 [2.1, 3.0]	0.003
after	1.1 [0.8, 1.4]	1.6 [1.3, 1.7]	
P^b	0.084	0.012	
	amplitude of NVCs, cmH_2O		
before	9.3 [7.0, 15.3]	10.3 [8.0, 14.4]	0.762
after	4.0 [1.8, 8.8]	6.90 [4.5, 11.0]	
P^b	0.009	0.012	

Data are shown as “median [25th percentile, 75th percentile]”.
P^a; Comparison between the (-) and (+) RTX groups.
P^b; Comparison between before and after administration of naftopidil.

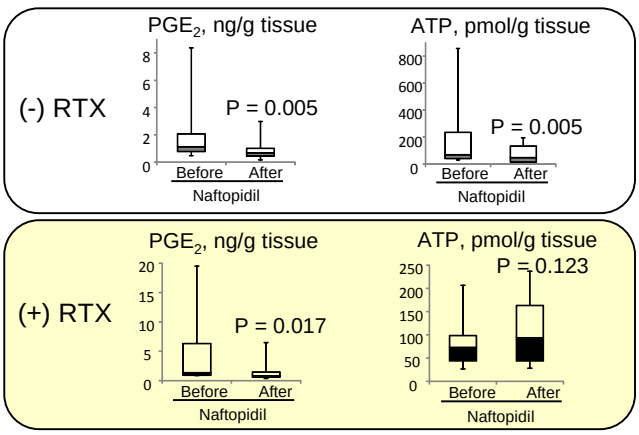

Fig.2 The effects of naftopidil on the levels of intravesical PGE_2 and ATP at 80% BC in BOO rats with and without RTX.

- Intravesically administered PGE_2 or α,β-methylene ATP is known to induce detrusor overactivity. BOO enlarged BC, enhanced NVCs and increased intravesically released amount of PGE2 and ATP. RTX also enlarged BC and enhanced NVCs without increase in intravesical levels of PGE_2 and ATP. Therefore, NVCs in BOO rats may be associated with the increase in BC, i.e., the bladder wall distension.
- The effect of naftopidil to increase BC was blocked by the RTX treatment. Therefore, naftopidil may enlarge BC via the suppression of TRPV1-sensitive afferents, which is a site of action of RTX.
- Even in BOO rats with the RTX treatment, i.e., under the condition of TRPV1 desensitization, naftopidil inhibited NVCs. Therefore, naftopidil inhibited NVCs via an action other than TRPV1 suppression. Naftopidil inhibited NVCs as well as decreased the intravesical level of PGE_2 but not ATP in BOO rats with the RTX treatment. This finding may imply that naftopidil inhibits PGE_2 release in the bladder and then inhibits NVCs.

Conclusions

In BOO rats, one cause of generation of NVCs may be bladder wall distension. Naftopidil enlarges BC by the inhibition of TRPV1-sensitive afferent nerves. Naftopidil inhibits NVCs and decreases the intravesical level of PGE_2, which are independent of TRPV1. These results suggest that the suppression of NVCs by naftopidil is associated with the urinary prostaglandin E_2 pathway.