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Title: PROSTATIC α_1-ADRENOCEPTOR STIMULATION COULD BE A CAUSE OF THE UNSTABLE BLADDER CONTRACTION IN RAT BENIGN PROSTATIC HYPERTROPHY MODEL

AIMS OF STUDY: Androgen-treatment, particularly both androgen and estrogen-treatments, causes prostatic hypertrophy[1] and results in a reduction in urine flow, an increase in urinary frequency[2], and the appearance of bladder overactivity[3, 4]. We recently developed a rat benign prostatic hypertrophy (BPH) model induced by androgen and estrogen-treatments as a modification of the method of Maggi et al.[3], and confirmed the appearance of unstable bladder contraction (UBC), which was suppressed by prazosin, a non-selective α_1-adrenoceptor (AR) antagonist, in the urine storage phase. This UBC seemed to correspond to the irritative symptom frequently observed in patients with BPH[4]. In the present study, in order to clarify the mechanisms responsible for UBC and to determine which α_1-AR subtype-selective antagonists suppress the UBC, we studied the effects of KMD-3213, a highly selective antagonist for the α_{1A}-AR subtype[5, 6], and tamsulosin, an α_{1A}- and α_{1D}-AR subtype-selective antagonist, on the rat BPH model.

METHODS: Male and female Sprague-Dawley rats (8 weeks old) were intramuscularly injected with testosterone and 17β-estradiol (T+E) (12.5 mg and 0.125 mg, respectively, in sesame oil) once a week for 4 weeks. After the (T+E)-treatments, various experiments were carried out. *In vivo studies*: 1. Pressure-flow studies were conducted by continuous saline-infusion into the bladder under urethane-anesthesia (1.0 g/kg, i.p.). Urodynamic parameters were compared before and after the intravenous administration of α_1-AR antagonists to male (T+E)-treated rats. Urodynamic parameters in female (T+E)-treated rats were compared with those in male BPH rats in order to estimate the role of the hypertrophied prostate. 2. Basal urethral perfusion pressure and phenylephrine (PE)-induced increase in the prostatic urethral perfusion pressure in BPH rats were measured, and compared with those in the non-treated rats. *In vitro studies*: Electrical field stimulation (EFS: supramaximum voltage, 0.5 msec pulse duration, 10 Hz and 5 sec train) was applied to isolated rat urinary bladder smooth muscle preparations. Effects of α_1-AR antagonists on the EFS-induced twitch response of the urinary bladder in BPH and non-treated rats were estimated.

RESULTS: Both prostate and bladder weights in BPH rats were significantly higher than those in the non-treated rats. In female rats, bladder weights increased significantly in the (T+E)-treated group. *In Vivo studies*: 1. In non-treated male rats, no apparent UBC was observed in the cystometrogram (Fig. 1). On the other hand, BPH rats showed UBC in the later phase of urine storage (Fig. 2-A). As to urodynamic parameters, BPH rats showed increases in micturition volume, micturition interval, threshold pressure and residual urine

volume, but no significant change in maximum micturition pressure or Qmax. Both KMD-3213 (Fig. 2-B and C) and tamsulosin diminished UBC, decreased micturition pressure at Qmax and threshold pressure, and tended to reduce the residual urine volume in BPH rats. In female rats, the micturition interval increased significantly in the (T+E)-treated group. However, the other urodynamic parameters in the (T+E)-treated group were not different from those in the non-treated group. An important point is that there was little, if any, bladder overactivity in spite of the increase in bladder weight. 2. Both basal urethral perfusion pressure and PE (30-300 μg/kg, i.v.)-induced increases in prostatic urethral perfusion pressure in the BPH rats were significantly higher than those in the non-treated rats. *In vitro studies*: KMD-3213 at 10 nM, which antagonizes only α_{1A}-AR, and prazosin at 10 nM, which antagonizes all of the α_1-AR subtypes, had no effect on EFS-induced bladder contraction in either BPH or non-BPH rats.

CONCLUSIONS: The results suggest that excessive response to sympathetic nerve stimulation, which is mainly mediated via α_{1A}-AR, in the hypertrophied prostate gives rise to the appearance of UBC in the urine storage phase. Thus, an α_{1A}-AR-specific antagonist, such as KMD-3213, would be sufficient to improve the irritative symptom associated with BPH patients.

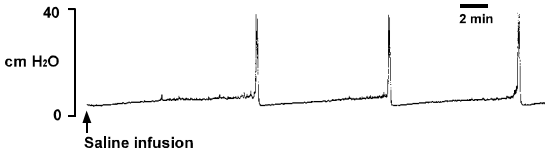

Fig. 1 Typical recording of cystometrogram in a non-treated male rat.

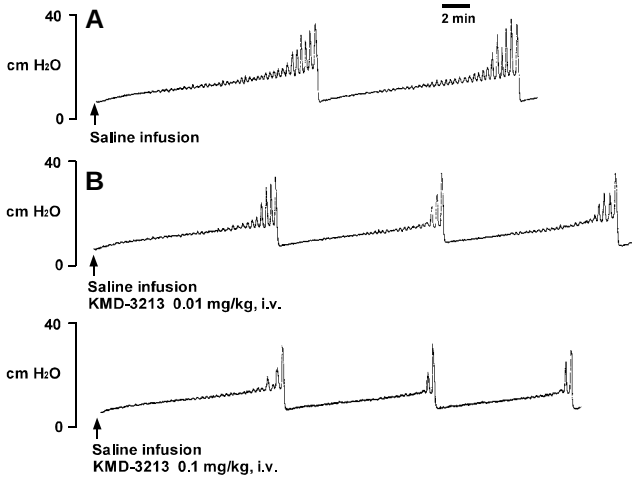

Fig. 2 Typical recordings of cystometrogram in a (T+E)-treated male rat.

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