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

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【概要】

2020 年 3 月 16～18 日に、パシフィコ横浜にて開催される予定であった第 93 回日本薬理学会年会に、以下の研究内容にて、ポスター発表申し込みを行った。本年会は、新型コロナウィルス感染症の拡大防止のため中止となり、誌上開催にての発表となった。

【Abstract】

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.