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EFFECTS OF C-FIBRE'S DESENSITIZATION AND ALPHA 1-BLOCKER ON NON-VOIDING CONTRACTIONS IN A RAT MODEL OF BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study

Non-voiding contractions (NVCs) are observed on cystometrogram in animal models of bladder outlet obstruction (BOO). NVCs are considered to be of myogenic origin. However, there may be a modulation of NVCs by the nervous system innervating the bladder because alpha 1-adrenoceptor blockers are known to attenuate NVCs. In a rat model of cerebral infarction, an alpha 1-blocker naftopidil is known to suppress C-fibre's signalling and increase bladder capacity (BC) [1]. Therefore, the inhibitory effect of alpha 1-blocker on NVCs may also be associated with the inhibition of C-fibre's signalling.

Isolated bladder strips develop spontaneous contractions (SCs) in-vitro, and SCs are considered to underlie NVCs. However, little is known about the direct effect of alpha 1-blocker on SCs in-vitro.

The aim of the present study was to investigate whether C-fibre's signalling is associated with the generation of NVCs and inhibitory effect of alpha 1-blockers on NVCs. The effect of alpha 1-blocker on SCs was also examined.

Study design, materials and methods

BOO was induced by incomplete urethral ligation in female Wistar rats (n=16). Cystometry was performed 4 weeks after the induction of BOO. To desensitize C-fibre afferent, resiniferatoxin (RTX) (0.3 mg/kg) was injected subcutaneously 3 days before cystometry in 7 rats. BC and the frequency and amplitude of NVCs at 80% BC were measured before and after intravenous administration of an alpha 1-blocker naftopidil (1 mg/kg). The effect of naftopidil (60 μM) on SCs in-vitro in bladder strips from female Wistar rats with BOO of 4 weeks duration (n=8) were also examined. Data were expressed as mean ± SEM. Statistical comparisons were performed using Wilcoxon matched pairs test and Mann-Whitney test, where $P \leq 0.05$ was considered significant.

Results

The mean values of bladder weights were 682 ± 54 mg and 627 ± 51 mg in BOO rats and RTX-treated BOO rats, respectively ($p>0.1$). The subcutaneous administration of RTX 3 days before cystometry increased BC and the frequency of NVCs in BOO rats (6.3 ± 0.9 and 9.5 ± 0.8 ml for BC, and 1.6 ± 0.2 and 2.5 ± 0.2 cycle/min for the frequency of NVCs in BOO rats and RTX-treated BOO rats, respectively; $p<0.05$ for both). Naftopidil increased BC and attenuated NVCs in BOO rats (6.3 ± 0.9 to 7.2 ± 0.8 ml for BC, and 11.1 ± 1.8 to 7.0 ± 1.8 cmH_2O for the amplitude of NVCs, $p<0.05$ for both), and decreased the frequency of NVCs even in RTX-pretreated BOO rats (2.5 ± 0.2 to 1.2 ± 0.1 cycle/min, $p<0.05$) with no effect on BC.

Naftopidil did not change the frequency and amplitude of SCs in bladder strips from rats with BOO.

Interpretation of results

The increase in BC by RTX suggests that C-fibre afferent is involved in neural circuits of the micturition reflex in rats with BOO. The decrease in afferent input in the bladder by C-fibre's desensitization may result in the delay of the initiation of micturition reflex and the increase in BC.

C-fibre's signalling is not essential for the generation of NVCs because NVCs were never inhibited by the treatment with RTX. On the contrary, C-fibre's desensitization by RTX enhanced NVCs. RTX-induced increase in BC, i.e., stretch of the bladder wall may enhance NVCs. The enhanced NVCs might act to stimulate a neural pathway involving afferents other than C-fibre so as to facilitate the micturition reflex.

That naftopidil increased BC in BOO rats but did not in RTX-treated BOO rats may support the finding observed in a rat model of cerebral infarction that naftopidil inhibited C-fibre's signalling [1]. However, naftopidil inhibited NVCs even in RTX-treated BOO rats and did not inhibit SCs in-vitro. Therefore, naftopidil may attenuate NVCs by the suppression of a neural pathway involving afferents other than C-fibres.

Concluding message

C-fibre afferent is involved in neural circuits of the micturition reflex in rats with BOO, but not essential for the generation of NVCs. C-fibre's desensitization by RTX enhanced NVCs and an alpha 1-blocker naftopidil inhibited NVCs even in RTX-treated BOO rats. Naftopidil did not inhibit SCs in-vitro. Therefore, the inhibitory effect of naftopidil on NVCs is not derived only from the inhibition of C-fibre's signalling or from the direct inhibition of spontaneous contractile activity of the bladder wall. Naftopidil may attenuate NVCs by the suppression of a neural pathway involving afferents other than C-fibres in RTX-treated BOO rats.

References

1. Yokoyama O, et al. Neurourol Urodyn 2006.

Disclosures

Funding: None **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Animal Care and Use Committee of the University of Fukui