

## ALPHA-1D ADRENERGIC RECEPTOR IN THE UROTHELIUM MEDIATES AFFERENT ACTIVITY DURING THE STORAGE IN THE RATS

### Hypothesis / aims of study

Alpha-1 antagonists have been used for the improvement of the symptom in benign prostatic hyperplasia patients. Many reports indicated that selective alpha-1D receptor antagonist is useful treatment for the storage symptom (1, 2). However, involvement of the alpha-1D receptor in the development of unusual sensation including irritation has not been clear yet. Thus, we investigate the localization of the alpha-1D receptors in the urinary bladder, and effect of alpha-1D antagonist in micturition reflex and afferent nerve activity during the acetic acid infusion of the urinary bladder.

### Study design, materials and methods

Presence of alpha-1D receptor in the rat urinary bladder was studied with Western blot. Immunohistochemical study of alpha-1D receptor was performed for demonstration of localization of the receptors in the urinary bladder. Acetic acid (0.1%) infusion into the urinary bladder was performed as the model of acute inflammation. Effect of alpha-1D antagonist for micturition reflex was studied in conscious-restrained rats using continuous infusion of acetic acid to the urinary bladder. Effect of alpha-1D antagonist in primary afferent nerve activity recorded from L6 dorsal root filaments was also studied with acetic acid infusion into the urinary bladder.

The animal care and use committee of our University approved the experimental protocols involving the use of animals. Data were expressed as mean±S.E.M. Statistical analyses were performed using a Mann-Whitney test and paired T test, with  $P < 0.05$  considered being significant.

### Results

Alpha-1D receptor (60 kDa) was detected in prostate (P), whole urinary bladder (B) and urothelium cell layer (U) lanes. Epithelium cell marker, cytokeratin 17 (47 kDa), was detected in B and U lanes. Smooth muscle actin (42 kDa) was detected in the P and B lanes. Immunohistochemical study demonstrated that strong reaction product for alpha-1D receptor was observed in the urothelium. Most of urothelium cells showed alpha-1D receptor in the cytoplasm. Submucosa and smooth muscle showed weak reactions.

Acetic acid (AA) infusion into the urinary bladder shortened the intercontraction interval (ICI) from  $387 \pm 68$  sec to  $149 \pm 52$  sec (31% of the control,  $P < 0.01$ ) in conscious-restrained rats. Naftopidil (1.0 mg/kg, i.v.), an alpha-1D selective antagonist, increased the ICI to  $329 \pm 87$  sec (87% of the saline infusion,  $P = 0.18$ ). Maximum voiding pressure and threshold pressure were not altered with AA and/or naftopidil. When vesical pressure increased from 0 cmH<sub>2</sub>O to 30 cmH<sub>2</sub>O, neuronal discharge from the L6 dorsal root filaments was recorded. The discharge was returned to silent immediately after the vesical pressure returned to 0 cmH<sub>2</sub>O. AA infusion increased the afferent activity during the 30 cmH<sub>2</sub>O pressure distension. Naftopidil (0.75-1.5 mg/kg i.v.) decreased or abolished the AA-induced discharge (averaged  $30.4 \pm 3.5$  % of the control).

### Interpretation of results

The alpha-1D receptor in the urinary bladder was mainly located at the urothelium. Alpha-1D receptor antagonist, naftopidil, reduced the AA-induced afferent activity to the level before the AA infusion. Tonic activation of alpha-1D receptors in the urothelium by circulating and/or neurally released catecholamines may be involved in bladder sensory mechanism in pathological conditions.

### Concluding message

Endogenous catecholamines might act on alpha-1D receptors in the urothelium to facilitate the afferent nerve activity during urine storage.

## References

- (1) Alpha-1 antagonists inhibit the primary afferent activity from the irritative bladder of the rat. *Neurourol. Urodyn.*, 23: 511-513, 2004.
- (2) The clinical efficacy of naftopidil on overactive bladder in patients with benign prostatic hyperplasia. *Neurourol. Urodyn.*, 22: 437-438, 2003.

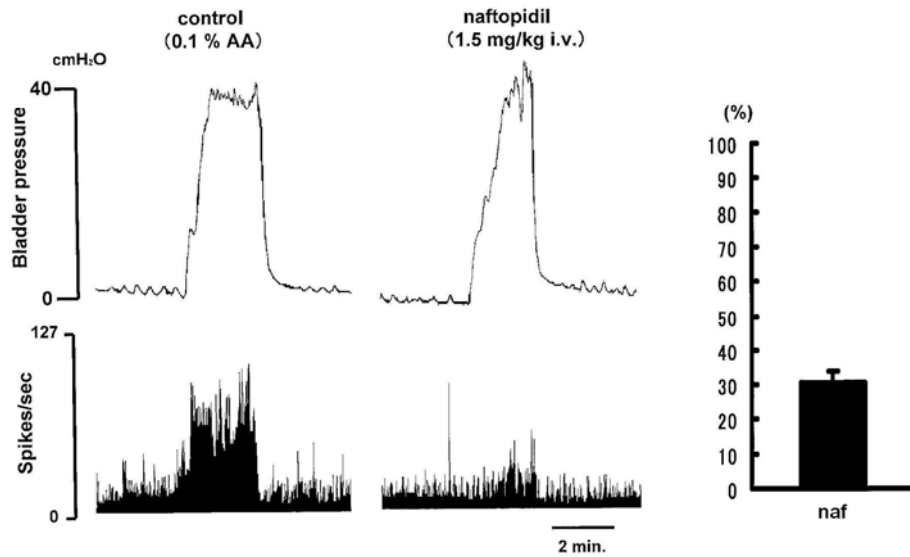


Figure: In acetic acid (AA, 0.1 %) infusion into the urinary bladder, larger volume of neural discharge was observed than saline infusion. Administration of naftopidil (naf, 1.5 mg/kg i.v.) reduced the neural discharge to  $30.4 \pm 3.5$  % of AA infusion.