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SYSTEMIC ADMINISTRATION OF AN ACID-SENSING ION CHANNEL BLOCKER ALLEVIATES BLADDER HYPERACTIVITY INDUCED BY INTRAVESICAL ACETIC ACID IRRITATION IN MICE

Hypothesis / aims of study

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 [1]. Genes of ASIC subunits are known to be largely expressed in the central nervous systems (CNS), the peripheral nervous system including dorsal root ganglia (DRG) that innervate the bladder, and the bladder (both mucosa and detrusor), suggesting the possibility that ASICs are involved in modulation of lower urinary tract (LUT) activity [2]. In this in-vivo study using A-317567, a non-amiloride blocker of ASICs [3], we examined if ASICs play a functional role in activity of LUT with or without acid irritation.

Study design, materials and methods

Female C57BL/6 mice (12-14 week-old) were anesthetized with sevoflurane during surgery including precollicular decerebration. After a low midline abdominal incision, a PE-50 tube was inserted into the bladder dome to record intravesical pressure. Cystometrogram (CMG) recordings under unanesthetized conditions were performed by continuously infusing (30 µl/min) saline or dilute acetic acid (A/A, pH 3). CMG parameters measured were: pressure threshold for inducing micturition (PT); maximal voiding pressure (MVP), bladder compliance (BCP), bladder contraction duration (BCD), and inter-contraction interval (ICI). A-317567 was injected i.p. (30 µmol/kg), and effects of the drug were compared with those of the vehicle. All values are expressed as mean ± S.E.M. For statistical analysis, two-way repeated measures ANOVA and Wilcoxon matched-pairs signed rank test were used, and $P < 0.05$ (*) was considered significant.

Results

I.p. injection of A-317567 increased PT and ICI and decreased BCP during saline infusion CMG, whereas it had no effects on MVP and BCD (Table 1A). The drug ameliorated an aberrance in urine storage such as bladder hyperactivity (i.e., exhibited as decreased ICI) induced by intravesical A/A perfusion (Fig. 1; Table 1B). The effect lasted for approximately 10 min. The i.p. dose produced no changes in MVP and BCD (i.e., during bladder contraction period). The vehicle injection did not produce any effects on either normal LUT activity (during saline infusion) or A/A-induced bladder hyperactivity.

Interpretation of results

ASICs are involved in afferent excitatory transmission controlling reflex bladder activity under conditions of the LUT either with or without acid irritation, showing a contribution to urine storage function; whereas they do not participate in modulation of bladder contractions. The systemic injection of A-317567 exhibited a short duration in the action.

Concluding message

Block of signal transmission via ASICs can be useful in treatment of urine storage dysfunctions such as overactive bladder and painful bladder syndrome. Responsible sites for action of A-317567 are unknown. Further study is necessary to elucidate the mechanism underlying the beneficial effect of the ASIC blocker.

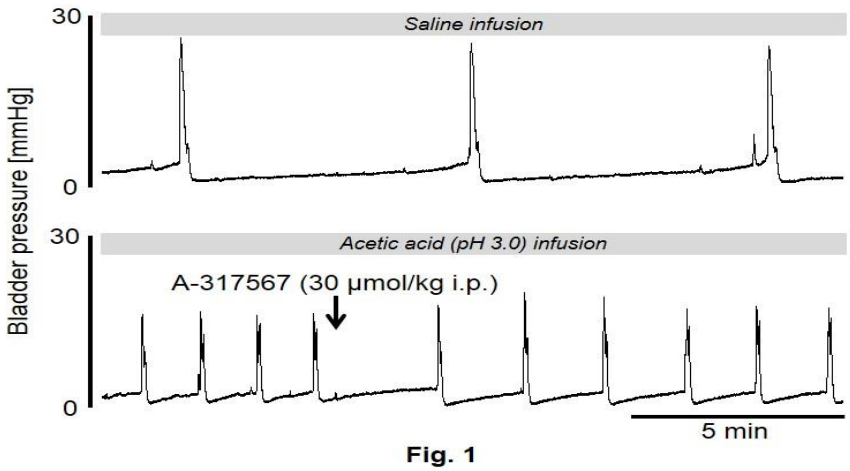

Fig. 1

Table 1A. ***Effects of A-317567 on normal LUT activity***

	PT	MVP	BCP	BCD	ICI

	(mmHg)	(mmHg)	(µl/mmHg)	(s)	(s)
Before	5.9 ± 0.6	22.6 ± 1.8	37.7 ± 2.8	26.1 ± 2.3	313.0 ± 26.5
After	19.1 ± 5.4*	26.1 ± 3.9	19.1 ± 5.2*	40.7 ± 8.9	398.9 ± 39.7*

Table 1B. ***Effects of A-317567 on A/A-induced LUT hyperactivity***

	PT (mmHg)	MVP (mmHg)	BCP (µl/mmHg)	BCD (s)	ICI (s)
Before	3.9 ± 0.3	15.7 ± 1.8	16.5 ± 1.7	20.3 ± 4.0	79.2 ± 9.1
After	4.8 ± 0.4*	15.7 ± 1.0	22.9 ± 3.4*	15.8 ± 1.0	134.9 ± 12.0*

References

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Disclosures

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