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ALPHA1D-ADRENOCEPTOR ANTAGONIST NAFTOPIDIL INHIBITS PROSTATE GROWTH WITHOUT APOPTOSIS IN BENIGN PROSTATIC HYPERPLASIA MODEL RAT

Hypothesis / aims of study
Alpha1-adrenoceptor (AR) antagonists relax prostatic smooth muscle and are now used as first line medical treatment for patients with lower urinary tract symptoms associated with benign prostate hyperplasia (BPH). Recently, three distinct subtypes of alpha1 adrenoceptors (alpha1A-, alpha1B-, and alpha1D-) have been reported to play a prominent role in cell growth in a variety of cells including cardiac myocytes and vascular smooth muscle cells. However, little is known about prostate growth and subtype-specific effects on cell proliferation. We have established an experimental rat BPH model resembling clinical BPH pathology by implanting of fetal urogenital sinus (UGS) into pubertal male rat ventral prostate. We examined the effect of subtype-selective alpha1-AR antagonists on prostate growth using this model.

Study design, materials and methods
Fetal urogenital sinus (UGS) isolated from male rat 20-day-embryo was implanted into pubertal male rat ventral prostate. The alpha1A-AR-subtype-selective antagonist tamsulosin (n=77, 0.02, 0.05 and 0.5 mg/kg), alpha1D-AR-subtype-selective antagonist naftopidil (n=70, 3, 10, 30 mg/kg), non-subtype selective alpha1-AR antagonist doxazosin (n=82, 0.02, 0.05 and 0.5 mg/kg), anti-androgen agent chlormadinone acetate (n=33, CMA; 10mg/kg) and vehicle (n=47) were given orally for 21 days from UGS implantation. . On day 21, the implanted UGS were collected and weighed. All grafts were fixed in formalin and embedded in paraffin. Proliferative and apoptotic indexes were determined using proliferating cell nuclear antigen (PCNA) staining and terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling (TUNEL) analysis, respectively.

Results
In the vehicle administration group, the weight of the implanted UGS was about 100 mg at 3 weeks after implantation. Administration of tamsulosin did not significantly inhibit the increase of implanted UGS weight at any dose, although naftopidil inhibited the increase 16.6% and 14% at doses of 10 and 30 mg/kg, respectively ($p<0.05$). Doxazosin at doses of 0.05 and 0.5 mg/kg and CMA also inhibited the increase significantly ($p<0.05$). There was no significant difference in either proliferative or apoptotic index after administration of tamsulosin . However, the stromal component of the proliferative index was lowered 28, 38 and 32% after administration of naftopidil at doses of 3, 10 and 30 mg/kg, respectively, although there was no significant change in the apoptotic index. The mean apoptotic index was lowered significantly after administration of doxazosin and CMA as reported previously, although there was no significant change in the proliferative index.

Interpretation of results
Although tamsulosin did not affect prostate growth, naftopidil inhibited the prostate growth by inhibiting the cell proliferation without apoptosis. On the other hand, doxazosin and CMA induced apoptosis correlated with prostatic stromal degeneration.

Concluding message
The effect of alpha1D-AR is related to the regulation of cellular hypertrophy and proliferation, and alpha1D-AR blockage (naftopidil) may not only improve lower urinary tract symptoms but also inhibit prostatic growth in BPH patients.

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