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RELATION BETWEEN EXPRESSION OF A1-ADRENOCEPTOR MRNAS IN BLADDER MUCOSA AND URODYNAMIC FINDINGS IN MEN WITH LOWER URINARY TRACT SYMPTOMS

Hypothesis / aims of study
A1-adrenoceptor (AR) antagonists are commonly used for treatment of lower urinary tract symptoms (LUTS) in men with benign prostatic obstruction (BPO). The common view is that they relieve voiding symptoms by decreasing smooth muscle tone in the prostate and prostatic urethra (effects on the "dynamic component" of outlet obstruction). The α_1-AR antagonists also improve the storage symptoms of BPO patients. The mechanism is unclear, but has been suggested to be related to effects on the bladder. There have been many reports suggesting that α_{1D} ARs are upregulated in obstructed bladders. However, there seem to be no reports (to the best of our knowledge) that correlate the expression of α_1-ARs in bladder urothelium to storage symptoms/sensations in patients. In the present study, we investigated the expression of α_1-AR mRNAs ($\alpha_{1A,}$ $\alpha_{1B,}$ α_{1D}) in the bladder mucosa (urothelium + suburothelium) of men with LUTS and BPO. We also determined the association of α_1-AR mRNAs with urodynamic parameters during storage of experimentally infused contrast medium, the international prostate symptom score (IPSS), and the overactive bladder symptom score (OABSS).
Study design, materials and methods
Mucosa was obtained from the posterior bladder wall from twenty patients with a diagnosis of LUTS and BPO undergoing prostatectomy. A1-AR subtype messenger RNA was quantified using competitive real-time reverse transcription polymerase chain reaction. A pre-operative video urodynamic study measured volumes for first desire to void (FDV) and strong desire to void (SDV). Patients were divided into Group 1 with volumes for FDV <200 ml or SDV <300 ml and Group 2 with volumes FDV >201 ml and SDV >301 ml. Pre- and post-operative international prostate symptom score (IPSS) and overactive bladder symptom score (OABSS) were evaluated.
Results
The average age was 71.5 ± 6.5 years in Group 1, and 72.6 ± 6.3 in Group 2 patients (p=0.552, Table 1). The PSA for Group 1 and 2 patients were 4.2 ± 0.4 ng/ml and 10.6 ± 6.7, respectively (p = 0.515, Table 1). There were no differences in the masses resected by TURP or retropubic prostatectomy (p = 0.485, Table 1). The Group 1 volume of FDV, 141.0 ± 13.5 ml, was significantly less than that of Group 2: 299.0 ± 48.1 ml (Table 1). Similarly, the SDV for Group 1 was 247.0 ± 21.9 ml, which was also significantly less than that of Group 2: 444.0 ± 32.5 ml. The pre-surgical IPSS and OABSS scores for Group 1 patients were 16.8 ± 5.9 and 7.5 ± 2.6, respectively. These scores were not significantly different from the pre-surgical scores of Group 2 patients (p = 0.534 and 0.566 respectively, Table 1). Expression of α_{1D}-, α_{1A}-, and α_{1B}-AR mRNAs in bladder mucosa from Group 1 and Group 2 patients revealed no significant differences between the groups with respect to α_{1A}-, and α_{1B}-AR mRNA levels (Fig. 1). However, mucosa from Group 1 patients had significantly more α_{1D}-AR mRNA than did Group 2 patients. There was no correlation between any of the mRNA expression levels and post-surgical IPSS, or pre- or post-surgical OABSS.
Interpretation of results
In the present study, we looked for a possible relation between urodynamic and symptom parameters and the urothelial levels of α_1-AR mRNAs. De Wachter et al. [Neurourol.Urodyn. 2008] demonstrated that in a group of patients with OAB, FDV was 300 ± 145 ml and SDV was 411 ± 167 ml. Based on their observations, we used breakpoint values of FDV 200 ml and SDV 300 ml to assign our Japanese patients to a high (Group 1) and low (Group 2) sensitivity group. In Group 1 patients, we found significantly higher level of α_{1D} AR mRNA in the urothelium (mucosa) of than in Group 2. There were no differences in the mRNA expression levels for α_{1A} – and α_{1B} -ARs between the two groups.
OAB is a constellation of LUTS that includes urinary urgency with or without urgency incontinence, frequency, and nocturia. As an aide for research and clinical practice, Homma et al. [Urology, 2006] developed the OABSS, which compiles a sum score of four symptoms: daytime frequency, night time frequency, urgency, and urgency incontinence. We did not find any relationship between pre- and post-OABSS (or IPSS) and the expression of α_1-ARs in the bladder urothelium. The reasons for this can only be speculated on. There seem to be many causes of storage symptoms, not all necessarily involving urothelial α_1-ARs. Nevertheless, our finding of a relation between urodynamic sensory parameters and the expression levels of urothelial α_1-AR mRNAs suggest that α_{1D}-ARs may play a role in storage symptoms in male LUTS patients.
Concluding message
There was a relationship between the expression of α_{1D} mRNA in the bladder mucosa and storage phase urodynamics in LUTS/BPO patients, suggesting a role of α_{1D} receptors in bladder sensation.

Table I. FDV, SDV, Age, IPSS, OABSS, resected mass and PSA in the two groups

	Group 1	Group 2	p-value
Age (year)	71.5± 6.5	72.6 ± 6.3	0.552
PSA (ng/ml)	4.2 ± 0.4	10.6 ± 6.7	0.515
FDV (ml)	141.0 ± 13.5	299.0 ± 48.1	0.003
SDV (ml)	247.0 ± 21.9	444.0 ± 32.5	0.003
pre-surgical IPSS	16.8 ± 5.9	18.7 ± 7.6	0.534
post-surgical IPSS	4.3 ± 0.8	5.0 ± 1.5	0.548

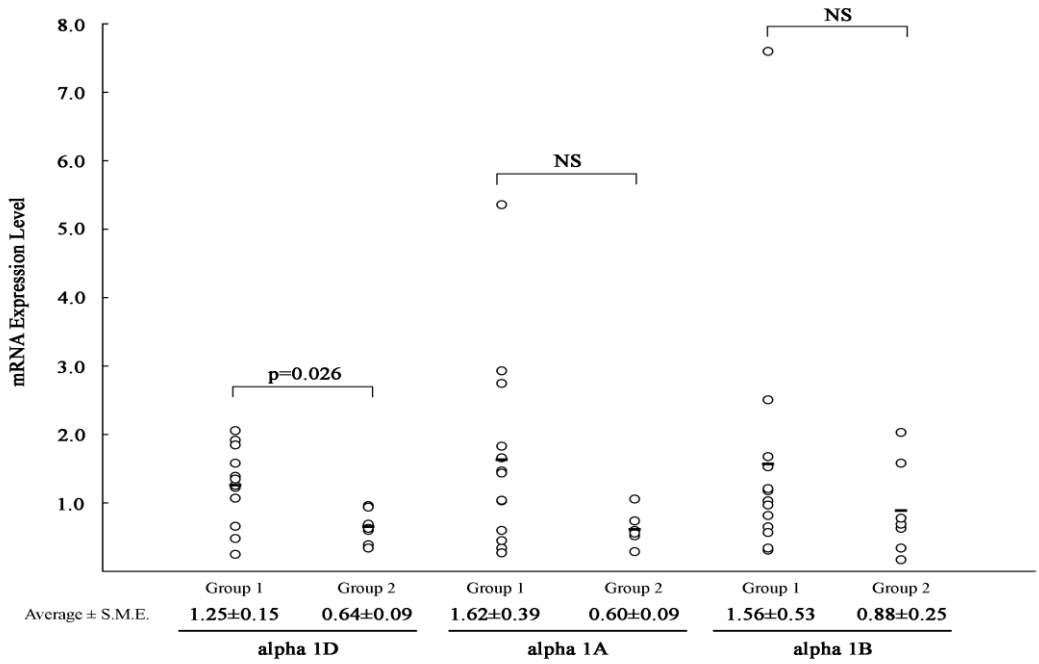
pre-surgical OABSS	7.5 ± 2.6	7.4 ± 3.1	0.566
post-surgical OABSS	3.3 ± 0.8	3.7 ± 1.8	0.543
resected mass (g)	53.4 ± 49.6	45.1 ± 60.9	0.485

All values were calculated as means ± standard error of means;

Group 1: volumes of first desire to void (FDV) < 200 ml or strong desire to void (SDV) < 300 ml

Group 2: FDV >201 ml and SDV>301 ml

Fig.1



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Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**No**
Is this a Randomised Controlled Trial (RCT)?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Ethics Committee of Shinshu University School of Medicine**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**