Molecular analysis of TRPA1 activation by JT010 in human, mouse, and chicken

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TRPA1, which is mainly expressed in sensory neurons, plays an important role as a pain receptor in mammals. TRPA1 is a six-transmembrane ion channel, and it is known that cysteine ☒☒residues in the intracellular N-terminal region are important for channel activation by allyl isothiocyanate (AITC), a typical TRPA1 agonist. JT010 is a newly discovered compound as a TRPA1-selective agonist, and it is reported to be a site-selective agonist against a 621-cysteine ☒☒residue (C621). However, the importance of other regions has not been understood for the TRPA1 activation, and the detailed activation mechanism is not clear. The purpose of this study is to reveal the mechanism of TRPA1 activation by JT010, focusing on species-specific differences in TRPA1. A heterologous expression system was used in which HEK293 cells are transfected with human TRPA1 (hTRPA1), mouse TRPA1 (mTRPA1), chicken TRPA1 (chTRPA1), and site-directed cysteine mutants of these TRPA1s. hTRPA1 was activated by application of 10 nM JT010, while mTRPA1 and chTRPA1 not. As a result of normalization of the sensitivity to JT010 with the response to 100 μM AITC each response was 40%, 7%, and 4% for hTRPA1, mTRPA1, and chTRPA1, respectively. Since both mTRPA1 and chTRPA1 conserve C621, it was suggested that there are other residues that contribute to TRPA1 activation by JT010.

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