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Comparative molecular modeling on 3D-structure of opioid receptor-like 1 receptor[1]

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KEY WORDS frog rhodopsin; ORL1 receptors; templates; molecular models; molecular mechanics

ABSTRACT

AIM: To build the three-dimensional structure of opioid receptor-like 1 (ORL1) receptor. **METHODS**: Structural elements of ORL1 receptor were predicted from sequence alignments of opioid and related receptors of G protein-coupled receptor (GPCR) based on (i) the consensus, biophysical interpretations of alignment-derived properties, and (ii) tertiary structural homology to frog rhodopsin; The extracellular loops of ORL1 were built by self-constructed database searching based on geometrical constraints; initial model was refined computationally with energy minimization by molecular mechanics method. **RESULTS**: The calculated structure of ORL1 receptor has clusters of hydrogen bonds existing in interhelices and extracellular loops; the ORL1 receptor has a possible ligand-binding "crevice" situated on the extraside of the transmembrane domains between helices 3, 5, 6, and 7, which is partially covered by the extracellular loop 2 (EL-2); The binding cavity may consist of a "highly conserved region" involving the residues of Asp130, Tyr131, and an outer "conservatively variable region" containing the residues near the interface of transmembrane (TM) helices-EL loops; The molecular model obtained is qualitatively consistent with ligand affinities, hybrid peptide studies, and other experimental data. **CONCLUSION**: The structural model of ORL1 receptor from this study is helpful for clarifying experimental observations of ligands interacting with opioid receptors, and for designing new biological investigations.

INTRODUCTION

The opioid receptor-like 1 (ORL1) receptor[1] is a non-opioid, G protein-coupled receptor (GPCR) whose primary structure is closely related to those of the μ, δ, and κ types of opioid receptors. In terms of homology percentage, based on sequence alignment, it displays extensive amino-acid identity with opioid receptors in the putative transmembrane (TM) helices (61% on average). Sequence conservation among the four receptors is high in the 2nd (17 out of 22 amino acid residues, 77.3 %), 3rd (16/22, 72.7 %), and 7th (15/20, 75.0 %) transmembrane helices, moderate in the 1st, 5th, and 6th TMs, and low in the 4th TM. Its acidic 2nd exofacial loop makes it resemble more closely the κ-opioid receptor than the μ- or δ- ones. The ORL1 receptor exists mainly in central and peripheral sites, particularly the cortical and cortico-limbic areas.

In spite of its high homology to opioid receptors, the ORL1 receptor binds opioids and opioid antagonists with considerably lower affinities than do opioid receptors. Among "classical" opioids, etorphine and lofentanyl have moderate or even high binding affinities with ORL1 receptor[2]. Etorphine is found to be nearly 100-fold less potent than lofentanyl (ED_{50} values are 700 nmol/L *vs* 7 nmol/L), and interestingly, fentanyl is inactive. These data show that the ORL1 receptor partially retains opioid receptor characteristics.

In order to gain a better understanding of the functional architecture of ORL1 receptor at the molecular level, we determined to construct a three dimensional (3D) structural model of ORL1 receptor by comparative molecular modeling method[3].

COMPUTATIONAL METHODS

The molecular modeling described here was done in

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three stages: 1) modeling the transmembrane α-helix bundles of ORL1 receptor, 2) modeling of the extracellular loops of ORL1 receptor; 3) optimizing the constructed receptor model.

Modeling the α-helix bundles of ORL1 receptor The primary amino acid sequence of ORL1 receptor was manually imported. After that, the hydrophobicity analysis was performed for ORL1 receptor using the Kyte-Doolittle scale[4] in the smoothing mode with the window size of 15, hydrophobic and hydrophilic levels were at 0.7 and −2.5, respectively. Sequence analysis was carried out among the conserved residues of other GPCR (ie, opsin, protein, peptide, amine receptors)[5] and opioid receptors (μ, δ, κ, and ORL1 types). These conserved residues play a significant role in the formation of 7 TM α-helices and their relative positions. Sequence alignment was made using the model of frog rhodopsin[6] as a template, after that, the 7 TM domains were transformed into α-helices with the normal dihedral angles ($\varphi = -70° \sim -50°$, $\psi = -50° \sim -30°$, for Pro residues $\varphi = -75°$) by assigning the coordinates of sequence conserved regions (SCR) of ORL1 receptor from the backbone of the template, which were used as geometric restraints in the process of structural modeling, and then the side chains were added automatically by homology module of Insight II[7], but if a different conformation of side chain was necessary in order to accommodate other helix-helix interaction criteria, an alternate rotamer was taken to replace the initial one. The α-helices geometry was also restrained by the backbone hydrogen bonds (limits for $NH_i \ldots O = C_{i-4}$ distances were 1.8 Å − 2.4 Å, except those broken by Pro residues) and some experimental results[11,13,14].

Modeling the extracellular loops The tentative structure of extracellular domain of ORL1 was modeled here. The crude structure of the EL-2 loop, together with the other two loops, were generated by the homology module of Insight II[7]. The conformation of these loops were searched through a database which was constructed by our group. The database was composed of more than 700 loops and proteins from Brokenheaven Data Bank (http://www.pdb.bnl.gov/pdblite) and the Insight II[7] package with medium to high sequence identity. Ensembles of candidate loop fragments were generated after database searching. The reasonable loop conformations were chosen from the top 10 candidates which had the lowest root mean square (RMS) values and considerable geometrical compatibility of a five-residue overlap with the TM cores.

Optimizing the structural model of ORL1 receptor The crude structure of ORL1 was relaxed in all the SCR by using the Refine routine in the Homology module of Insight II[7]. Further structural modifications to the loop and side chain conformations of residues in the TM core were made to avoid trapping of the loop in a high energy local minimum during minimization. The final model was achieved with the molecular modeling package Sybyl 6.5[8]. The interactive modeling and displaying were performed on SGI XZ 10000 work station. The receptor was optimized, in Sybyl 6.5, using molecular mechanics with the following parameters: a distance-dependent dielectric constant of 5.0, nonbonded cut-off 8 Å, Tripos force field with Kollman-all-atom charges, conjugate gradient minimization until the energy gradient RMS < 0.05 kcal $(mol \cdot Å)^{-1}$. The whole receptor was minimized to convergence.

RESULTS AND DISCUSSION

3D-model of ORL1 receptor Fig 1 represents the results of sequence alignment between ORL1 receptor and the frog rhodopsin template[6]. This alignment is chosen not only according to the alignment score but also based on the conserved residues in GPCR and opioid receptors. Together with the results of hydrophobicity analysis of ORL1 receptor amino acid sequence, the three-dimensional model of ORL1 receptor is constructed and shown in Fig 2. The model is principally based on the TM helical bundles of frog rhodopsin template which was built by Herzyk and Hubbard[6] in 1998, by combining a lot of biophysical and biochemical information with the electron density projection map of frog rhodopsin at 6 Å resolution. This template is more appropriate than the bovine rhodopsin model, so it can be used to model the structure of ORL1 receptor in case no high resolution crystal structures of the GPCR superfamily are available. Some structural flaws of the TMs region of ORL1, such as violations of restraints, appearance of hindrance or holes produced by incorrectly packed side chains were found and corrected. Helices that are multiply curved by contradictory constraints or are loosely packed because of insufficient constraints are also corrected in a stepwise fashion, consequently improving the side-chain-packing errors and distortions in incorrectly aligned regions.

EL-2 connects transmembrane helices 4 and 5 and is attached to the end of EL-1 loop by a conserved disulfide bond between Cys123 and Cys200. Sequence alignment shows hydrophobic residues at positions 198 and 202

TM1	FRh	38	SMLAAYMFLLIMLGFPINFLVLYVTV	63
	ORL1	52	VTIVGLYLAVCVGGLLGNCLVMYVIL	77
TM2	FRh	71	PLNYILLNLAVADLFMVFGGFTTTL	95
	ORL1	85	ATNIYIFNLALADTLVLLTLPFQGT	109
TM3	FRh	111	NLEGFFATLGGEIALWSLVVLAIERYVVVC	140
	ORL1	124	KTVIAIDYYNMFTSTFTLTAMSVDRYVAIC	153
TM4	FRh	152	HAIMGVAFTWVMALACAAPPLVGWS	176
	ORL1	166	KAQAVNVAIWALASVVGVPVAIMGS	190
TM5	FRh	200	NESFVIYMFVVHFIIPLIVIFFCY	223
	ORL1	212	GPVFAICIFLFSFIVPVLVISVCY	235
TM6	FRh	248	KEVTRMVIIMVIAFLICWLPYAGVAFYIFT	277
	ORL1	258	LRRITRLVLVVAVFVGCWTPVQVFVLAQGL	287
TM7	FRh	286	IFMTIPAFFAKTSAVYNPVIYIMMN	310
	ORL1	299	AILRFCTALGYVNSCLNPILYAFLD	323
EL-1	ORL1	110	DILLGFWPFGNALC	123
EL-2	ORL1	191	AQVEDEETECLVEIPTPQDYW	211
EL-3	ORL1	288	GVQPSSETAV	298

Fig 1. Alignment of ORL1 receptor with frog rhodopsin (FRh) structural model template[13] in the transmembrane helices (TM1-TM7) and determination of the EL-loops (EL1-EL3). Residues which are in arial-black are the most conserved residues that are from four subfamilies (opsin, protein, peptide, amine receptors) of rhodopsin-like GPCR[12], Cys123 and Cys200 that form the disulfide bond between the end of EL-1 loop and EL-2 are also labeled black.

(ORL1 receptor numbering) in the opioid receptor family. This peptide chain has the general (i, i+2) pattern of alternate polar and nonpolar residues around the disulfide bond that is common in amino acid sequences of opioid receptors[9]. The pattern is similar to p-n-p-Cys-p-n-p, where p, n denote polar, nonpolar residues respectively. These connecting residues with extended characteristics in conformation suggest that they cannot form any additional regular secondary structure such as α-helix or β-sheet, and they are highly variable in the families of opioid receptors and other GPCR. The Pro205-Thr206-Pro207-Asn208 sequence is an excellent breaker of both α-helix and β-structure. The nonregular structure of these connections can also be suggested based on insertions in this region arising from many different GPCR, such as insertions of Ser220 and Val205-Asp206 residues in the κ-receptor.

The atomic RMS difference of the final model over 186 C^{α} atoms comprising the TM helix bundles of ORL1 receptor (Fig 2) is 1.95 Å compared with the starting template. This well-packed helical model assumes that each helix is adjacent to at least two other neighbouring helices, the face directed toward the lipid bilayer mainly consists of the aromatic and nonpolar hydrophobic residues, whereas the inside of the 7 helix bundles are mainly the conserved, polar residues. The side chain dihedrals of all the TM residues were found in the allowed regions of the Ramachandran plot. Furthermore, the bond lengths and dihedrals were checked using the ProStat rountine in the Insight II[7], and the Profiles-3D rountine of Insight II[7] was applied to verify the residue environment according to the PDB classification in the smoothing mode, the overall self-compatibility score of 7 TM was 116.35, and the score of every residue in the TM region was above zero, that is to say, the TMs arrangement was in accordance with the helical conformation of GPCR. The EL-1 loop forms an arch between TM helices 2 and 3, with Cys123 of the conserved disulfide bridge located at the junction with helix 3. The longest EL-2 loop, composed of 7 acidic residues, erected around the outside

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edge of the binding pocket, is clearly able to control the entrance of ligands. The EL-3 loop forms a flat span between helices 6 and 7.

Structural features of ORL1 receptor model

Geometrical distances between C^{α} atoms of the most conserved residues[5] are listed in Tab 1 and are consistant with some orientation constraints of the template[6]. These data not only offer validation of our constructed model but also provide a valuable check on the relative positions of the helices and the integrity of the receptor bundle. On one hand, these conserved residues are structural determinants that keep the backbone of the helices stable, on the other hand, they could influence directly or indirectly the binding strength of lignads. For example, any changes near the pair cluster of Tyr58, Thr305, and Arg302 will adversely affect the proximity of their side chains, and indirectly make the shape of the binding site change, although the distance between the Cαs of these two residues is as far as 10 Å, but the polar groups of their side chains are very near. The side chain of Arg302 is surrounded by some hydrophobic residues Ile54, Val55, Leu59, Val126, Leu301, Ala306 and hydrophilic, inside orientated residues Tyr58, Thr305. The mutation of Leu59 to Serine, which cause the binding loss of iodinated [Y14]-nociceptin to the ORL1 receptor[10], can result in great conformational change in the pair cluster Tyr58, Thr305, and Arg302, and thereby indirectly transform the shape of binding pocket.

Another important characteristics of ORL1 receptor model is that there are many hydrogen bonds formed by the residues in the TM helices and extracellular domains. These hydrogen bonds are summarized in Tab 2 where it

Tab 1. Geometrical distances between C^{α}s of conserved residues in the transmembrane helical bundles of ORL1 receptor.

$C^{\alpha}1$	$C^{\alpha}2$	Distance (Å)	Location	$C^{\alpha}1$	$C^{\alpha}2$	Distance (Å)	Location
Asn69	Asn315	9.396	TMs1-7	Arg148	Tyr235	9.493	TMs3-5
Val72	Tyr319	8.871	TMs1-7	Tyr149	Ile231	9.259	TMs3-5
Gly65	Asp97	9.271	TMs1-2	Leu141	Val268	9.033	TMs3-6
Asn69	Asn87	11.525	TMs1-2	Phe224	Trp276	10.461	TMs5-6
Asn69	Asn92	11.525	TMs1-2	Phe224	Pro278	13.989	TMs5-6
Gly65	Ala94	10.051	TMs1-2	Pro227	Cys275	17.222	TMs5-6
Tyr58	Asp97	13.178	TMs1-2	Pro227	Phe272	12.965	TMs5-6
Ile90	Val72	9.249	TMs2-1	Ile231	Val268	11.430	TMs5-6
Leu93	Gly65	13.150	TMs2-1	Tyr235	Val268	13.731	TMs5-6
Leu141	Leu93	7.889	TMs3-2	Val268	Asn315	8.024	TMs6-7
Asp147	Asn87	11.654	TMs3-2	Phe272	Asn315	10.759	TMs6-7
Val268	Asn319	10.297	TMs6-7	Asp97	Asn315	7.725	TMs2-7
Leu141	Pro316	12.711	TMs3-7	Tyr58	Arg302	10.742	TMs1-7
Leu141	Phe272	11.602	TMs3-6	Ala216	Leu287	10.034	TMs5-6
Pro184	Pro278	25.859	TMs4-6	Tyr131	Phe224	11.451	TMs3-6

Tab 2. Some hydrogen bonds (besides the backbone hydrogen bonds) formed by residues from TM helices and extracellular loops in ORL1 receptor.

Location	Donor		Acceptor		Location	Donor		Acceptor	
	Residue	Group	Group	Residue		Residue	Group	Group	Residue
Loop 1	Asn120	-NH	O=C<	Pro117	Loop 3	Ser294	-NH	O=C<	Pro292
	Trp116	-NH	O=C<	Gly114		Ile300	-NH	O=C<	Val297
	Ile111	-NH	O=C<	Thr109		Lei301	=NH	O=C<	Val298
Loop 2	Thr206	-NH	O=C<	Ile204	Helix 1-2	Asn69	-$N^{\delta2}$H	-OH	Thr98
	Gln208	-NH	O=C<	Pro205	Helix 3-7	Tyr131	-OH	-OH	Thr305
	Tyr210	-NH	(-)$O^{\delta2}$-	Asp209	Helix 2-3	Tyr89	-OH	(-)$O^{\delta1}$-	Asp147
	Thr206	-OH	(-)$O^{\delta2}$-	Glu197	Helix 3-3	Arg148	-N^{ε}H	(-)$O^{\delta2}$-	Asp147
	Gln208	-$N^{\varepsilon2}$H	(-)$O^{\varepsilon2}$-	Glu208	Helix 3-3	Ser145	-OH	O=C<	Thr142
	Gln208	-$N^{\varepsilon2}$H	(-)$O^{\varepsilon2}$-	Glu196	Helix 2-4	Asn92	-$N^{\delta2}$H	(-)$O^{\delta1}$-	Asn171
	Leu201	-NH	O=C<	Glu197	Helix 3-3	Thr136	-OH	O=C<	Tyr132
	Ile198	-NH	(-)$O^{\delta1}$-	Asp195	Helix 7-7	Ser312	-OH	O=C<	Tyr309
	Glu197	-NH	(-)$O^{\delta2}$-	Asp195	Helix 3-2	Thr140	-OH	O=C<	Asn92
	Glu196	-NH	O=C<	Glu194	Helix 2-2	Thr103	-OH	O=C<	Leu99

is evident that the hydrogen bonds cluster in the EL-2 loop makes it structurally more stable and act potently as the filter of peptide ligand for its entrance into the binding site. The key role of this loop has been proven by a lot of structure-activity studies about nociceptin-ORL1 receptor system[11,12]. The hydrogen bonds cluster around the binding site plays an important role in the binding process of nociceptin. This cluster includes the hydrogen bonds formed between the side chains of Tyr132 and Thr136, Thr305 and Tyr131, and the side chain of Ser312 and carbonyl oxygen of Tyr309 backbone. The hydrogen bonds near the intracellular end may be one of the reasons that the helical end toward the cytoplasmic is packed more tightly than the other end. This hydrogen bond cluster exists mainly among the residues of Asp147, Arg148, Ser145, Thr103, and some residues from the intracellular loops.

Validation of the structural model of ORL1 receptor The 3D structural model of ORL1 receptor described in this paper is constructed by comparative molecular modeling method[3] using frog rhodopsin molecular model as a template. This model represents a specific application of computer modeling techniques in the absence of high resolution 3D structure of GPCR for the time being, it is a good example for exploring further the functional architecture of by combining information derived from site-directed mutagenesis and other experimental results. In our molecular model of ORL1 receptor, the structures of three extracellular loops are just tentative and require further experimental verification. However, several arguements support our models. First of all, the model is in consistence with some general principles of protein structures, it provides satisfactory distance constraints between residues of different helices. The hydrogen bonds listed in Tab 2 demonstrate that spatially close side chains are necessary for maintaining the close packing within the transmembrane domain and extracellular loops, especially the EL-2 loop which is highly significant in controlling the entrance of ligands into the conserved binding site. Secondly, our model stems from the frog rhodopsin model[6] with structural and experimental data available for this prototypical GPCR. Thirdly the site-directed mutagenesis data of opioid receptor family[13] supports our results, some mutated residues in the ORL1 receptor or the three opioid receptors inducing significant changes to either binding and/or activity properties with respect to at least one ligand-receptor system are shown in Fig 3. These residues are orientated towards the center of the helical bundles and are expected to be accessible to the ligand, especially the negatively charged residue Asp130, which probably takes part in the electrostatic interaction with ligand.

On further inspection of the ORL1 receptor model, the possible binding site can be revealed in a cavity formed by helices 3, 5, 6 and 7, which corresponds to the conserved transmembrane opioid binding site mapped in the δ and μ-receptors[14]. It has been reported that the mutation of five residues (Ala216, Val219, Gln280, Val281 and Thr305) to their entirely conserved opioid receptor counterparts can restore a functional opioid binding site[15], which indicates that these residues are situated geometrically near or around the conserved binding pocket. This possible conserved binding pocket, which seems similar to the one in rhodopsin and needs further verification by ligand docking, is almost equal in topology to that of other three opioid receptors, and is possibly composed of two parts: the inner part, involving the conserved residue Asp130, the outer part formed near the extracellular loops-TMs interface.

To conclude, we have generated a 3D-structural model of ORL1 receptor by comparative molecular modeling, and related the verifications for the reliability of this model. The method of modeling the extracellular loops of ORL1 can also be used in case of other GPCR. As a whole, our model carries some significance in the theoretical studies about biological interaction of opioid receptors with their ligands.

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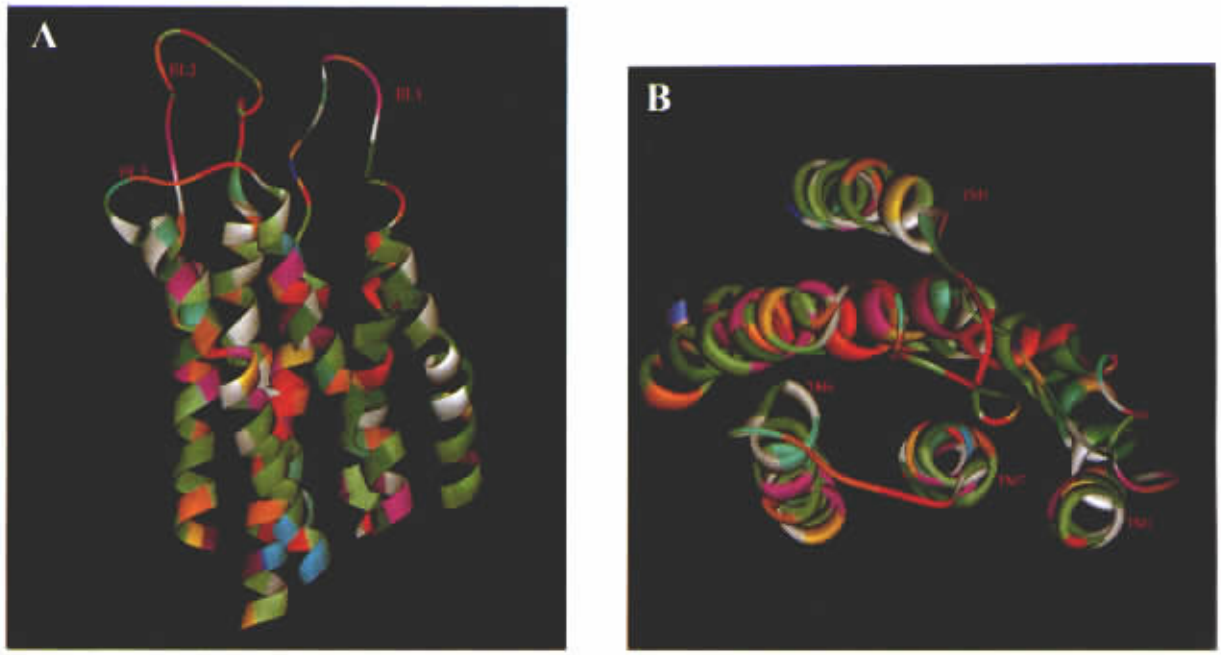

Fig 2. Cartoon representation of transmembrane helices and extracellular loops of ORL1 receptor model. Side view (A) and top view (B) from the extracellular surface.

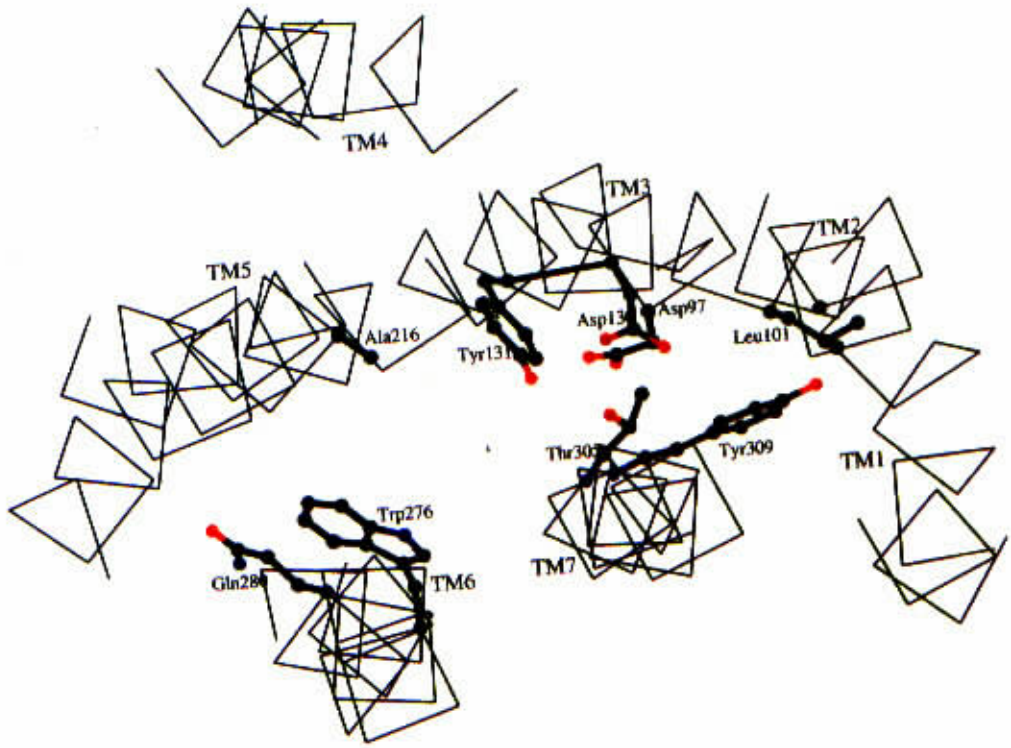

Fig 3. Stereo view of the ORL1 receptor transmembrane helical bundle. Side chains of equivalent residues deduced from site-directed mutagenesis data, which are important for opioid receptor family function, are presented in ball-and-stick style.

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阿片孤儿受体三维结构的比较分子模拟

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关键词 蛙视紫红质；阿片孤儿受体；模板；分子模型；分子力学

目的：建立阿片孤儿受体(ORL1)的三维结构. **方法**：以蛙视紫红质为模板，用比较分子模拟方法进行序列联配，建立阿片孤儿受体七段跨膜区的结构；通过自己构件的数据库进行搜寻确立膜外环区的构象；对初始模型进行分子力学优化. **结果**：建立了阿片孤儿受体的三维结构模型；有多个氢键集中区分别存在于跨膜区和膜外环区；保守性的结合口袋位于第三、五、六、七跨膜区；预测可能的结合位点由包含 Asp130、Tyr131 残基的高度保守区和靠近膜外端的部分可变区组成. **结论**：模拟膜外环区的方法可用于其他 GPCR 的分子模拟；所建立的三维结构模型有助于阿片受体的结构功能研究并能为相关实验提供有益信息.

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