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THE INFLUENCES OF 5ALPHA-REDUCTASE INHIBITOR DUTASTERIDE ON CONTRACTION AND ALPHA1-ADRENOCEPTOR EXPRESSION IN RAT PROSTATE

Hypothesis / aims of study

Benign prostatic hyperplasia (BPH) is a frequent cause of lower urinary tract symptoms (LUTS), with a high prevalence in the aging male population. Medical management of LUTS due to BPH with alpha1-adrenergic antagonists and/or 5alpha-reductase inhibitors is the first-line treatment. The efficacy of alpha1-adrenergic antagonist tamsulosin on voiding dysfunction is due to its influence on functional obstruction in BPH patients. Alpha1-adrenergic receptors play a major role in smooth muscle contraction of the prostate, which is the main reason for using alpha1-adrenergic antagonists for functional obstruction. 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 is 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]. Dutasteride can inhibit both isoenzymes of 5alpha-reductase and results in near-complete suppression of serum dihydrotestosterone, which causes the reduction in prostate volume and corresponding improvement of voiding problems. To our knowledge, there has not been any report on the influence of dutasteride-induced change of androgen levels on alpha1-adrenergic receptors responsible for functional obstruction, which might lead to unexpected effects of medical treatment. In this study, we try to elucidate the effects of dutasteride on the expression of alpha1-adrenergic receptors and relevant contraction in rat prostate 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 (n=8) were orally treated with dutasteride 0.5mg/kg/day (provided by GlaxoSmithKline), whereas the control group received only vehicle in the same amounts. After 2 months of treatment, ventral and dorsal prostate lobes were isolated and subjected to contraction and expression experiments. Contraction study was conducted by the induction of phenylephrine (0.01 to 1000 microM). Silodosin (1 nanoM) was used to study its antagonistic effects on phenylephrine-induced contraction. Maximum binding assay of [3H]-silodosin (1000 picoM) was conducted to reveal alpha1-A adrenoceptor amounts in the ventral prostate using tissue segment binding method [2]. mRNA amounts of three alpha1-adrenergic subtypes, alpha1-a, alpha1-b, and alpha1-d were determined using quantitative real-time polymerase chain reaction. Unpaired t-test was used for statistical analysis.

Results

After the administration of dutasteride for 2 months, the ventral and dorsal prostate weights decreased significantly from 431.4 ± 4.5 to 220.4 ± 12.7 mg and from 279.3 ± 11.0 to 151.9 ± 5.3 mg, respectively. pEC50 and antagonistic effects of silodosin were not significant different between both groups. Maximum binding (Bmax) was 18.2 ± 1.6 femtomol/mg protein in dutasteride group compared with 14.0 ± 0.9 femtomol/mg protein in control group. However the value did not reach statistical difference. Moreover, the relative mRNA amounts of alpha1-a and alpha1-d subtypes increased in both ventral and dorsal prostates compared with control group. However, there were no significant differences for all three alpha1-adrenergic receptor subtypes between control and dutasteride groups.

Interpretation of results

Our study showed that dutasteride has prominent effects on rat prostate growth, which is consistent with its functional properties. Dutasteride could not significantly influence the contraction induced by alpha1-adrenergic receptor agonist phenylephrine and the amounts alpha1-A adrenoceptor which is mainly responsible for smooth muscle contraction in the prostate during the current 2 months of treatment. However, the relative increase of alpha1-A subtype although not statistically significant indicates a possible enhancement of alpha1-adrenergic receptors-mediated contraction of prostate after long-term treatment of dutasteride.

Concluding message

The present data suggest that dutasteride has the possibility to cause increased contraction of the prostate after long-term usage. Therefore, long-term combination therapy would be a better choice for patients with moderate-to-severe LUTS due to BPH.

References

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