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THE INHIBITION OF NON-VOIDING CONTRACTIONS DUE TO BLADDER OUTLET OBSTRUCTION BY ALPHA1-ADRENOCEPTOR BLOCKER: WHAT IS THE MECHANISM UNDERLYING THIS EFFECT?

Hypothesis / aims of study

Non-voiding contractions (NVCs) are observed by cystometrography in animal models of bladder outlet obstruction (BOO), and alpha (α)1-blockers are known to inhibit NVCs induced by BOO. However, the mechanism underlying the inhibition of NVCs by α1-blockers has not been identified. One study found that the α1-adrenoceptor blocker naftopidil suppresses resiniferatoxin (RTX)-sensitive afferent C-fiber signalling and then inhibits detrusor overactivity in a rat model of cerebral infarction [1]. This suggests that NVCs may also be inhibited by the suppression of afferent C-fibers by α1-adrenoceptor blockers. Additionally, little is known about the effect of α1-adrenoceptor blockers on spontaneous contractions (SCs) in *in vitro* whole bladders with BOO. We examined the effect of naftopidil on NVCs in rats with BOO with and without C-fiber desensitization by RTX as well as the effect of naftopidil on SCs in isolated *in vitro* whole bladders from rats with BOO *in vitro*.

Study design, materials and methods

BOO was induced by incomplete urethral ligation in female Wistar rats (urethral outer diameter of 1.1 mm).
Experiment 1. Cystometry was performed 4 weeks after the induction of BOO. RTX (0.3 mg/kg) was injected subcutaneously 3 days before cystometry. The bladder capacity (BC) of each rat was determined by cystometry repeated at least three times. Post-void residual was drained via the cystometry catheter after each micturition. After the BC was determined, the frequency and amplitude of NVCs were measured at the 30% BC and 80% BC distension. Naftopidil (1 mg/kg) was administered intravenously. The BC was determined again in the same way. The measurement of the frequency and amplitude of NVCs was repeated at the same volumes of the perfusate as before the administration of naftopidil. Finally, the bladder was removed and weighed.
Experiment 2. For the *in vitro* experiment, bladders were removed and weighed 4 weeks after the induction of BOO. A catheter was inserted into the bladder though the urethra. *In vitro* whole bladders were set in an organ bath containing Krebs solution. The bladder was distended with Krebs solution by an infusion pump until the intravesical pressure reached 10 cmH_2O. Once the intravesical pressure stabilized after the infusion pump was stopped, naftopidil (0.2 to 60 μM) or vehicle was added cumulatively in the organ bath. The frequency and amplitude of SCs were measured before and after the addition of naftopidil. Data were expressed as mean ± SEM.

Results

Experiment 1. The BC was greater in the BOO rats treated with RTX (n=10) than in those without the treatment (n=8) (9.5 ± 0.8 and 5.9 ± 0.9 ml, respectively; $p < 0.05$). The frequency of NVCs was increased in the BOO rats treated with RTX compared to those without the treatment (Table). The BC was increased by naftopidil in the BOO rats without RTX treatment (5.9 ± 0.9 to 6.7± 0.9 ml; $p < 0.01$). However, this was not the case in BOO rats treated with RTX. Naftopidil decreased the frequency and amplitude of NVCs in the BOO rats treated with RTX as well as in those without the treatment (Table).

Table. The frequency and amplitude of NVCs in BOO rats with and without RTX treatment and changes induced by naftopidil administration

		BOO rats (n=10)		BOO rats treated with RTX (n=8)	
		Baseline	Naftopidil	Baseline	Naftopidil
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 ± 02	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*

†$p < 0.05$ vs. BOO rats; *$p < 0.05$, **$p < 0.01$ vs. baseline

Experiment 2. Naftopidil decreased the frequency of SCs by approximately 30 % in *in vitro* whole bladder with BOO in the concentration range of 0.6 to 6 μM, although a significant difference was observed only at 0.6 μM between the whole bladders treated with naftopidil and those treated with vehicle (Figure). When compared to the baseline values, the frequency of SCs was decreased at 2 and 6 μM of naftopidil, but increased at 60μM (for each, $p < 0.05$). The amplitude of SCs was not changed by naftopidil (Figure).

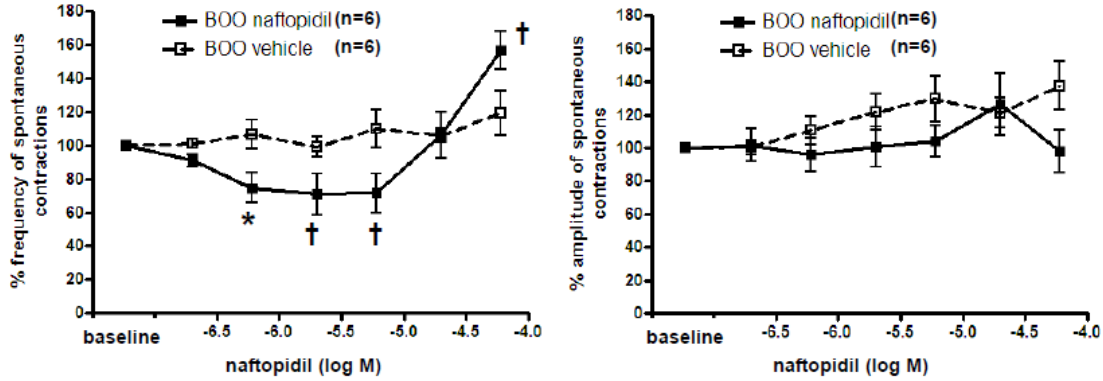

Figure. Changes by naftopidil and vehicle in the frequency (left) and amplitude (right) of SCs in *in vitro* whole bladder with BOO. The baseline values were set at 100%. *p <0.05 vs. vehicle; †p <0.05 vs. baseline

Interpretation of results

Naftopidil increased the BC in BOO rats without RTX treatment, but not in those with the treatment, while naftopidil inhibited NVCs irrespective of RTX treatment. These findings imply that naftopidil inhibits RTX sensitive afferents and increases BC as seen in rats with cerebral infarction; however, the inhibition of NVCs by naftopidil was not found to be associated with the inhibition of RTX sensitive afferents by naftopidil. Furthermore, the desensitization of RTX sensitive afferents increased the frequency of NVCs in BOO rats, suggesting that the suppression of the afferent neural pathway enhances the NVCs. The effect of naftopidil on the frequency of SCs in *in vitro* whole bladders from BOO rats became inconsistent with increasing concentration, and naftopidil had no effect on the amplitude, suggesting that the inhibition of NVCs by naftopidil *in vivo* is not associated with the effect of naftopidil on intramural machinery responsible for the generation of SCs in the bladder. These findings indicate that the inhibitory effect of naftopidil on NVCs is not derived from the inhibition of RTX-sensitive afferent fiber signalling or from the direct inhibition of spontaneous contractile activity in the bladder. Therefore, the inhibition of NVCs by naftopidil may be associated with its effect on the urethra and/or an efferent neural pathway innervating the lower urinary tract.

Concluding message

The inhibitory effect of α1-adrenoceptor blocker naftopidil on NVCs induced by BOO is not derived from the inhibition of RTX-sensitive afferent fiber signalling or from the direct inhibition of spontaneous contractile activity in the bladder.

References

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Disclosures

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