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Original article

Study of interactions between odorant molecules and the hOR1G1 olfactory receptor by molecular modeling

Assia Belhassan [a,c], Hanane Zaki [b,c], Samir Chtita [a], Mohamed Benlyas [b], Tahar Lakhlifi [a], Mohammed Bouachrine [c,*]

[a] MCNS Laboratory, Faculty of Science, Moulay Ismail University, Meknes, Morocco
[b] Biology Environment and Health Laboratory, Faculty of Science and Technics, Moulay Ismail University, Errachdia, Morocco
[c] Materials, Environment & Modeling Laboratory, High School of Technology, Moulay Ismail University, Meknes, Morocco

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ABSTRACT

In order to initiate the process of determining how the molecular level receptor-odorant interactions are related to odor perception, we used the SWISS-MODEL modeling server to predict the three dimensional (3D) structure of the human olfactory receptor (hOR1G1). The model was refined using minimization and side-chain optimization using *SCWRL*. We then used the *Autodockvina* and *Autodock* tools to predict the binding site and binding energy for the library of 13 odorants characterized by different retention/release property values to hOR1G1 receptor, to investigate the relationship between this property and the ligand-hOR1G1 interactions. We find that when the retention property increases, hydrogen bond interactions between ligands and olfactory receptor (hOR1G1) become favorable.

1. Introduction

Olfactory receptors (ORs) are used to detect odors. They are composed of 172 families and contained in 339 genes and 297 pseudogenes in humans.[1] These are transmembrane proteins composed of 7 alpha helices. An olfactory receptor can recognize several odorant molecules and one odorant can activate several receptors. The mammalian olfactory system uses combinatorial coding by receptors to identify and discriminate odorants.[2,3]

Humans perceive an immense variety of molecules as having distinct odors. Odor perception initiates in the nose, where odorants are detected by a large family of olfactory receptors (ORs). The initial step of the olfactory biochemical cascade is the interaction of an odorant with an olfactory receptor (OR) protein, embedded in the ciliary membrane of olfactory sensory neurons. The electrostatic interactions between the ligand and the transmembrane segments of the olfactory receptor and Van Der Waals interactions between the ligand and the hydrophobic pocket of the receptor are responsible for activation of the receptor.[4]

Research in bio-chemistry can't currently do without the computer tools to process the data produced and optimize its advances. One of these tools is molecular modeling and more precisely molecular docking. Docking is the basis for molecular recognition and determination of the type of interactions ligand-receptor.

In our previous work[5] we have studied a series of 51 odorant molecules using statistical methods to establish relationship between the structures of these molecules and their retention/release coefficient k in Water, then we have established mathematical models that we have validated and finally we have designed new molecules with higher and lower values of the property than the existing ones.[5]

As continuation of our research on the development of quantitative structure property relationship (QSPR) of the retention/release property of odorant molecules in Water,[5] this actual work consists of studying the interactions between 13 odorant molecules and the hOR1G1 olfactory receptor by molecular modeling methods (Docking molecular). These ligands are characterized by different retention/release property values, to investigate the relationship between this property and the ligands-ORs interactions.

2. Material and methods

2.1. Data collection

2.1.1. Ligands

The chemical compounds used in this study are odorant molecules which have varied retention/release properties values. The

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* Corresponding author.
E-mail address: m.bouachrine@est-umi.ac.ma (M. Bouachrine).

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retention/release property of the selected molecules was quantified by the vapor-liquid partition coefficient k.

Our database was composed of 13 molecules separated into two groups; the group X_i: composed of the (4*Z*)-hex-4-en-1-ol derivatives with the highest retention (lowest release) property values and the group Y_i composed of the 2-methylbutyl 2-methylbutanoate derivatives with the lowest retention (highest release) property values (Table 1).

The retention/release property of X_0 and Y_0 compounds was examined using pectin gels (pectin concentration of 0.8% w/w), this property was quantified by the vapor-liquid partition coefficient k, All experimental vapor-liquid partition coefficient k were converted to the Log(1/k) values,[6] while that for the molecules X_1, X_2, X_3, Y_1, Y_2, Y_3, Y_4, Y_5, Y_7 and Y_8; the values of Log(1/k) are predicted from a multiple linear regression equation (MLR) linking the retention/release property of a series of studied molecules (51 compounds) reported in the literature[6] of their chemical descriptors with a regression coefficient of 0.958.[5]

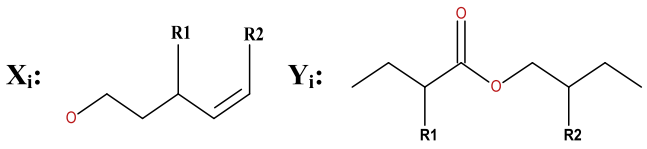
The regression equation (MLR) used was as follows:

$$\mathbf{Log}\left(\frac{1}{\mathbf{k}}\right) = 9.905 - 2.976 \times 10^{-4} \times H^{\circ} + 0.651 \times KH - 6.154 \times \mathrm{n} - 0.145 \times J$$

H° is the Heat of formation, K_H is the Henry's law constant, n is the Index of refraction and *J* is the Balaban index (J) [5].

The comparison of *t*-test and standardized coefficient values of descriptors (H°, K_H, n and *J*)[5]indicates that the influences of the Henry's law constant K_H on Log(1/k) are stronger than those of the others. The equations of the RLM methods indicated the positive correlation of the Henry's law constant K_H. The obtained results show that, to increase retention property of odorant molecules, we will increase Henry's law constant K_H. Moreover, to increase release property, we will decrease Henry's law constant K_H of this molecules, by adding suitable substituents and calculated their property using the regression equations. The structures of the designed compounds and their Log(1/k) values theoretically predicted by the MLR model are listed in Table 1.[5]

Table 1
Log (1/k) values of the studied compounds.



Molecules		Log (1/k)
X_0	R1 = H; R2 = CH_3	3.480
X_1	R1 = OH; R2 = CH_3	3.661
X_2	R1 = H; R2 = CH_2OH	3.756
X_3	R1 = CH_2OH; R2 = CH_3	3.523
Y_0	R1 = CH_3; R2 = CH_3	1.863
Y_1	R1 = C_2H_5; R2 = CH_3	1.498
Y_2	R1 = CH_3; R2 = C_2H_5	1.509
Y_3	R1 = C_2H_5; R2 = C_2H_5	1.396
Y_4	R1 = CH_3; R2 = F	1.601
Y_5	R1 = F; R2 = CH_3	1.601
Y_6	R1 = CH_3; R2 = $CH(CH_3)_2$	1.389
Y_7	R1 = $CH(CH_3)_2$; R2 = CH_3	1.371
Y_8	R1 = $CH(CH_3)_2$; R2 = $CH(CH_3)_2$	1.159

2.1.2. Olfactory receptor

The human olfactory system involves 396 olfactory receptors (ORs) that are responsible for the sense of smell. These ORs provide a unique connection between fundamental signaling at the molecular level and macroscopic perceptual problems.[7]

In this study, we chose the hOR1G1 as a representative in the OR family because it is regarded as prototypical of broadly tuned hORs. It has been shown to have a large recognition spectrum,[8] and structure-odor relationships indicate that hOR1G1 binds odorants that do not correspond to the same olfactophores.[8]

2.2. Molecular modeling

2.2.1. Preparation of macromolecules

Given the lack of structural information on olfactory receptors and the unavailability of its 3D structure in databases such as *Protein Data Bank* (PDB; http://www.rcsb.org), we decided to use homology modeling which proves useful and which has been used successfully for several works. It is a comparative technique that assumes that proteins with homologous sequences have similar structures. This approach begins with the generation of an amino acid sequence of olfactory protein (hOR1G1) from the database of the *UniProt* protein knowledge base (www.uniprot.org) under the identifier *P47890* comprising 313 residues.This sequence, using the SWISS-MODEL modeling server (http://swissmodel.expasy.org), is necessary to identify the "Template" protein structure from the PDB protein bank by the tool "Blast" and "HHblits".[9,10,11] The model was refined using minimization and side-chain optimization using SCWRL (http://dunbrack.fccc.edu/scwrl4).[12]

2.2.2. Preparation of ligands

The molecular structures of the ligands were sketched with sketch module in *SYBYL* and minimized using the Tripos force field with *Gasteiger-Huckel* charges, the conjugate gradient method, and gradient convergence criteria of 0.01 (kcal/mol).[13,14]

3. Results and discussions

3.1. Generation of 3D structure of hOR1G1

At the end of the homology modeling step, several crystallographic structures will be provided. The results show that the beta-1 adrenergic receptor (entry code: 2ycz) which is a transmembrane receptor coupled to the adenyl cyclase by a *G-protein* (the adrenergic receptors are *G-protein* coupled receptors)[15] reveals the best Identity with a percentage of 21.35%, a similarity of 30% and a resolution of 3.65 Å. The manually refined alignment of the two sequences is shown in Fig. 1.

```
Target    MEGKNLTSISECFLLGFSEQLEEQKPLFGSFLFMYLVTVAGNLLIILVIITDTQLHTPMYFFLANLSLADACFVSTTVPKMLANIQIQSQAISYSGCLLQLYFFMLFVML  110
2ycz.1.A ----------------------QWEAGMSLLMALVVLLIVAGNVLVIAAIGSTQRLQTLTNLFITSLACADLVVGLLVVPFGATLVVRGTWLWGSFLCELWTSLDVLCVTA  97

Target    EAFLLAVMAYDCYVAICHPLHYILIMSPGLCIFLVSASWIMNALHSLLHTLLMNSLSFCANHEIPHFFCDINPLLSLSCTDPFTNELVIFITGGLTGLICVLCLIISYTN  220
2ycz.1.A SIETLCVIAIDRYLAITSPFRYQSLMTRARAKVIICTVWAISALVSFLPIMMHWWRDE----DPQALKCYQDP----GCCDFVTNRAYAIASSIISFYIPLLIMIFVALR  199

Target    VFSTILKIPSA------------QGKRKAFSTCSSHLSVVSLFFGTSFCVDFSS--PSTHSAQKDTVASVMYTVVTPMLNPFIYSLRNQEIKSSLRKLIWVRKIHSP      313
2ycz.1.A VYREAKEQIRKIDRASKRKRVMLMREHKALKTLGIIMGVFTLCWLPFFLVNIVNVFNRDLVPDWLFVAFNWLGYANSAMNPIIYC-RSPDFRKAFKRLLAFPRKA--      303
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Fig. 1. Alignment of the target hOR1G1 receptor sequences and the Template (2ycz) (identical residues are shown in green and non-identical residues in black).