
Structural Analysis of the Histamine H₁ Receptor

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Abstract

The crystal structure of the human histamine H₁ receptor (H₁R) has been determined in complex with its inverse agonist doxepin, a first-generation antihistamine. The crystal structure showed that doxepin sits deeply inside the ligand-binding pocket and predominantly interacts with residues highly

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conserved among other aminergic receptors. This binding mode is considered to result in the low selectivity of the first-generation antihistamines for H₁R. The crystal structure also revealed the mechanism of receptor inactivation by the inverse agonist doxepin. On the other hand, the crystal structure elucidated the anion-binding site near the extracellular portion of the receptor. This site consists of residues not conserved among other aminergic receptors, which are specific for H₁R. Docking simulation and biochemical experimentation demonstrated that a carboxyl group on the second-generation antihistamines interacts with the anion-binding site. These results imply that the anion-binding site is a key site for the development of highly selective antihistamine drugs.

Keywords

Crystal structure • Doxepin • First-generation antihistamines • Histamine H₁ receptor • Receptor inactivation mechanism • Receptor selectivity of antihistamines

1 Introduction

Histamine H₁ receptor (H₁R), originally cloned from bovine H₁R (Yamashita et al. 1991), is a G protein-coupled receptor (GPCR) implicated in type I hypersensitivity allergic reactions caused by various kinds of allergens. H₁R is expressed in various tissues throughout body, including the airway, vascular smooth muscle, and brain (Hill 1990). Allergic reactions occur when allergens activate mast cells, which in turn release histamine and other bioactive substances. The released histamine then binds to and activates H₁R on surrounding vascular endothelial cells, causing vasodilation and vascular hyperpermeability, resulting in allergic inflammation. H₁R expressed in the brain plays an important role in the regulation of sleep-arousal cycle and memory by binding histamine as it acts as a neurotransmitter (Schwartz et al. 1991; Hill et al. 1997).

Antihistamines are first-line drugs for relief of allergic reactions and are inverse agonists of H₁R. Antihistamines suppress allergic reactions by stabilizing the equilibration of H₁R into its inactive state (Bakker et al. 2000). The long history of the development of antihistamines, and the fact that H₁R has one of the highest numbers of drugs approved to target its activity, illustrates the importance of this receptor (Overington et al. 2006). First-generation antihistamines have high blood-brain barrier permeability and low receptor selectivity, causing various side effects including drowsiness and dry mouth (Cusack et al. 1994). These days, second-generation antihistamines are developed, which significantly reduce brain permeability, although residual central nervous system effects are still remained (Tashiro et al. 2009). Challenges remain even for second-generation drugs, such as low affinity to the receptor and cardiotoxicity because of their interaction with cardiac potassium channels (Woosley et al. 1993; Yap and Gamm 2002). In this chapter, we

explain findings regarding the crystal structure of human H₁R complexed with its inverse agonist doxepin.

2 Stabilization and Production of H₁R Protein for Structural Study

The largest obstacle for the determination of a crystal structure is the preparation of milligram quantities of highly purified and stable receptor protein. To produce the receptor protein in a sufficient quantity and obtain high-quality crystals, an H₁R variant was constructed (Shiroishi et al. 2012). Human H₁R is difficult to overexpress owing to its very long third intracellular loop (ICL3), presumably because this long flexible region is a target of degradation and/or destabilizes the receptor in the cell. To overcome this difficulty, the lysozyme derived from T4 lysozyme (T4L), which was a successful fusion partner for structural determination of β_2 -adrenergic receptor (Rosenbaum et al. 2007), was fused onto the region of the i3-loop (Gln222-Gly404). This fusion had a significant effect not only on stabilizing the receptor but also on improving crystallization. Furthermore, the unstructured N-terminal 19 residues including a predicted N-linked glycosylation site were deleted, because heterogeneous glycosylation hampered crystallization. The H₁R variant was overexpressed in the methylotrophic yeast *Pichia pastoris* and purified in milligram quantities (Shiroishi et al. 2011). The H₁R variant expressed in yeast showed the same ligand-binding properties as the wild-type receptor. The purified receptor was crystallized in complex with its inverse agonist doxepin by the lipidic cubic phase (LCP) method. The diffraction data were collected using the synchrotron light source, and the structure was determined at 3.1 Å resolution (Shimamura et al. 2011).

3 Overall Structure of H₁R

As observed in the other GPCRs whose structures are known, H₁R consists of seven transmembrane (TM) helices (TM1–TM7) and a short amphipathic helix (H8) (Fig. 1a). The intracellular loops (ICLs) and extracellular loops (ECLs) that connect the helices were observed except for ICL3, because this ICL had been replaced with the fused T4L. The electron density of a portion (Phe168–Val174) of ECL2, which is the longest extracellular loop, could not be resolved, presumably because of its high degree of flexibility. The relative orientation of TM helices of H₁R was similar to other inactive GPCR structures. Comparing the root mean square deviations (RMSDs) of 175 C α atoms on seven TM helices showed that the orientation of H₁R was most similar to the following aminergic receptors: β_1 -adrenergic receptor (AR) (1.5 Å) (Warne et al. 2008), β_2 -AR (1.3 Å) (Cherezov et al. 2007), and dopamine D₃ receptor (D₃R) (1.3 Å) (Chien et al. 2010). Larger deviations were observed for adenosine A_{2A} receptor (A_{2A}R) (2.3 Å) (Jaakola

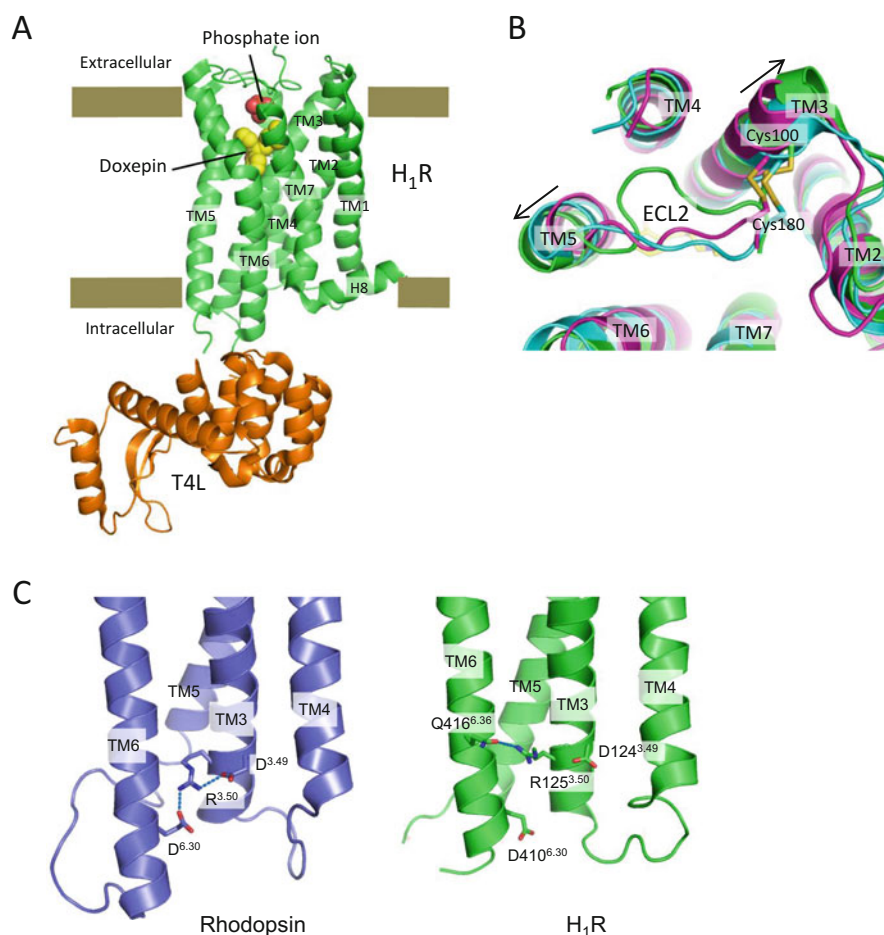


Fig. 1 (a) Overall structure of H₁R-doxepin complex. H₁R is represented by the *green* ribbon. Fused T4 lysozyme (T4L) replacing ICL3 is represented by the *orange* ribbon. Doxepin and phosphate ion are depicted as *yellow* and *orange* spheres, respectively. (b) Top view of the entrance of the ligand-binding pocket. H₁R, β_2 -AR, and D₃R are superimposed and are represented by *green*, *cyan*, and *magenta* ribbons, respectively. The cysteine residues that form disulfide bond are shown as *yellow* sticks. (c) (*Left*) Ionic lock formation between Arg^{3.50} and Asp^{6.30} in rhodopsin. (*Right*) The structure of the side chains in the equivalent region in H₁R

et al. 2008) and CXCR4 chemokine receptor (2.2 Å) (Wu et al. 2010), which are more phylogenetically distant.

GPCR crystal structures have elucidated the structural diversity among their extracellular regions. In particular, ECL2 is the most variable region among GPCR receptors in amino acid sequence and structure. In H₁R, a disulfide bond conserved among many GPCRs was formed between Cys100 in the extracellular end of TM3 and Cys180 in ECL2 (Fig. 1b). This disulfide bridge anchored ECL2 to the entrance

of the ligand-binding pocket. Seven amino acids existed between the disulfide bridge and the extracellular end of TM5 in ECL2 in H₁R. This was greater than the number of amino acids found in this location in other aminergic receptors: β_2 -AR has five amino acids at this location and D₃R has three. This seemed to extend the distance between the extracellular ends of TM3 and TM5 in H₁R compared to that in β_2 -AR and D₃R, creating a larger space within the ligand-binding pocket (Fig. 1b).

A unique characteristic observed in the TM4 helix of H₁R is the kink induced by Pro161^{4.59} (4.59 position of the Ballesteros-Weinstein numbering). Where an i + 4 turn is formed in β_2 -AR and D₃R, a tighter i + 3 turn is formed in H₁R. This tighter turn allows accommodation of the bulky side chain of Trp158^{4.56}, where a serine is located in β_2 -AR and D₃R. Trp158^{4.56} is considered important for ligand specificity of aminergic GPCRs since mutations of this tryptophan to alanine, methionine, or phenylalanine reduce the affinity against the antagonist pyrilamine in the guinea pig H₁R (Wieland et al. 1999).

A D(E)RY motif in TM3 is well conserved among many GPCRs. Since the first observation of salt bridge formation between Arg^{3.50} in this motif and Asp^{6.30} in bovine rhodopsin, it has been suggested that this salt bridge (called an “ionic lock” in this context) stabilizes the inactive conformation (Palczewski et al. 2000). An ionic lock is observed in D₃R, but not in other GPCR structures. In H₁R, an ionic lock was not observed between Arg125^{3.50} and Glu410^{6.30} in the crystal structure (Fig. 1c). Instead, a hydrogen bond was formed between Arg125^{3.50} and Gln416^{6.36}. This change in bond type could be induced by the fusion of T4L into ICL3. To reveal the structure of a possible ionic lock, determination of the structure without a fusion protein is necessary.

4 Structure of the Ligand-Binding Pocket and Low Selectivity of Doxepin

The inverse agonist doxepin consists of a tricyclic dibenzo[b,e]oxepin ring and an amine moiety, connected by a carbon chain (Fig. 2a). Doxepin was observed in the bottom of the ligand-binding pocket of the receptor (Fig. 1a). The lower side of the tricyclic ring sits in the ligand-binding pocket as deeply as the trimethylcyclohexane ring of retinal sits in rhodopsin, which is located deeper than the ligands in other GPCRs whose structures have been determined (Fig. 2b). As observed in the other aminergic receptors, the amino group of doxepin formed a salt bridge to Asp107^{3.32} in TM3 (Fig. 2c). This salt bridge was found to be essential for binding both agonist and antagonist by mutational study (Bruysters et al. 2004; Nonaka et al. 1998; Ohta et al. 1994).

Doxepin, a first-generation antihistamine, binds to H₁R with very high affinity ($K_d = 0.69$ nM). However, due to its low receptor selectivity, it also binds to the other aminergic receptors with considerable affinities (serotonin receptor 5HT_{2A}, 3.3 nM; muscarinic M₁ receptor, 6.8 nM; α_1 -AR, 38 nM; D₂R, 63 nM) (Nonaka et al. 1998). The crystal structure of the H₁R-doxepin complex revealed that the

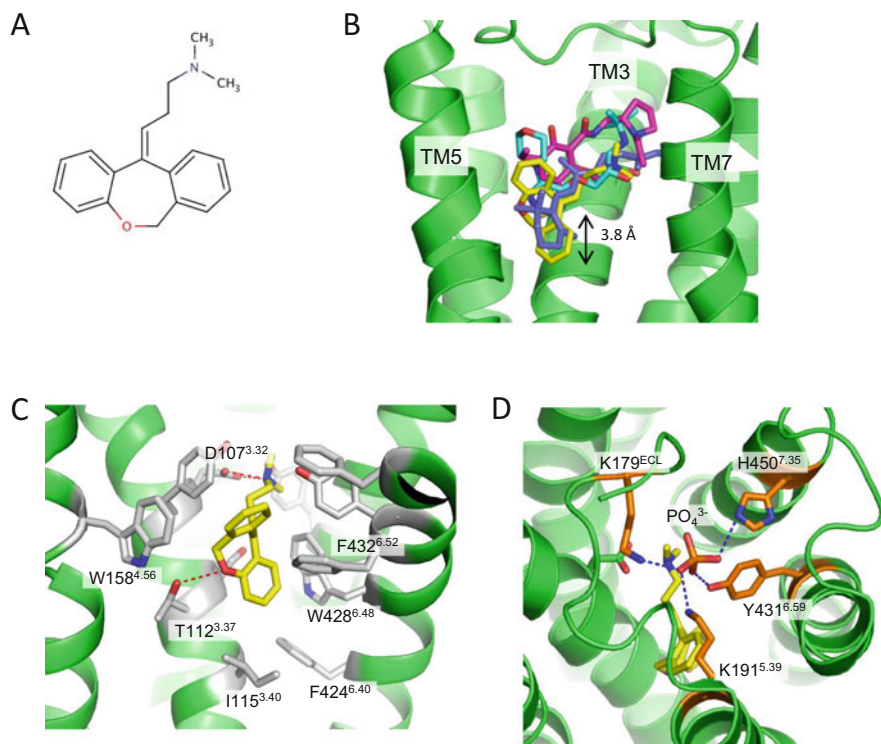


Fig. 2 (a) Chemical formula of doxepin. (b) The relative positions of the ligands bound in GPCRs. The coordinates of H₁R-doxepin complex, rhodopsin-retinal complex, β_2 -AR-timolol complex (Hanson et al. 2008), and D₃R-eticlopride complex are superimposed, and H₁R is represented by the *green* ribbon. Doxepin, retinal, timolol, and eticlopride are shown as *yellow*, *purple*, *cyan*, and *magenta* sticks, respectively. TM6 is not shown for easier viewing. Doxepin bound more deeply compared to timolol, by 3.8 Å. (c) H₁R residues interacting with doxepin. H₁R is represented by the *green* ribbon. Doxepin and interacting residues are shown as *yellow* and *gray* sticks, respectively. Oxygen and nitrogen atoms are shown in *red* and *blue*, respectively. The salt bridge to Asp107 and hydrogen bond to T112 are represented by *red dashed lines*. (d) The phosphate-binding site of H₁R. H₁R is represented by the *green* ribbon. Phosphate ions and interacting residues are shown as *orange* sticks. Oxygen and nitrogen atoms are shown in *red* and *blue*, respectively. The electrostatic interactions are shown as *blue dashed lines*

tricyclic dibenzo[b,e]oxepin ring of doxepin interacts with hydrophobic residues in H₁R such as Ile112^{3.37}, Ile115^{3.40}, Phe424^{6.44}, Trp428^{6.48}, and Phe432^{6.52} (Fig. 2c). These residues are highly conserved among aminergic receptors (Table 1). Low receptor selectivity of doxepin is likely derived from the interactions with these highly conserved residues.

Table 1 Residues in the doxepin-binding site of H₁R and their equivalents in other aminergic receptors

	H ₁ R	H ₂ R	5-HT _{1A-F}	5-HT _{2A-C}	M ₁₋₅	α _{1A-D}	α _{2A-C}	β ₁₋₃	D _{1,5}	D ₂₋₄
TM3	D107	D	D	D	D	D	D	D	D	D
	Y108	V	V/I/M	V	Y	V	V	V	I	V
	S111	C	C	S	S	C	C	V	S	C
	T112	T	T	T	N	T	T	T	T	T
	I115	I	I	I	I	I	I	I	I	I
TM4	W158	L	I	I	L	L	I	T	I	I/V
TM5	T194	D	S	G	T	S	S	S	S	S
	N198	T	A	S/A	A	S	S	S	S	S
TM6	F424	F	F	F	F	F	F	F	F	F
	W428	W	W	W	W	W	W	W	W	W
	Y431	Y	F	F	Y	F	F	F	F	F
	F432	F	F	F	F	F	F	F	F	F
	F435	F	A/S/E	N	V	M/L	Y	N	N	H
TM7	Y458	Y	Y	Y	Y	Y	Y	Y	W	Y

Abbreviations of receptors; H₂R histamine H₂ receptor, 5-HT_{1A-F} serotonin 5-HT_{1A-F} receptors, 5-HT_{2A-C} serotonin 5-HT_{2A-C} receptors, M₁₋₅ M₁₋₅ muscarinic acetylcholine receptors, α_{1A-D} α_{1A-D}-adrenergic receptors, α_{2A-C} α_{2A-C}-adrenergic receptors, β₁₋₃ β₁₋₃-adrenergic receptors, D_{1,5} dopamine D₁ and D₅ receptors, D₂₋₄ dopamine D₂₋₄ receptors

5 Implications for the Development of Highly Specific Ligands of H₁R

Another notable characteristic of the H₁R-doxepin complex structure was the identification of an “anion-binding site” comprised of basic amino acids Lys191^{5,39}, Lys179^{ECL2}, and His450^{7,35} on the extracellular portion of H₁R (Figs. 1a and 2d). A phosphate ion, which was present in the crystallization reservoir solution, was observed at the anion-binding site forming electrostatic interactions to the basic amino acids. The thermal stability of H₁R increased in the presence of phosphate ions even at physiological concentrations (~1.5 mM) (Shimamura et al. 2011). This indicates that the phosphate ion binds to the receptor at this site and serves as a positive modulator of ligand binding. Since the amino acids that form this anion-binding site are not conserved among other aminergic receptors, this site is unique to H₁R (Table 2).

Some second-generation antihistamines, showing higher specificity for H₁R, have a carboxyl group. The binding modes of these compounds to H₁R were predicted by molecular dynamics simulation *in silico*, showing that the carboxyl group of second-generation antihistamines sits in the anion-binding site. Furthermore, the thermal stability of H₁R complexed with the second-generation antihistamine cetirizine did not change in the presence of phosphate ion. Together, these results suggest that the carboxyl group of cetirizine sits in the anion-binding site and competes with the phosphate ion. Since the anion-binding site is unique to

Table 2 Residues in the phosphate-binding site of H₁R and their equivalents in other aminergic receptors

	H ₁ R	H ₂ R	5-HT _{1A-F}	5-HT _{2A-C}	M ₁₋₅	α _{1A-D}	α _{2A-C}	β ₁₋₃	D _{1,5}	D ₂₋₄
ECL2	K179	K	A/E/D/Q	T/S	E/Q	I/E/F	R/Q	C	N	E/V
TM5	K191	G	T	V/M	T	V/A	V/I	A/V	A	V
TM6	Y431	Y	F	F	Y	F	F	F	F	F
	F435	F	A/S/E	N	V	M/L	Y	N	N	H
TM7	H450	E	F/G/A/S	L	W	F	F	F/Y	F	Y/V
	I454	L	N/T/A	V	Y	F	F	N	V	T

Abbreviations of receptors; H₂R histamine H₂ receptor, 5-HT_{1A-F} serotonin 5-HT_{1A-F} receptors, 5-HT_{2A-C} serotonin 5-HT_{2A-C} receptors, M₁₋₅ M₁₋₅ muscarinic acetylcholine receptors, α_{1A-D} α_{1A-D}-adrenergic receptors, α_{2A-C} α_{2A-C}-adrenergic receptors, β₁₋₃ β₁₋₃-adrenergic receptors, D_{1,5} dopamine D₁ and D₅ receptors, D₂₋₄ dopamine D₂₋₄ receptors

H₁R, this could be a potential site for the development of antihistamines with higher specificity.

In recent years, structure-based virtual screening (SBVS), a computational screening method using a homology model of the target receptor, has been utilized as a strategy for rational drug screening. With the SBVS strategy using the crystal structure of H₁R, novel fragment-like compounds (less than 22 heavy atoms) with substantial affinities for H₁R ($K_d = 10 \mu\text{M}$ –6 nM) have been successfully found with a high hit rate of 73% (de Graaf et al. 2011). These results highlight the importance of elucidating GPCR structures to assist in rational drug discovery.

6 Structural Insights into the Inverse Agonism of Doxepin

Since the active conformation of H₁R has not been crystallized, the activation mechanism is unclear. However, comparing known structures of active (agonist-bound) and inactive GPCRs has elucidated common features of GPCR activation. Translocation of several helices (TM1, TM3, TM5, TM6, and TM7) is found on the extracellular and intracellular side. In particular, TM3 and TM6 play a central role. It is speculated that the hydrophobic residues located in the core of the receptor, such as Ile/Leu/Val^{3,40}, Phe^{6,44}, and Trp^{6,48}, are involved in these movements (Tehan et al. 2014).

The CWxP^{6,50} motif in TM6 is well conserved among family-A GPCRs and is one of the key molecular switches for activation of these receptors. Trp^{428,6,48}, located in the bottom of the ligand-binding pocket, is called a “rotamer toggle switch” (or a “transmission switch”), because the ligand-induced shift of this residue results in a large rotation and movement of TM6 through rearrangement of the TM3-5-6 interface. This change in receptor configuration is essential for G protein activation upon agonist binding. This large structural change is observed in rhodopsin, A_{2A}R, and M₂R, but not in β₂-AR. In rhodopsin, retinal directly interacts with Trp^{6,48} and stabilizes the receptor’s inactive state. In the H₁R-doxepin structure, the tricyclic ring interacts extensively with Trp^{428,6,48}, similarly to retinal’s

interaction with inactive rhodopsin (Fig. 2c). This type of binding could stabilize the hydrophobic packing around TM6 and is unique among the known GPCR structures. The tricyclic ring of doxepin also interacts with Ile115^{3,40} and Phe424^{6,40}, which are presumably involved in receptor activation. The ring moiety also interacts with Ser111^{3,36}, which acts as a toggle switch for activation upon agonist binding (Jongejan et al. 2005). The crystal structure of the H₁R-doxepin complex has clarified the interactions that stabilize H₁R in its inactive state, leading to large reduction of the basal activity of the receptor.

7 Conclusion

At present, X-ray crystallography is the only way to clarify ligand-receptor interaction at the atomic level. Over the past decade, the technologies of sample preparation, crystallization, and data collection have improved dramatically, and finally the crystal structure of H₁R was solved. The structure of the H₁R-doxepin complex provided critical information about receptor specificity of antihistamines and the mechanism of receptor inactivation. However, a number of points still remain to be clarified. For example, the resolution is not sufficient to understand the internal receptor-bound water molecules, which have recently been suggested to be important for receptor function (Sun et al. 2014). The structure of the activated form of H₁R also remains to be determined to delineate the activation mechanism. Moreover, the crystal structures of H₁R in complex with other antihistamines are needed to clarify the ligand specificity.

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