

## NEITHER SYSTEMIC NOR INTRAVESICAL ADMINISTRATION OF A-317567, AN ACID-SENSING ION CHANNEL BLOCKER AFFECT THE LOWER URINARY TRACT ACTIVITY IN DECEREBRATE UNANESTHETIZED MICE

### Hypothesis / aims of study

Acid-sensing ion channels (ASICs) represent an H<sup>+</sup>-gated subgroup of the degenerin/epithelial Na<sup>+</sup> channel (DEG/ENaC) family of cation channels that has been proposed as transducers of sensory stimuli. ASICs are composed of 4 subunits, ASIC1, ASIC2, ASIC3, and ASIC4; and ASIC1 and ASIC2 have "a" and "b" forms [1]. Recent study revealed that genes of ASIC subunits are largely expressed in the mouse urinary bladder (i.e., detrusor and urothelium) and L6/S1 dorsal root ganglia (DRGs) innervating the bladder, suggesting the possibility that ASICs are involved in modulation of lower urinary tract (LUT) function [2]. Thus, present *in-vivo* study using A-317567, a non-amiloride blocker of ASICs [3] was conducted to investigate whether ASICs play a functional role in control of LUT activity.

### Study design, materials and methods

C57BL/6 female mice (12-13 week-old) were used. The animals were anesthetized with sevoflurane during surgery including precollicular decerebration. A low midline abdominal incision was made, and a PE-50 tube was inserted into the bladder dome to record intravesical pressure. Cystometrogram (CMG) recordings conducted under unanesthetized conditions were started 2 h after decerebration, by continuously infusing saline (pH 6.0-6.3) (infusion rate: 30  $\mu$ l/min) at room temperature. ASIC1 is the richest subunit in bladder mucosa [2]; and ASIC1a and ASIC1b are known to have pH sensory thresholds for 6.2-6.8 and 5.1-6.2, respectively [1]. CMG parameters evaluated were: pressure threshold for inducing micturition contraction (PT), maximal voiding pressure (MVP), bladder compliance (BCP), bladder contraction duration (BCD), and inter-contraction interval (ICI). A-317567 was dissolved in saline for intravesical administration (100  $\mu$ M) or i.p. injection (30  $\mu$ mol/kg). The dose of 30  $\mu$ mol/kg for i.p. injection was chosen because it has been shown to produce marked analgesic effects in previous study [3]. All values are expressed as mean  $\pm$  S.E.M. Statistical analysis was made using Wilcoxon matched pairs test. P < 0.05 was considered significant.

### Results

As shown in Fig. 1, an intravesical administration (Fig. 1a) or i.p. injection (Fig. 1b) of A-317567 had little effect on bladder activity. A-317567 (intravesical or i.p. administration) produced no change in CMG parameters evaluated in this study (Table 1a,b).

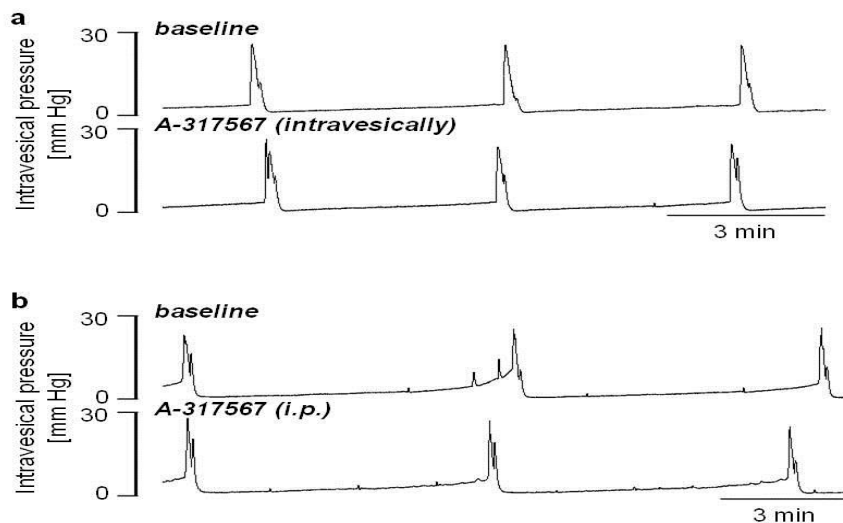


Fig.1

Table 1a.	Effects of intravesical infusion of A-317567 on the LUT activity				
	PT (mmHg)	MVP (mmHg)	BCP ( $\mu$ l/mmHg)	BCD (s)	ICI (s)
Baseline	5.0 $\pm$ 0.1	22.2 $\pm$ 1.2	47.3 $\pm$ 5.9	31.3 $\pm$ 4.4	317.3 $\pm$ 42.8
100 $\mu$ M	4.6 $\pm$ 0.3	21.6 $\pm$ 0.9	47.7 $\pm$ 8.5	27.0 $\pm$ 2.6	271.3 $\pm$ 34.0
Table 1b.	Effects of A-317567 (i.p.) on the LUT activity				
	PT (mmHg)	MVP (mmHg)	BCP ( $\mu$ l/mmHg)	BCD (s)	ICI (s)
Baseline	7.0 $\pm$ 0.5	25.3 $\pm$ 1.4	17.1 $\pm$ 1.8	30.1 $\pm$ 1.7	334.1 $\pm$ 26.3
30 $\mu$ mol/kg	10.7 $\pm$ 2.3	25.2 $\pm$ 2.6	16.7 $\pm$ 2.7	33.3 $\pm$ 3.3	346.6 $\pm$ 21.3

### Interpretation of results

Blockade of signal transduction *via* ASICs by intravesically or systemically administered ASIC blocker (A-317567) did not affect the LUT activity during fast infusion CMGs in unanesthetized decerebrate female mice.

### Concluding message

Since genes of ASICs are more abundantly expressed in the mouse bladder and L6/S1 DRGs than those of transient receptor potential channel vanilloid type 1 (TRPV1) [2], a significant participation of ASICs in control of the LUT has been greatly anticipated. However, pharmacological blockade of the ASICs did not produce any effects on the LUT activity. Further studies are necessary to determine a role of ASICs in control of the LUT function.

### References

1. Lingue E, J Biol Chem 282: 17325-17329 (2007)
2. Kobayashi H et al., BJU Int 104: 1746-1751 (2009)
3. Dubé GR et al., Pain 117: 88-96 (2005)

### Disclosures

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