Acidic Sensitivity of TRPV1 and its Regulation Mechanisms in Chickens

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論　文　内　容　の　要　旨

Chickens, one of the most important industrial animals, are a biological animal model. Here I focused on the transient receptor potential vanilloid 1 (TRPV1) to understand the pain system for acidic stimuli in chickens compared with mice. By using a whole-cell patch clamp system, I confirmed that acidic stimuli activate both chicken TRPV1 (cTRPV1) and mouse TRPV1 (mTRPV1), but the peak current of cTRPV1 is lower than that of mTRPV1, and it is difficult to desensitize cTRPV1 with an acidic stimulus compared to mTRPV1. Since the C-terminal of the calmodulin (CaM) binding site in TRPV1 was reported as one of the important structures for TRPV1 desensitization, I made chimeric cTRPV1 in which the CaM binding site of chicken is changed to that of mouse (cTRPV1-mCaM). I also compared the acidic responses of native chicken dorsal root ganglion (DRG) cells with that of mouse DRG cells. The cTRPV1-mCaM results showed that the desensitization of mutant cTRPV1 was similar to that of mTRPV1, and that the basal activities of mutant cTRPV1 were significantly higher than those of cTRPV1. It was also difficult to desensitize the chicken DRG cells with an acidic stimulus, unlike the mouse DRG cells. These results suggest that there are differences in the pain transduction systems for acidic stimuli between chickens and mice that are caused by the dysfunction of the C-terminal CaM biding site of cTRPV1. These results imply that chickens repeatedly feel weak pain from an acidic stimulus, without desensitization.

Next, to understand the binding regulation of cTRPV1 deeply, I made the point mutant cTRPV1-A558T and confirmed the response to capsaicin and bigger response to acidic stimuli rather than that in wild-type cTRPV1. Although the capsaicin-induced desensitization was observed in cTRPV1-A558T, the acid-induced current was still hard to be desensitized. At last, I made the point mutant mTRPV1-T551A and examined the acid-induced desensitization in mTRPV1-T551A. T551 of mTRPV1 is capsaicin binding site and corresponding amino acid to A558 of cTRPV1. The tachyphylaxis in mTRPV1-T551A by acid stimuli was weaker than that in wild-type mTRPV1. These results suggest that T551 of mTRPV1 is not only

an important amino acid in capsaicin binding, but also A558 of cTRPV1 is a key residue to lost the capsaicin response. These results also indicated that T551 in mTRPV1 or A558 in cTRPV1 regulates the sensitivity of acids. And, these results also implied that the regulation mechanisms of TRPV1 desensitization are different by variety of stimuli.

Taken together, the present study revealed some mechanisms of TRPV1 desensitization and partly contributed to fundamental understanding of avian pain sensing system.