Deciphering the molecular basis for activation and inhibition of olfactory receptors.

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Olfactory receptors (ORs) are part of the largest family of G protein-coupled receptors and constitute the molecular basis for the detection and discrimination of a vast chemical space of volatile compounds. ORs function through a combinatorial mechanism, meaning that a single odorant can activate multiple receptors, while a single receptor can respond to structurally diverse ligands. Beyond their sensory role, select ORs are ectopically expressed in non-olfactory tissues; Olfr412, for instance, is expressed in spermatozoa and participates in chemotaxis, highlighting the broader physiological relevance of this receptor family. Despite significant advances in the field regarding the molecular mechanisms of odorant recognition and receptor activation, receptor inhibition remains poorly understood.

This study integrates computational modeling with experimental validation to decipher and further understand the molecular determinants of OR activation and inhibition. Olfr412, the ectopically expressed OR in mice, bound with different types of odorants served as the selected model systems. We combine molecular docking and simulations to characterize agonist, and inverse agonist binding at the atomic level. Comparative analysis of OR-agonist and OR-inverse agonist complexes reveals differences in receptor-ligand interactions highlighting the differences between activation and inhibition. The selected odorants were subsequently tested experimentally to validate their effect on OR activity. Furthermore, Umbrella Sampling was employed to map the translocation pathways of odorants through the Olfr412.

Collectively, this work deepens our understanding of OR activation and inhibition at the molecular level, implicating both their sensory and ectopic function and enabling the design of modulators.

Bibliography :

[1] Lalis M.; et al. Chem. Senses, 2024, 49, bjae037.
[2] Malnic B.; et al. Cell, 1999, 96, 713-723.
[3] Pfister P.; et al. Curr. Biol., 2020, 30, 2574-2587.
[4] Katada S.; et al. J. Neurosci., 2005, 25, 1806-1815.
[5] Pilpel Y.; Lancet D. Protein Sci., 1999, 8, 969-977.
[6] Jumper J.; et al. Nature, 2021, 596, 583-589.
[7] Choi C.; et al. Nat. Commun., 2023, 14, 8105.
[8] Billesbølle C.B.; et al. Nature, 2023, 615, 742-749.
[9] Hladiš M.; Lalis M.; Fiorucci S.; Topin J. The Eleventh International Conference on Learning Representations, 2023.
[10] Spehr M.; et al. Science, 2003, 299, 2054-2058.
[11] Natsch A.; et al. Chem. Biodivers., 2006, 3, 1-20.
[12] Sorokowska A.; et al. Pers. Soc. Psychol. Bull., 2022, 48, 1167-1176.
[13] de March C.A.; et al. Angew. Chem., 2018, 130, 4644-4648.
[14] Meinert C.; Meierhenrich U.J. Angew. Chem. Int. Ed., 2012, 51, 10460-10470.