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LIMITATION OF ANTI-ANDROGEN THERAPY ON BENIGN PROSTATE HYPERPLASIA; VERIFICATION IN NOVEL STROMAL HYPERPLASIA MODEL

Aims of Study

Anti-androgen therapy has been expected to work well in the treatment of patients with benign prostate hyperplasia (BPH) based on its potent efficacy in rodent models of BPH. However, clinical trials showed that Chlormadinone acetate (CMA) and finasteride reduced prostate volume at most 30%. The major reason for discrepancy between clinical and animal studies regarding to anti-androgen therapy is assumed that rodent BPH is pathologically and physiologically different from human one. To verify the mode of actions of anti-androgen agents, we examined CMA and finasteride in a newly developed rat model for BPH that is particularly characterized by stromal hyperplasia.

Methods

Urogenital sinus (UGS) isolated from a male rat 20-day-embryo was implanted into a pubertal male rat ventral prostate. Two to 8 weeks after the operation, the implanted UGS was collected and weighed. All the grafts were fixed in formalin, embedded in paraffin, and sectioned at 2? m. Epithelial cells (Keratin), collagen (Masson's trichrome), smooth muscle components (? -smooth muscle actin) and proliferating cells (PCNA) were stained respectively. Testosterone-induced prostate hyperplasia model in rats was induced by subcutaneous infusion of testosterone at the dose of 3 mg/body/day for 14 days. Test agents were given orally for 21 days from UGS implantation or for 14 days from testosterone treatment.

Results

Implanted UGS weighting approximately 1 mg grew time-dependently; its weight was over than 100 mg at 3 weeks after implantation. Histological observation showed that the ratio of stromal to total area was approximately 70% throughout the experimental period. This ratio was obviously higher than that in the age-matched rat ventral prostate and in testosterone-induced prostate hyperplasia model (approximately, 20% and 15%, respectively). CMA at the dose range of 3-30 mg/kg/day reduced the UGS weight in a dose-dependent manner (about 30% at 30 mg/kg/day), while it suppressed prostate weight about 80% at the dose of 3 mg/kg/day in testosterone-induced prostate hyperplasia. In addition, finasteride at the dose range of 1-10 mg/kg/day reduced the UGS weight about 20%, but no dose-dependency was seen.

Conclusions

The efficacy of anti-androgen agents in the present study was comparable to that seen in clinical trials. The maximum suppression of UGS weight was around 20 to 30 % at the doses showing strong effect on testosterone-induced epithelial hyperplasia. The results suggest that anti-androgen therapy is not enough to improve stromal hyperplasia that is a major component of BPH. More importantly, further studies on pathological mechanism of stromal hyperplasia in the present model will explore a rational approach to develop new therapeutics for BPH.