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EFFECTS OF TAMSULOSIN ON BLADDER BLOOD FLOW AND BLADDER FUNCTION IN RATS WITH BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study

Patients with benign prostatic hyperplasia (BPH) are known to show both voiding and storage symptoms. Several clinical studies have reported that α_1-adrenoceptor antagonists, which are the major therapeutic agents, improve both types of symptoms in patients with BPH. α_1-Adrenoceptor antagonists are widely thought to improve voiding symptoms by relaxing the urethra and prostate via α_1-adrenoceptor blockade. In contrast, no explicit consensus exists on the mechanism by which these antagonists improve storage symptoms, although several theories have been proposed. In an effort to elucidate this mechanism, focus was placed on bladder blood flow. In this study, the effects of tamsulosin, one of the dominant α_1-adrenoceptor antagonists, on bladder blood flow and bladder function were evaluated in rats with bladder outlet obstruction (BOO). In addition, the possibility that tamsulosin affects vesical arterial smooth muscle was also explored. The expression ratio of α_1-adrenoceptor subtypes (α_{1a}, α_{1b}, and α_{1d}) is known to vary by type of artery, and that in rat vesical artery has not yet been reported. Therefore, the degree of α_1-adrenoceptor subtype mRNA expression in the vesical artery of rats was also measured in this study.

Study design, materials and methods

BOO was produced by partial ligature of the proximal urethra, which was maintained for 2 weeks. Tamsulosin was subcutaneously administered by osmotic pump for 2 weeks starting immediately after the BOO procedure. Saline was administered in a similar fashion in sham-operated and control BOO rats. Afterwards, bladder blood flow in sham-operated rats, control BOO rats, and tamsulosin (0.1 and 1 μg/kg/h, 2 w)-treated BOO rats were measured using the fluoro-microsphere method. For micturition data (total voided volume and micturition frequency) measurement, tamsulosin (1 μg/kg/h, 2 w) was administered as it was for bladder blood flow measurement. Two weeks later, micturition data was collected over a 2-h period for all rats while in metabolic cages and after water loading (20 mL/kg, p.o.). The mean voided volume was calculated using the following formula: mean voided volume = total voided volume / micturition frequency. The expression of α_1-adrenoceptor subtype mRNA in the vesical artery was measured using the RT-PCR method in sham-operated and BOO rats. The quantity of mRNA in each rat was normalized by adjusting for the amount of housekeeping gene (G3PDH) mRNA. All experiments were conducted separately using different animals.

Results

For bladder blood flow measurement, the numbers of animals in the sham-operated, control BOO, tamsulosin 0.1 μg/kg/h-treated BOO, and 1 μg/kg/h-treated BOO groups were 11, 11, 12, and 11, respectively. Bladder blood flow in control BOO rats fell significantly compared to that in sham-operated rats, while tamsulosin (1 μg/kg/h) significantly increased bladder blood flow in BOO rats. In the study to investigate micturition behavior, the mean voided volume for control BOO rats was significantly lower than that for sham-operated rats when data analysis was limited to BOO rats with bladder masses less than 500 mg. Tamsulosin (1 μg/kg/h) ameliorated the decrease in mean voided volume in BOO rats within the same range of bladder masses. The number of animals that met this criteria were 12, 8, and 6 in the sham, control BOO, and tamsulosin-treated groups, respectively. In the RT-PCR study, the relative α_1-adrenoceptor subtype ratio (α_{1a}:α_{1b}:α_{1d}) in the vesical arteries was 83.8:0.3:15.9 in sham-operated rats and 81.5:1.4:17.1 in BOO rats (n=3 for each group).

Interpretation of results

Reduction of bladder blood flow in patients with BPH [1] and in rats with BOO [2] has been reported in previous studies. Several reports have suggested that decreased bladder blood flow may induce bladder overactivity [3]. In the present study, an increase in bladder blood flow and improvement of bladder overactivity were shown in tamsulosin-treated BOO rats. This may indicate that tamsulosin improves bladder overactivity by increasing bladder blood flow. No significant change in the mean voided volume was observed in rats with bladder masses higher than 500 mg. It has been reported that bladder contractile ability in BOO rats decreases as bladder mass increases, which indicates that highly-hypertrophied bladders are in the decompensated stage. Rats with low bladder masses are therefore regarded as suitable for use in investigations of drug efficacy on bladder overactivity induced by BOO. In addition, we elucidated the abundance ratio of α_1-adrenoceptor subtypes in rat vesical artery for the first time ever, the results of which indicated: $\alpha_{1a}>\alpha_{1d}>>\alpha_{1b}$. This finding suggests that tamsulosin may increase bladder blood flow via its antagonistic effect on α_{1a} and/or α_{1d}-adrenoceptors in rat vesical artery.

Concluding message

The results indicate that tamsulosin increases bladder blood flow via an antagonistic effect on the α_{1A} and/or α_{1D}-adrenoceptors in the vesical artery, and improves storage dysfunction in BOO rats. These results suggest that increases in bladder blood flow might contribute to the improving effect on storage symptoms in patients with BPH that α_1-adrenoceptor antagonists have.

References

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