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IS ALPHA-1D ADRENERGIC RECEPTOR RESPONSIBLE FOR STORAGE SYMPTOMS IN MICE? : EFFECTS OF ACETIC ACID ON BLADDER FUNCTION IN MICE LACKING ALPHA-1D ADRENERGIC RECEPTOR.

Hypothesis / aims of study

Alpha-1 adrenergic receptor (alpha-1 AR) antagonists are effective for relieving voiding and storage symptoms in patients with bladder outlet obstruction. Many investigators have reported that a highly selective alpha-1A AR antagonist did not appear to relieve storage symptoms in patients with benign prostatic hyperplasia (BPH) despite of a significant increase in urinary flow rate. Furthermore recent study reported that alpha-1 AR antagonist, which shows high affinity for both alpha-1A AR and alpha-1D AR, improved storage symptoms as well as voiding symptoms derived from BPH (1). The predominant subtype mRNA in bladder have been reported to be alpha-1D AR (2). We speculated that alpha-1D AR might be responsible for storage symptoms. Therefore, we evaluated the bladder function in mice lacking alpha-1D AR.

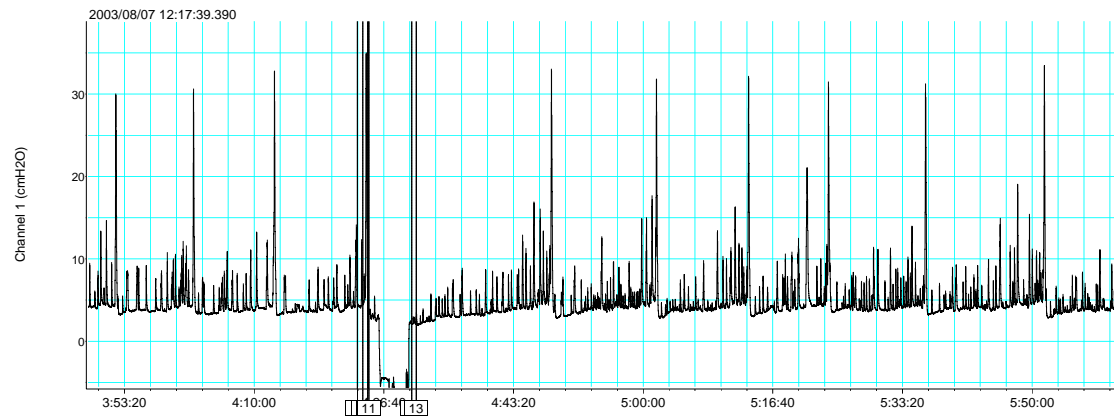
Study design, materials and methods

1. Cystometry in conscious restrained mice. Male mice lacking alpha-1D AR (1D KO; n=7) and matching wild type control (WT; n=7), 11-12 weeks of age, were anesthetized with sevoflurane for surgical insertion of an intravesical catheter (PE-50). After the surgery, cystometry was performed in conscious restrained mice by infusing saline into the bladder at a constant rate (0.5 ml/hr). After control measurement, 0.1% acetic acid (AA) was infused intravesically.
2. Cystometry in conscious freely moving mice. For the purpose of excluding the influence on surgical procedure and restrained stress, further experiments were performed. Female 1D KO (n=31) and WT mice (n=31), 8 weeks of age, were anesthetized for surgical insertion of an intravesical catheter. Six days after operation, cystometry was performed in conscious freely moving mice by infusing saline or 0.1% AA into the bladder at a constant rate (1.2 ml/hr).
3. Measurements of noradrenaline release. Male 1D KO (n=4) and WT mice (n=4), 12-13 weeks of age, were studied in a room at 23-25 degrees centigrade with a 12/12-hour light-dark cycle. Individual mice were placed in mice metabolic cages. The urine was collected during 48 hours. The amount of noradrenaline released in the urine was measured by HPLC.

Results

1. Cystometry in conscious restrained mice. Under control condition, there was no significant difference in any cystometric parameters between WT and 1D KO mice. In WT mice, intravesical infusion of 0.1% AA significantly decreased intercontraction interval (ICI) and pressure threshold (PT) (before AA, 657 ± 155 s, 6.6 ± 1.5 cmH₂O; after AA, 281 ± 68 s, 4.4 ± 0.7 cmH₂O, p<0.05, respectively). In 1D KO mice, neither ICI nor PT differ before and after intravesical infusion of 0.1% AA (before AA, 727 ± 89 s, 6.6 ± 0.9 cmH₂O; after AA, 715 ± 93 s, 6.9 ± 1.0 cmH₂O, respectively). There was no significant difference in maximal voiding pressure before and after intravesical infusion of 0.1% AA.
2. Cystometry in conscious freely moving mice. During intravesical infusion of saline, there was no significant difference in ICI between WT and 1D KO mice. During intravesical infusion of 0.1% AA, ICI in WT mice (150 ± 14 s) was significantly smaller than that in 1D KO mice (211 ± 27 s, p<0.05).
3. Measurements of noradrenaline release. The amount of noradrenaline released in urine of 1D KO mice (294.7 ± 93.3 pg) was significantly smaller than that in urine of WT mice (612.0 ± 53.5 pg, p<0.05).

Figure: Cystometrogram in conscious restrained mice lacking alpha-1D adrenergic receptor
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Event: 11 = ending point of intravesical infusion of saline; 13 = starting point of intravesical infusion of 0.1% acetic acid.

Interpretation of results

0.1% AA could not induce overactivity on bladder in 1D KO mice.

Concluding message

These findings indicated that alpha-1D AR might be responsible for storage symptoms in mice.

References

- (1) The clinical efficacy of naftopidil on overactive bladder in patients with benign prostatic hyperplasia. *Neurourol. Urodyn.* 22: 437-438, 2003.
- (2) Alpha-1 adrenergic receptor subtypes in human detrusor. *J. Urol.* 160: 937-943, 1998.

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