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NON-VOIDING CONTRACTIONS AND INTRAVESICAL RELEASE OF ADENOSINE TRIPHOSPHATE AND PROSTAGLANDIN E2 IN A RAT MODEL OF BLADDER OUTLET OBSTRUCTION: EFFECTS OF RESINIFERATOXIN AND AN A1-BLOCKER, NAFTOPIDIL

Hypothesis / aims of study

Non-voiding contractions (NVCs) on cystometrogram are observed in animal models of bladder outlet obstruction (BOO) and α1-blockers are known to inhibit NVCs induced by BOO. The mechanism underlying the inhibition of NVCs by α1-blockers has not been identified. There is evidence to suggest that the spontaneous contractile activity of the bladder *in vitro* that may underlie NVCs *in vivo* can be regulated or modulated by the urothelium. The urothelium can release various substances including adenosine triphosphate (ATP), acetylcholine and prostaglandins (PGs). An α1-blocker naftopidil has been reported to decrease ATP release from the urothelium [1]. These findings suggest that the decrease in ATP release from the urothelium by α1-blockers is associated with the inhibition of NVCs in BOO, although a decrease in ATP release by α1-blockers has not been demonstrated *in vivo*. In the process of the ATP release, transient receptor potential vanilloid 1 (TRPV1) is the key molecule for stretch-induced ATP release from the urothelial cells [2]. TRPV1 channels are desensitized by a TRPV1 agonist, i.e. capsaicin or resiniferatoxin (RTX). The effect of TRPV1 desensitization on intravesical ATP release has not been examined *in vivo*.
In the present study, we examined the effects of TRPV1 desensitization on intravesical ATP release and NVCs in a rat model of BOO, and we determined the effects of the α1-blocker naftopidil on NVCs and the intravesical release of ATP in BOO rats with or without TRPV1 desensitization. We also examined the changes in intravesical PGE2 release by TRPV1 desensitization and/or naftopidil, because an increase in the intravesical release of PGE2 as well as ATP in BOO rats occurred in our previous study [3].

Study design, materials and methods

BOO was induced by incomplete urethral ligation (urethral outer diameter of 1.1 mm) in female Wistar rats (n=18). A polyethylene catheter for cystometry was inserted through the bladder dome 4 weeks after the induction of BOO and cystometry was performed with physiological saline 7 days after the insertion of the catheter. RTX (0.3 mg/kg) was used for the desensitization of TRPV1 and subcutaneously injected 3 days before cystometry in eight BOO rats. Vehicle was injected in the other rats (n=10). Two to three hours before the cystometry was performed, the rats' bilateral ureters were cut to prevent urine from entering the bladder. The bladder capacity (BC) for each rat was determined with repeated cystometry at least three times. Post-void residual was drained via the cystometry catheter after each micturition. After the BC was determined, the bladder was distended to 30% BC twice and then to 80% BC twice. The frequency and amplitude of NVCs were measured at the 30% and 80% BC distension and the instilled perfusate was collected for the measurement of the amounts of ATP and PGE2. Naftopidil (1 mg/kg) was administered intravenously. The BC was determined again, and the measurement of the frequency and amplitude of NVCs and the collection of infused perfusate were repeated. Finally the bladder was removed and weighed. ATP and PGE2 were measured with the luciferin-luciferase assay and the enzyme immunoassay, respectively. The ATP and PGE2 release are expressed as pmol/g tissue and pg/g tissue, respectively.

Results

The main results are shown in the Table.
Bladder weight was not significantly different between the BOO rats treated with vehicle and those treated with RTX. NVCs were observed in all BOO rats. The BC was greater and the frequency of NVC was increased in the RTX-treated BOO rats compared to the vehicle-treated rats. The intravesical ATP and PGE2 release were not significantly changed by the RTX-treatment, but we observed trends in which the intravesical ATP release was decreased but the PGE2 release was increased in the RTX-treated rats. Naftopidil attenuated the NVCs not only in the BOO rats treated with vehicle but also in those treated with RTX. The BC was increased by naftopidil in the vehicle-treated BOO rats. However, this was not the case in BOO rats treated with RTX. Both the intravesical ATP and PGE2 release were inhibited by naftopidil in the BOO rats treated with vehicle. In the BOO rats treated with RTX, the intravesical ATP release was not inhibited by naftopidil, but the intravesical PGE2 was inhibited again by naftopidil.

Table. Bladder weight, bladder capacity, NVCs and intravesical ATP and PGE2 release in BOO rats with and without RTX-treatment and the changes induced by naftopidil administration

		BOO rats treated with vehicle (n=10)		BOO rats treated with RTX (n=8)	
		Baseline	Naftopidil	Baseline	Naftopidil
Bladder weight (mg)		650.6 ± 58.4		581.3 ± 64.4	
Bladder capacity (BC) (ml)		5.9 ± 0.9	6.7± 0.9**	9.5 ± 0.8†	9.5 ± 0.8
Frequency of NVCs (/min.)	30% BC	1.1 ± 0.2	0.2 ± 0.1**	1.9 ± 0.1†	0.8 ± 0.2*
	80% BC	1.5 ± 0.2	1.1 ± 0.2	2.5 ± 0.2†	1.6 ± 0.1*
Amplitude of NVCs (cmH_2O)	30% BC	3.7 ± 0.7	1.0 ± 0.5**	6.2 ± 1.0	2.8 ± 0.8*
	80% BC	10.4 ± 1.6	5.8 ± 1.6**	11.8 ± 1.4	8.4 ± 1.3*
ATP release (pmol/g tissue)	30% BC	70 ± 39	43 ± 20	29 ± 6	23 ± 5
	80% BC	175 ± 80	72 ± 22**	82 ± 23	114 ± 29
PGE2 release (pg/g tissue)	30% BC	0.8 ± 0.2	0.5 ± 0.2	3.7 ± 2.1	1.3 ± 0.8*
	80% BC	2.0 ± 0.7	0.9 ± 0.2**	4.8 ± 2.6	1.7 ± 0.8*

The values are means ± SEM. Only the baseline values were compared between BOO rats treated with vehicle and those treated with RTX. Each value at 80% BC was significantly greater than each corresponding value at 30% BC irrespective of RTX or naftopidil administration ($p < 0.05$). † $p < 0.05$ compared to BOO rats treated with vehicle: * $p < 0.05$, ** $p < 0.01$ compared to baseline

Interpretation of results

We found that TRPV1 desensitization enhanced the NVCs and was likely to decrease the intravesical ATP release in the present study. These findings do not suggest that TRPV1 channels and ATP are indispensable for the generation of NVCs induced by BOO. However, TRPV1 channels and ATP may be involved in the micturition reflex in BOO rats because the BC was significantly increased by TRPV1 desensitization and by naftopidil. Naftopidil attenuated the NVCs in BOO rats with and without TRPV1 desensitization and inhibited the intravesical ATP release in those without TRPV1 desensitization, but it did not do so in those with TRPV1 desensitization. Therefore, in BOO rats without TRPV1 desensitization, the possibility that the inhibition of ATP release by naftopidil was related to the inhibition of NVCs cannot be excluded, but our finding that naftopidil inhibited NVCs without being accompanied by the decrease in ATP release in BOO rats with TRPV1 desensitization clearly indicates the presence of another pathway other than the modulation of ATP release for the inhibition of NVCs by naftopidil. In the present study, intravesical PGE2 release was likely to be increased along with the enhancement of NVCs by TRPV1 desensitization and was significantly decreased by naftopidil along with the inhibition of NVCs in BOO rats irrespective of TRPV1 desensitization. These findings suggest that PGE2 is related to NVCs due to BOO and that naftopidil attenuates NVCs via the inhibition of PGE2 release from the urothelium.

Concluding message

TRPV1 channels and ATP are not indispensable for the generation of NVCs induced by BOO although they may be involved in the micturition reflex. Intravesical PGE2 release is associated with NVCs, and the α1-blocker naftopidil may attenuate NVCs by inhibiting PGE2 release from the urothelium.

References

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Disclosures

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