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Yoshiyama M[1], Araki I[2], Kobayashi H[2], Zakoji H[2], Takeda M[2]
1. *Yumura Onsen Hospital,* ***2.*** *Department of Urology, University of Yamanashi Interdisciplinary Graduate School of Medicine and Engineering*

INTRAVESICAL INFUSION OF A NON-AMILORIDE BLOCKER OF ACID-SENSING ION CHANNELS FAILS TO AFFECT LOWER URINARY TRACT ACTIVITY IN UNANESTHETIZED DECEREBRATE MICE

Hypothesis / aims of study

Painful inflammation and ischemic conditions are accompanied by a decrease in the extracellular pH. Such acidosis can activate nociceptors and produce pain that can be attenuated by the degenerin/epithelial Na^+ channel (DEG/ENaC) inhibitor. Acid-sensing ion channels (ASICs) represent an H^+-gated subgroup of the DEG/ENaC family of cation channels that has been proposed as transducers of sensory stimuli. Recent study showed that genes of ASIC subunits are largely expressed in the mouse urinary bladder, suggesting the possibility that ASICs in the bladder are involved in modulation of inflamed lower urinary tract (LUT) activity [1]. Thus, present *in-vivo* study using intravesical infusion of A-317567, a non-amiloride blocker of ASICs [2] was conducted to examine whether ASICs in the bladder play a functional role in LUT activity under pathophysiological conditions generated by intravesical acid irritation. It has been reported that A-317567 is a small molecule blocker of ASICs which is more potent than amiloride [2].

Study design, materials and methods

Twenty-four 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 (30 μl/min) at room temperature. CMG parameters measured after an equilibration period of 2 h were: maximal voiding pressure (MVP, or 1st phase peak pressure), closing peak pressure (CPP, or 2nd phase peak pressure), bladder compliance (BCP), bladder contraction duration (BCD), and inter-contraction interval (ICI) [3]. A-317567 (100 μM in pH 6.0 or pH 3.0 solution) and its vehicle solution (pH 6.0 with HCl or pH 3.0 with HCl and acetic acid) were prepared, and effects of either solution intravesically applied after baseline saline (pH 6.3) infusion were evaluated and compared. All values are expressed as mean ± S.E.M. Statistical analyses were made using Mann-Whitney *U* test and two-way repeated measures ANOVA with actual values. $P < 0.05$ was considered significant (ns, not significant; $^*P < 0.05$).

Results

Fig. 1 shows the graphs presenting value changes in CMG parameters during infusion of pH 6.3 saline and subsequent pH 6.0 or pH 3.0 solution containing either A-317567 or the vehicle (n=6 for each group). There were no differences between A-317567's and the vehicle's effects in any of CMG parameters in response to pH change either from 6.3 to 6.0 (Fig. 1A-E) or from 6.3 to 3.0 (Fig. 1F-J) (*ns* in *italic* characters, by two-way repeated measures ANOVA).

Interpretation of results

A-317567 did not affect the value changes in any CMG parameters produced by the intravesical pH changes in unanesthetized decerebrate female mice.

Concluding message

Despite the ASIC genes are abundantly expressed in the bladder [1], acute blockade of these ASICs do not produce any significant effects on LUT activity responded to the intravesical pH change. Further studies are warranted to elucidate contributions of ASICs to the LUT function.

References
1. Kobayashi et al., BJU Int 104: 1746-1751 (2009)
2. Dubé et al., Pain 117: 88-96 (2005)

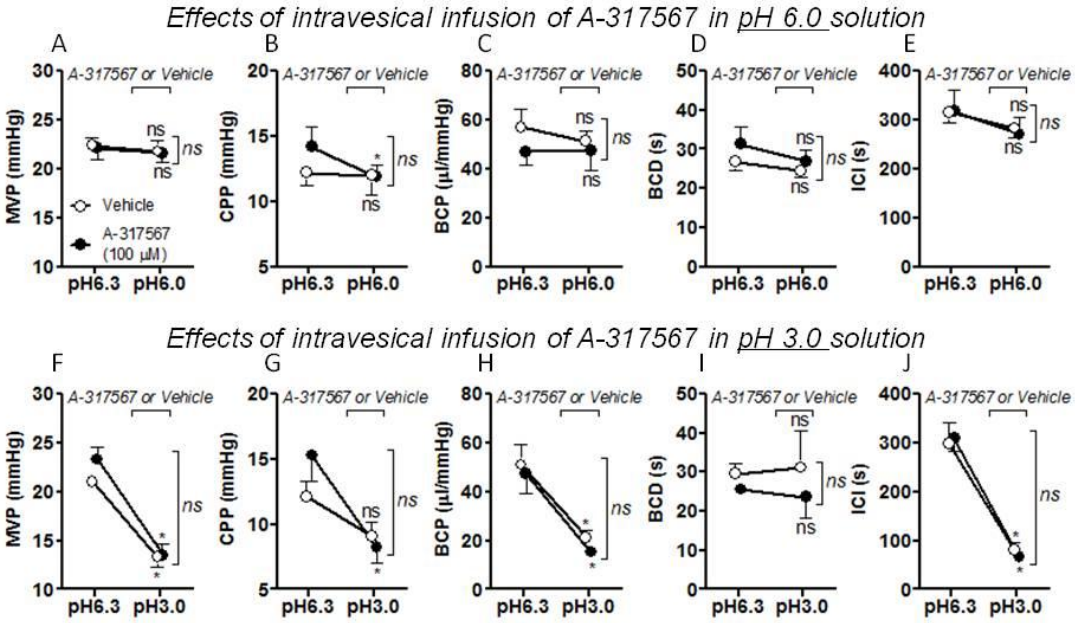

Fig. 1

3. Yoshiyama et al., Am J Physiol 295: R954-R960 (2008)

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