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# THE INFLUENCES OF 5ALPHA-REDUCTASE INHIBITOR DUTASTERIDE AND CASTRATION ON NERVE-MEDIATED CONTRACTION OF RAT PROSTATE

Hypothesis / aims of study

Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) are highly prevalent in aging men. Medical therapy with alpha1-adrenergic antagonists and/or 5alpha-reductase inhibitors is the first-line treatment. The efficacy of alpha1-adrenergic antagonist such as tamsulosin on voiding dysfunction is due to its influence on functional obstruction in BPH patients. Dutasteride, which inhibits both isoenzymes of 5alpha-reductase can thereafter cause the reduction in prostate volume and corresponding improvement of voiding problems. Tamsulosin can be used in combination with dutasteride to achieve rapid onset of symptom relief, which is maintained in the majority of patients after tamsulosin was removed from the combination therapy. However, many patients with relative severe baseline symptoms reported a worsening of their symptoms after the withdrawal of tamsulosin [1]. At the 42nd annual meeting of the ICS, we reported the effects of dutasteride on phenylephrine induced contraction and alpha1-adrenoceptor expression in rat prostate for the first time. In this study, we further investigated the influences of dutasteride and castration on the nerve-mediated contraction of rat prostate, and tried to provide a better guidance for combination treatment with 5alpha-reductase inhibitor and alpha1-adrenergic antagonist.

Study design, materials and methods

Ten-week-old male Sprague-Dawley rats were separated in two experiments. Within one group, rats (n=4) were castrated, and the parallel control rats were kept intact. One week after castration, ventral and dorsal prostate lobes were isolated and mounted in an organ bath for electrical field stimulation (EFS) under the parameters (0.2 ms pulse duration, 50 V, 1 - 50 Hz, 2 s trains of duration, stimulation interval 120 s). In the other group, rats (n=8) were orally treated with dutasteride 0.5mg/kg/day (provided by GlaxoSmithKline) for two months, whereas the parallel control rats received vehicle only. After 2 months of treatment, ventral and dorsal prostate lobes were isolated and subjected to the same EFS stimulation. The amplitude of EFS-induced contraction was expressed as percentage of KCl-induced force. Unpaired t-test was used for statistical analysis.

Results

One week after castration, the contractions at 1 and 2 Hz were decreased markedly in ventral prostate; whereas in dorsal prostate, the contraction was decreased significantly only at 1 Hz. The contractions at 30, 40, and 50 Hz were increased greatly in dorsal prostate, but no statistically significant increases were found in ventral prostate. However, the contraction profiles in both ventral and dorsal prostate lobes showed the same trend toward increased force at higher frequencies. After the administration of dutasteride for 2 months, the EFS-induced contraction showed no significant differences in either ventral prostate or dorsal prostate between control and treated rats.

Interpretation of results

Our study showed that dutasteride could not significantly influence the nerve-mediated contraction of rat prostate during the current 2 months of treatment. Whereas, castration caused decreased contraction at low frequencies, but increased the contraction at high frequencies in both ventral and dorsal prostate lobes. As EFS-induced contractions at low frequencies are mediated by both neurotransmitters ATP and noradrenaline, while at high frequencies only attributed to noradrenaline [2], it is reasonable to assume that castration decreases ATP-mediated contraction, whereas increases adrenergic nerve controlled contractile responses. There are several reports about increased alpha1-a receptor amounts in prostatic tissues from BPH patients, and combined with our previous study, the present results showed that dutasteride has the potential for increasing alpha1-adrenoceptor mediated contraction of prostate after long-term treatment, although might not be too much.

Concluding message

Alpha1-adrenergic antagonists remain an important position in the combination therapy with dutasteride, and long-term combination therapy would be a better choice for patients with moderate to severe LUTS due to BPH.

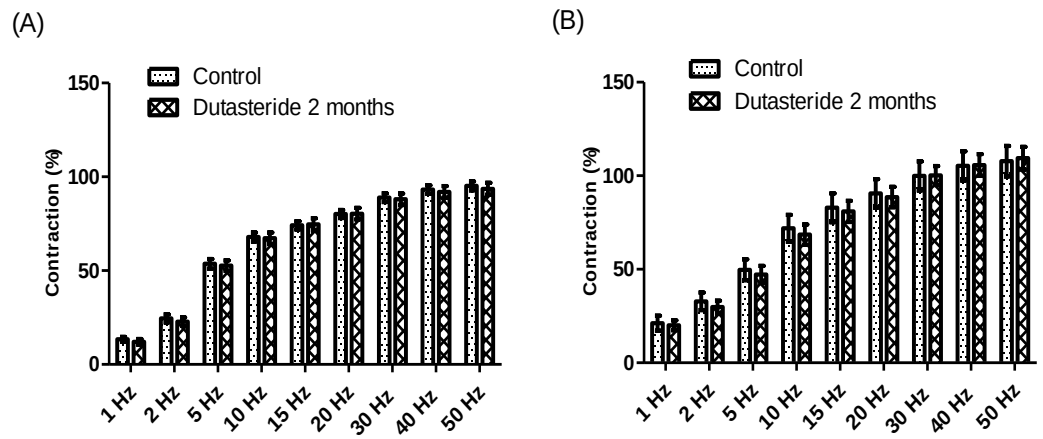

Fig. 1. Mean contractile responses to EFS in ventral prostate (A) and dorsal prostate (B) obtained from dutasteride and vehicle treated rats. Each column represents the mean±s.e.m of at least 11 determinations. Asterisk (*) indicates a significant difference from control response (P < 0.05).

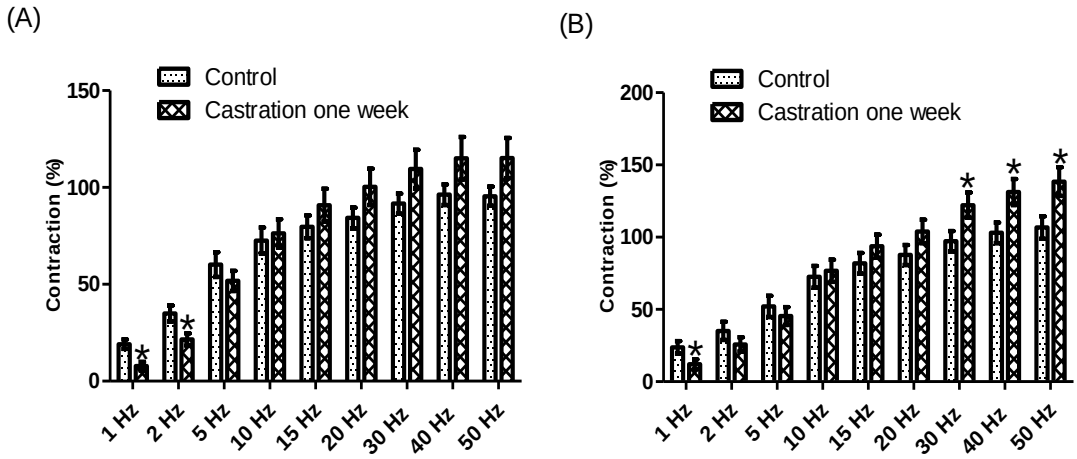


Fig. 2. Mean contractile responses to EFS in ventral prostate (A) and dorsal prostate (B) obtained from castrated and untreated rats. Each column represents the mean ±s.e.m of at least 8 determinations. Asterisk (*) indicates a significant difference from control response (P < 0.05).


References

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Disclosures

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