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SEX DIFFERENCE IN EXPRESSION PROFILES OF ACID-SENSING ION CHANNELS AND TRANSIENT RECEPTOR POTENTIAL CHANNEL V1 IN THE MOUSE URINARY BLADDER

Hypothesis / aims of study

In bladder-innervating sensory neurons, proton-evoked currents are mediated largely by acid-sensing ion channel (ASIC) in addition to transient receptor potential channel V1 (TRPV1) [1]. ASICs are encoded by four different subunit genes, ASIC1, ASIC2, ASIC3 and ASIC4, and the subunits form homo- or hetero-multimeric channels. In central and peripheral nervous systems, ASICs have emerged as key receptors for extracellular protons, and recent studies have suggested diverse roles for these channels in the pathophysiology of acid-evoked pain [2]. It has been reported that the female bladder is more sensitive and vulnerable to acidic irritation than male bladder [3]. This result has stimulated us to further investigate the underlying mechanisms for the sex difference. Thus, the present study was conducted to examine whether there was a sex difference in gene expressions of ASIC subunits and transient receptor potential channels in the mouse urinary bladder.

Study design, materials and methods

The urinary bladders of male and female mice were harvested to examine expressions of two acid-sensitive channel genes, ASICs and TRPV1, using real-time RT-PCR. We also examined gene expressions of other candidates for nociceptive ion channel, ie, TRPA1 and TRPM8, in bladders of male and female mice. Further investigation using the separated mucosa and muscle layer was performed for ASIC subunits that were dominant in the gene expression compared to the others. All values are expressed as mean ± S.E.M. Statistical analysis was made using Student's *t* test (*P<0.05; **P<0.01; ***P<0.001; n.s., not significant).

Results

In the whole bladder, ASIC1 and ASIC2 subunit genes were abundant, whereas ASIC3 was scanty and ASIC4 was virtually not detected (Fig. 1). Sex difference in gene expression level was found only in ASIC2 (Fig.1). ASIC1 was predominant ASIC subunit expressed in the mucosa, whereas both ASIC1 and ASIC2 were largely expressed in the muscle layer (Fig.2). In the mucosa, ASIC1 was more highly expressed in male than in female, whereas the expression level of ASIC2 in the muscle layer was higher in female than in male mice (Fig.2). The sex difference was found in the TRPV1 gene expression level, albeit the quantitative expressions of TRPV1, TRPA1 and TRPM8 were very poor (Figs.3 and 4).

Interpretation of results

The gene expression level of ASICs was dominant against that of the transient receptor potential channels (ie, TRPV1, TRPA1, and TRPM8) in the mouse bladder, while the expression pattern of the ASICs and TRPV1 showed the sex difference. ASIC1 gene was highly expressed in the mucosa and muscle, and ASIC2 gene was abundant in the muscle, suggesting the possibilities that ASIC1 is involved in both afferent signal transduction and detrusor activity and that ASIC2 regulates detrusor contractility. There was the sex difference in expression patterns of ASIC1 in the mucosa and ASIC2 in the muscle.

Concluding message

The present results suggest the possibilities that ASICs may be involved in afferent signal transduction and detrusor contractility and that ASICs and TRPV1 participate in sex difference in activity of lower urinary tract irritated by acid [3]. *In vivo* functional study is further necessary to determine if these channels are involved in mechanisms generating irritative bladder symptoms.

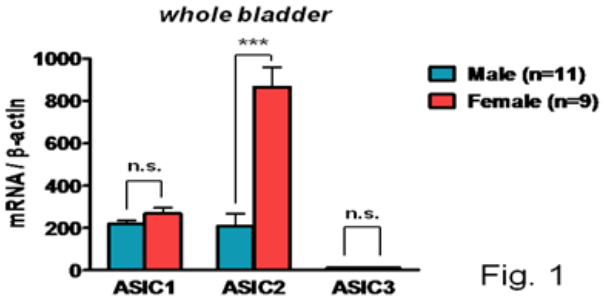

Fig. 1

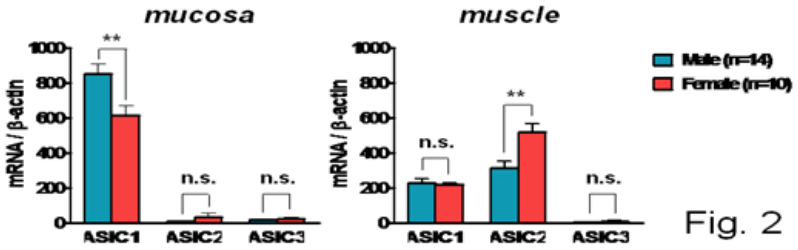

Fig. 2

Fig. 3

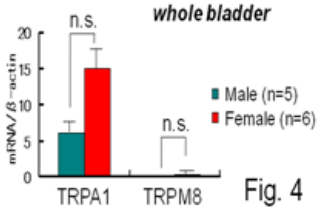

Fig. 4

References

1. J Neurosci 2005; 25: 3973
2. Trends Neurosci 2006; 29: 578
3. Am J Physiol Regul Interg Comp Physiol 2008; 295: R954

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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**University of Yamanashi Animal Care and Use Committee**