THEORETICAL INVESTIGATION ON STRUCUTRE AND FUNCTION OF ODORANT RECEPTORS

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Humans possess approximately 300 intact odorant receptors. They are integral membrane proteins belonging to family A of the large superfamily of G-protein-coupled receptors (GPCRs). With this repertoire, humans can distinguish between numerous chemical diverse odorants. To explain this enormous discriminating power, knowledge of the three dimensional structure and mapping of ligands to specific receptors are necessary. Due to experimental difficulties with membrane proteins up to date only the crystal structure of bovine rhodopsin [1] from family A has been solved. Therefore, homology-modeling techniques on the human odorant receptors, particularly hOR17-4 and hOR17-40 were applied using rhodopsin as template. These two receptors are excellent targets because hOR17-4 selectively binds canthoxal while hOR17-40 is solely activated by the structural related helional. The models were built using various modeling approaches and the ligand-binding site of each receptor was identified with specialized search programs. The location of these putative binding sites corresponds well to binding pockets found in other GPCRs. To analyze the nature of the active site, docking studies were performed with known ligands and structurally related molecules. Most of the key residues involved in odorant recognition are located in the space formed by the transmembrane helices 3, 5 and 6. These findings are consistent with studies performed on other odorant receptors. By comparing the docking results of helional, which exclusively activates hOR17-40 [2] and the structurally related canthoxal which only activates hOR17-4 [3] we were able to explicitly assign ligand specificity to structural features in the binding site. These results shed light on how the olfactory family has evolved the ability to recognize such a large variety of distinct chemical structures.

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[3] Wetzel C, Oles M, Wellerdieck C, Kuczkowiak M, Gisselmann G, Hatt H (1999) Specificity and sensitivity of a human olfactory receptor functionally expressed in human embryonic kidney 293 cells and Xenopus laevis oocytes. J. Neurosci. 19:7426-7290.

[2] Spehr M, Gisselmann G, Poplawski A, Riffel JA, Wetzel Ch, Zimmer RK, Hatt H (2003) Identification of a Testicular Odorant Receptor Mediating Human Sperm Chemotaxis. Science 299: 2054-2058.