300

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UP-REGULATION OF ALPHA1A- AND ALPHA 1D-ADRENOCEPTORS IN THE PROSTATE BY ADMINISTRATION OF SUBTYPE-SELECTIVE ALPHA 1-ADRENOCEPTOR ANTAGONIST TAMSULOSIN FOR BENIGN PROSTATIC HYPERPLASIA PATIENTS

Hypothesis / aims of study

Alpha1-adrenoceptor (alpha $_1$-AR) antagonists have emerged as a first-line treatment for aging men with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). They interrupt motor sympathetic adrenergic nerve supply to the prostate, reducing urethral pressure and inhibiting smooth muscle tone in the prostate and lower urinary tract, thus improving LUTS/BPH. Tamsulosin, a subtype-selective alpha $_1$-AR antagonist, has proved to be effective for LUTS/BPH in randomized studies. In several studies in vitro testing human tissue, it has been shown to bind preferentially to prostatic smooth muscle compared to vascular muscle. The relative lack of cardiovascular side effects and lack of interactions with antihypertensives associated with tamsulosin therapy are probably due to its subtype selectivity for alpha $_{1a}$- and alpha $_{1d}$-ARs; however, there is no evidence of the subtype selectivity of tamsulosin in the prostate in vivo, and it is controversial whether the good tolerability of tamsulosin can be solely or predominantly explained by its moderate alpha $_{1a}$-selectivity.

Generally, repeated exposure to the same drugs causes adaptive changes that may manifest as either tolerance or sensitization; however, there is no report about therapeutic tolerance by chronic administration of tamsulosin. We speculated that the change of alpha $_1$-AR subtypes by chronic administration of alpha $_1$-AR antagonists might depend on each patient and cause the alternation of its efficiency. In this study, we examined the change of alpha $_1$-AR subtype expression levels in the prostate after the administration of tamsulosin to the BPH rat model and patients, and discussed the subtype selectivity of tamsulosin and the long-term efficiency of alpha $_1$-AR antagonists in BPH patients.

Study design, materials and methods

We have recently established an experimental BPH rat model with pathologically not only epithelial hyperplasia but also stromal hyperplasia. We measured alpha $_1$-AR subtype expression levels after tamsulosin administration in the prostate of the BPH rat model using TaqMan® RT-PCR.

We enrolled 61 patients with LUTS secondary to untreated BPH diagnosed in the outpatient urology clinic from 2002 to 2005. BPH was diagnosed on the basis of the International Prostate Symptom Score (IPSS), quality of life (QOL) index, ultrasonography, uroflowmetry and prostate needle biopsy. We excluded all patients with neuropathic disorders or urinary tract infections. None of the patients had received an alpha-AR antagonist, a hormonal drug acting on the autonomic nervous system or antidepressants. Diagnostic transperineal ultrasound prostate needle biopsies were performed for untreated BPH patients with slightly elevated PSA (average 6.4 ± 2.3 ng/ml; range 4.1-9.9 ng/ml), and pathological malignancies were excluded. Apart from biopsy specimens for malignant or benign diagnosis, four biopsy specimens were obtained from the transition zone in the patients to examine the expression levels of alpha $_{1a}$-, alpha $_{1b}$- and alpha $_{1d}$-ARs mRNA by TaqMan® RT-PCR.

One month after biopsy, 0.2 mg tamsulosin was given to patients once a day after breakfast for 12 weeks. The standard doses of this drug that are commonly used in clinical practice in Japan were chosen. A second biopsy was then performed. Fourteen patients consented to a second biopsy. The patients continued to receive tamsulosin monotherapy after the second biopsy. TaqMan® RT-PCR was performed using these biopsy specimens to assess the expression level of each alpha $_1$-AR subtype. The expression levels of alpha $_1$-AR subtypes were compared before and after 12-week tamsulosin treatment.

We also measured these expression levels before and after 12-week tamsulosin treatment in the prostate of BPH patients, and examined the correlation between the change of alpha $_1$-AR subtype expression levels by tamsulosin treatment and the development of acute urinary retention (AUR) during long-term follow-up.

Results

The expression levels of alpha $_{1a}$- and alpha $_{1d}$-ARs were significantly increased dose-dependently by tamsulosin administration to the BPH rat model. The median (interquartile range) expression levels of mRNA for subtype alpha $_{1a}$- and alpha $_{1d}$-AR were 1.4 (0.6, 3.0) and 1.7 (0.9, 2.4) x1,000 copies/1ng beta-actin, respectively, before treatment, and 6.0 (2.0, 8.0) and 2.2 (1.7, 3.6) x1,000 copies/1ng beta -actin, respectively, after treatment. The alpha $_{1a}$- and alpha $_{1d}$-AR expression levels significantly increased after tamsulosin treatment ($p<0.01$, $p<0.05$, respectively). This increase was observed in patients who did not develop AUR (n=10) during long-term follow-up, while it was not observed in patients who developed AUR (n=4).

Interpretation of results

We showed the up-regulation of alpha $_{1a}$- and alpha $_{1d}$-ARs in the prostate by tamsulosin administration in a BPH rat model and patients alpha $_{1a}$- and alpha $_{1d}$-AR expression levels were up-regulated after tamsulosin treatment in patients without AUR, while this change was not observed in patients with AUR, suggesting that up-regulation of alpha $_{1a}$- and alpha $_{1d}$-ARs does not indicate the induction of therapeutic tolerance, and patients with less receptor binding ability of tamsulosin or less distribution of tamsulosin to the prostate have a lower adaptive response to chronic tamsulosin administration in the prostate and, consequently, may lose therapeutic efficiency with long-term use.

Concluding message

Our in vivo study demonstrated that the antagonist potency of tamsulosin was mediated by alpha $_{1a}$- and alpha $_{1d}$-ARs. Although there are several possible reasons why alpha $_1$-AR antagonist monotherapy loses effectiveness with long-term use, such as the development of prostate volume and bladder dysfunction with age, the difference in the response to alpha $_1$-AR antagonists among patients may contribute to the diversity in the long-term efficiency of alpha $_1$-AR antagonists.

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What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Nagoya City University Ethics Committe**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**