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CHANGE OF ALPHA1 ADRENOCEPTOR SUBTYPES EXPRESSION LEVELS BY ADMINISTRATION OF ALPHA1D-ADRENOCEPTOR-SUBTYPE-SELECTIVE ANTAGONIST NAFTOPIDIL FOR THE BENIGN PROSTATE HYPERPLASIA PATIENTS

Hypothesis / aims of study

Alpha1-adrenoceptor (AR) antagonists are now often used as first line medical treatment for patients affected by lower urinary tract symptoms (LUTS) associated with benign prostate hyperplasia, since they have been proven effective in numerous randomized studies. However, the long-term effectiveness has not been established. We speculated that the chronic administration of alpha1-AR antagonists might cause the alternation of its effectiveness. We examined whether the change of alpha1-AR subtypes expression levels in the prostate occurred by administration of alpha1d-AR-subtype selective antagonist naftopidil to benign prostate hyperplasia (BPH) patients.

Study design, materials and methods

Diagnostic transperineal ultrasound prostate needle biopsy specimens were obtained from 50 patients with untreated BPH aged 58 to 76 (mean age, 68.3 $\pm$ 7.9 years). All patients had slightly elevated levels of prostate specific antigen, but pathologically no malignancy. Four biopsy specimens were obtained from the transition zone. The patients were administered 50 mg naftopidil daily for 12 weeks. Then a second biopsy was performed. Taqman quantitative reverse transcription polymerase chain reaction (RT-PCR) was performed using these biopsy specimens to estimate the expression level of each alpha1-AR subtype. The expression levels of alpha1-AR subtype before and after the naftopidil administration were compared. Informed consent was obtained from all patients before the study, after explaining to them the purpose and method of this study. This study was approved by the ethics committee at our institution.

Results

The mean expression levels of mRNAs for total alpha1-AR, and the subtypes alpha1a-AR, alpha1b-AR and alpha1d-AR were 4.72+/-4.77, 2.19+/-2.50, 0.49+/-0.58 and 2.03+/-2.27 x1,000 copies/ 1ng beta-actin, respectively, before the naftopidil administration, and were 4.88+/-2.70, 1.30+/-1.30, 0.42+/-0.60 and 3.15+/-1.81 x1,000 copies/ 1ng beta-actin, respectively, after the naftopidil administration The ratio of alpha1a-AR expression level to alpha1d-AR expression level was significantly changed after the naftopidil administration ($p<0.05$). There was no correlation between the change of alpha1-AR expression levels after the 12-week administration period, and the efficacy of naftopidil.

Interpretation of results

Naftopidil administration did not alter the expression level of total alpha1-AR mRNA in the prostate. However, it downregulated the expression of alpha1a-AR mRNA and upregulated the expression of alpha1d-AR mRNA.

Concluding message

The change of the expression levels of alpha1a-AR and alpha1d-AR may be regarded as a compensatory adaptation to chronic alpha1d-AR antagonist naftopidil administration. This may mean that the long-term use of the same alpha1-AR antagonist may induce development of therapeutic tolerance in the BPH patient.