様式３

# 論　文　内　容　の　要　旨

| 氏　名　（　森　山　さ　く　ら　） | |
|---|---|
| 論文題名 | Studies on interaction between olfactory receptor and transient receptor potential vanilloid 1<br>（嗅覚受容体とTRPV1の相互作用に関する研究） |

論文内容の要旨


Olfaction is a critical sensory modality for detecting a diverse array of odorant molecules, influencing behavior and emotion. Olfactory receptors (ORs) are expressed in olfactory sensory neurons (OSNs) in the nasal cavities of humans. In the initial step of odor recognition, the binding of odorant molecules to ORs transduces signals in OSNs. However, it remains unclear whether OR signals alone contribute to the formation of brain-transmitting signals. Both transient receptor potential vanilloid 1 (TRPV1) and ORs are known to be expressed not only in OSNs but also in various other cell types, including prostate cancer cells. The present studies aimed to elucidate whether OR and TRPV1 can influence each other's intracellular signaling, employing HEK293T cells co-expressing the two receptors by transfecting expression plasmids. The findings of the studies revealed a bidirectional regulatory mechanism between ORs and TRPV1.

The initial study discovered that ORs play a role in regulating TRPV1 activation. Interestingly, the effects of ORs varied depending on the vanilloid ligands for TRPV1. For example, TRPV1 responses ($Ca^{2+}$ influx) to capsaicin were potentiated upon OR activation, whereas those to eugenol were attenuated. This mechanism was as follows. Ligand-stimulated OR liberates GTP-Gs/olf, which activates adenylate cyclase, leading to the elevation of intracellular cAMP., Elevated cAMP activates protein kinase A, which promotes the phosphorylation of TRPV1. Consequently, ORs differentially regulate ligand-dependent TRPV1 activation through the phosphorylation of TRPV1. Furthermore, OR-induced changes in TRPV1 responses allowed vanilloid ligands for TRPV1 to be classified into three groups: the capsaicin type (enhancement), the eugenol type (suppression), and the 10-shogaol type (no significant change), each distinguished by unique chemical structures.

Subsequently, the effect of TRPV1 on cAMP production induced by ligand-activated OR was examined. TRPV1 activated by capsaicin suppressed cAMP production by ligand-stimulated OR51E1. This suppression was proven to be mediated by elevation of intracellular $Ca^{2+}$ levels through TRPV1. Furthermore, it was found that GPCR kinase (GRK) activation by $Ca^{2+}$ influx is involved in the suppression process. These results suggest that TRPV1 activation suppresses ligand-stimulated OR signal transduction by promoting desensitization of activated OR51E1 via $Ca^{2+}$ influx and GRK activation.

In conclusion, these studies revealed the mechanisms that OR and TRPV1 mutually regulate each other's activation when expressed in HEK293T cells. Future research will be necessary to determine whether such mutual regulation occurs in OSNs or other cells that naturally express both receptors. Nevertheless, the findings of the present studies offer valuable insights into a potential mechanism through which signals generated by ORs (for example, critical for olfaction in OSNs) are dynamically regulated via multi-directional crosstalk between ORs and other receptors, including TRPV1.

様式 7

# 論文審査の結果の要旨及び担当者

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## 論文審査の結果の要旨

本研究は、嗅覚受容体（OR）とTRPV1の相互作用を明らかにしたものである。HEK293T細胞に両受容体を共発現させた実験により、ORの活性化がTRPV1のリガンド応答を修飾することを見出した。具体的には、カプサイシン応答は増強され、オイゲノール応答は抑制され、10-ショウガオールは変化を示さなかった。これは、OR活性化に伴うcAMP上昇とPKA依存的なTRPV1リン酸化による調節機構で説明される。また、TRPV1の活性化は$Ca^{2+}$ 流入を介してOR51E1のcAMP産生を抑制し、GRK依存的な脱感作を誘導することが示された。以上より、ORとTRPV1は相互に活性を制御し合う双方向性クロストークを有することが明らかとなった。本成果は嗅覚情報伝達の新たな調節機構の理解に資するものであり、博士の学位を授与するに値するものと認める。なお、チェックツール“iThenticate 2.0”を使用し、剽窃、引用漏れ、二重投稿等のチェックを終えていることを申し添えます。