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Molecular docking of human histamine H1 receptor with chlorpheniramine to alleviate cat allergies

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Cat allergen Fel d 1, secreted by the cat's sebaceous glands and that covers the cat's skin and fur is the major cat allergen responsible for cat allergies in human. It interacts with and cross-links surface IgE antibodies on mast cells and basophils. Once the mast cell-antibody-antigen complex is formed, a complex series of events occurs that eventually leads to cell-degranulation and the release of histamine from the mast cell or basophil. Histamine, acting on H1-receptors, produces pruritis, vasodilatation, hypotension, flushing, headache, tachycardia, and bronchoconstriction and also increases vascular permeability and potentiates pain. Chlorpheniramine is a histamine H1 antagonist of the alkyl amine class. It competes with histamine for the normal H1-receptor sites on effector cells of the gastrointestinal tract, blood vessels and respiratory tract. It binds to the histamine H1 receptor and blocks the action of endogenous histamine there by providing effective, temporary relief of sneezing, watery and itchy eyes, and runny nose due to hay fever and other upper respiratory allergies. Homology modeling of Histamine H1 Receptor is done using SWISSPDBVIEWER – SWISSMODEL. It showed 27 helices, 6 strands and 37 turns. The stereochemistry of the theoretical model of Histamine H1 Receptor is studied by subjecting it into energy minimization in SWISSPDBVIEWER. The model was subjected to structure verification and evaluation using PROCHECK. The Ramachandran plot for the model showed 92.5% residues in most favored regions and hence the model was revealed to have good stereo chemistry. A molecular docking study of modeled structure of Histamine H1 Receptor with the drug chlorpheniramine is done using PatchDock program. Receptor–Drug complex has a complementarity score of 4846, Atomic Contact Energy (ACE) of -139.35. The docking studies which involves the interaction of Histamine H1 Receptor with the drug chlorpheniramine provided valuable insight into the role of chlorpheniramine having anti histamine activity and in alleviating cat allergies produced by the cat allergen namely Fel d 1 protein.

Key words: Fel d 1 protein, cat allergy, histamine H1 receptor, chlorpheniramine, SWISSPDBVIEWER, SWISSMODEL, PROCHECK, PatchDock, homology modeling, molecular docking, receptor-drug complex.

INTRODUCTION

Cat allergen, Fel d 1, is the major cat allergen responsible for cat allergies in human. It is a small, sticky protein secreted by the cat's sebaceous glands and covers the cat's skin and fur which is rubbed off on furniture, carpeting, clothing, etc. Further, the allergen is so light that it easily becomes airborne and contaminates the entire indoor environment. When people allergic to cats come in contact with Fel d 1, they develop a type 1 allergic hypersensitivity reaction which may include the rapid onset of sneezing, runny nose, itchy and swollen eyes, mucus production and difficulties breathing (http://www.felixpets.com). Studies have shown that significant concentrations of cat allergen remain in a home years after a cat has left the house. Cat allergen Fel d 1 has also been identified as one of the three major risk factors for developing childhood allergies, asthma, and other respiratory diseases. The cat allergen Fel d 1 interacts with and cross-links surface IgE antibodies on mast cells and basophils. Once the mast cell-antibody-antigen complex is formed, a complex series of events
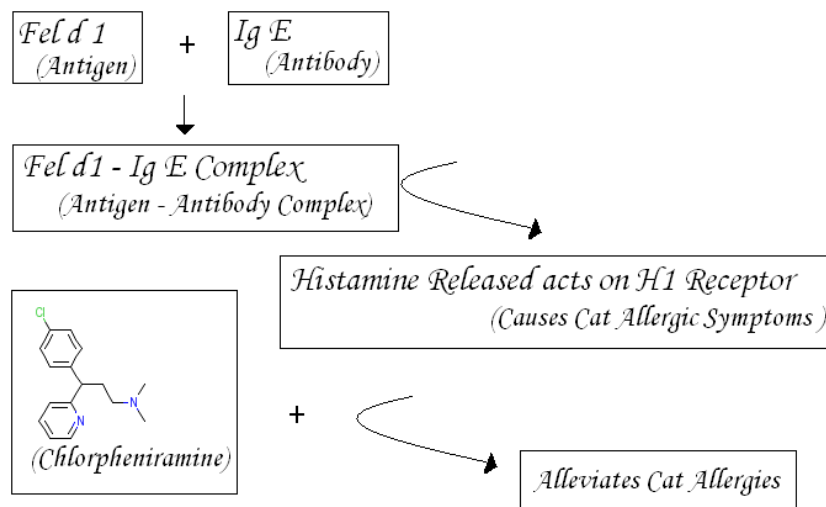
Figure 1. Mechanism of alleviating cat allergies.

occurs that eventually leads to cell-degranulation and the release of histamine (and other chemical mediators) from the mast cell or basophil. Once released, histamine can react with local or widespread tissues through histamine receptors. Histamine, acting on H1-receptors, produces pruritis, vasodilatation, hypotension, flushing, headache, tachycardia, and bronchoconstriction. Histamine also increases vascular permeability and potentiates pain. Chlorpheniramine, is a histamine H1 antagonist of the alkylamine class (http: //redpoll. pharmacy.ualberta.ca/drugbank/index.html). It competes with histamine for the normal H1-receptor sites on effector cells of the gastrointestinal tract, blood vessels and respiratory tract. Chlorpheniramine binds to the histamine H1 receptor and blocks the action of endogenous histamine (Figure 1) there by providing effective, temporary relief of sneezing, watery and itchy eyes, and runny nose due to hay fever and other upper respiratory allergies (http://www.drgreene.com).

This work is an attempt of the three dimensional structure prediction of the Histamine H1 Receptor followed by an *in silico* study of the binding interactions of the drug chlorpheniramine with the histamine H1-receptors which alleviates the cat allergies in humans.

METHODOLOGY

The protein sequence of Histamine H1 receptor with primary accession number P35367 is extracted from the UniProtKB/Swiss-prot (http://www.expasy.org/uniprot) database. The program SWISSPDBVIEWER is employed in the construction of theoretical three dimensional structure of Histamine H1 receptor. SWISS-MODEL, a fully automated protein structure homology-modeling server, accessible via the program DeepView (SWISSPDBVIEWER) is used to model the protein sequence of Histamine H1 receptor with primary accession number P35367 that's extracted from the UniProtKB/Swiss-prot.

The theoretical model generated is subjected to validation using the program PROCHECK for assessing the stereochemistry of the model. The program PROCHECK (Morris et al., 1992) concentrates on the parameters such as bond length, bond angle, main chain and side chain properties, residue-by residue properties, RMS distance from planarity and distorted geometry plots. It assess how normal, or conversely how unusual, the geometry of the residues in a given protein structure is, as compared with stereo chemical parameters derived from well-refined, high-resolution structures (Laskowski et al., 1993).

The model of Histamine H1 receptor is docked with the drug chlorpheniramine using the molecular docking algorithm called PatchDock (Schneidman-Duhovny et al., 2005). This algorithm is inspired by object recognition and image segmentation techniques used in Computer Vision. Docking using this algorithm is compared to assembling a jigsaw puzzle which involves matching two pieces by picking one piece and searching for the complementary one (Schneidman-Duhovny et al., 2003). It concentrates on the patterns that are unique for the puzzle element and look for the matching patterns in the rest of the pieces. It employs a technique in which the surfaces are divided into patches according to the surface shape and these patches correspond to patterns that visually distinguish between puzzle pieces. Once the patches are identified, they can be superimposed using shape matching algorithms which notify that a hybrid of the Geometric Hashing and Pose-Clustering matching techniques are applied to match the patches detected. Concave patches are matched with convex and flat patches with any type of patches. All complexes with unacceptable penetrations of the atoms of the receptor to the atoms of the ligand are discarded. Finally, the remaining candidates are ranked according to a geometric shape complementarity score.

RESULTS AND DISCUSSION

Target sequence of histamine H1 receptor

The protein sequence of Histamine H1 receptor of Homo sapiens (Uniprot/SwissProt ID: P3536) extracted from the UniProtKB/Swiss-prot database (Bairoch et al., 2004) shown below is 487 amino acids in total length, and is of
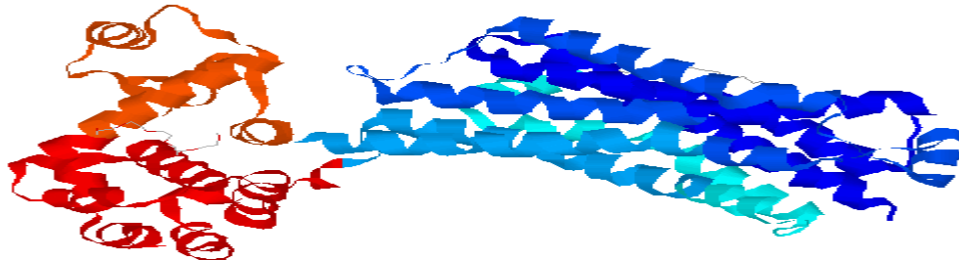
Figure 2. Structure of template - human B2-adrenergic G protein-coupled receptor.

Figure 3. The sequence alignment between Histamine H1 Receptor and Human B2-Adrenergic G Protein-Coupled Receptor (EXPDB ID: 1rh1a) performed using SWISSMODEL template selection.

molecular weight 55784 Da.

>P35367|HRH1_HUMAN Histamine H1 receptor - Homo sapiens (Human).
MSLPNSSCLLEDKMCEGNKTTMASPQLMPLVVVLSTIC
LVTVGLNLLVLYAVRSERKLHTVGNLYIVSLSVADLIVGA
VVMPMNILYLLMSKWSLGRPLCLFWLSMDYVASTASIF
SVFILCIDRYRSVQQPLRYLKYRTKTRASATILGAWFLS
FLWVIPILGWNHFMQQTSVRREDKCETDFYDVTWFKV
MTAIINFYLPTLLMLWFYAKIYKAVRQHCQHRELINRSLP
SFSEIKLRPENPKGDAKKPGKESPWEVLKRKPKDAGG
GSVLKSPSQTPKEMKSPVVFSQEDDREVDKLYCFPLDI
VHMQAAAEGSSRDYVAVNRSHGQLKTDEQGLNTHGA
SEISEDQMLGDSQSFSRTDSDTTTETAPGKGKLRSGS
NTGLDYIKFTWKRLRSHSRQYVSGLHMNRERKAAKQL
GFIMAAFILCWIPYFIFFMVIAFCKNCCNEHLHMFTIWLG
YINSTLNPLIYPLCNENFKKTFKRILHIRS

Template identification

Selecting appropriate ExPDB template for the protein

sequence of Histamine H1 receptor of Homo sapiens (Uniprot/SwissProt ID: P3536) via the SWISSPDBVIEWER yielded a structure of human B2-adrenergic G protein-coupled receptor (ExPDB ID: 1rh1A, Figure 2) as a template with a length of 442 residues.

Target-template sequence alignment

The most successful techniques for prediction of three dimensional structures of protein rely on aligning the sequence of a protein of to a homolog of known structure. Histamine H1 receptor showed 26% identity, 46% positives, 154 score bits, and 2e-37 e-value with the template human B2-adrenergic G protein-coupled receptor (Figure 3).

Homology modeling of histamine H1 receptor

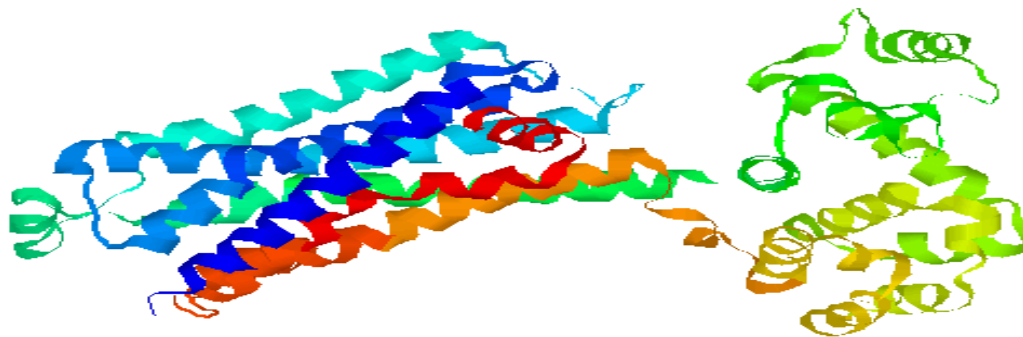The lack of 3D structure for Histamine H1 receptor

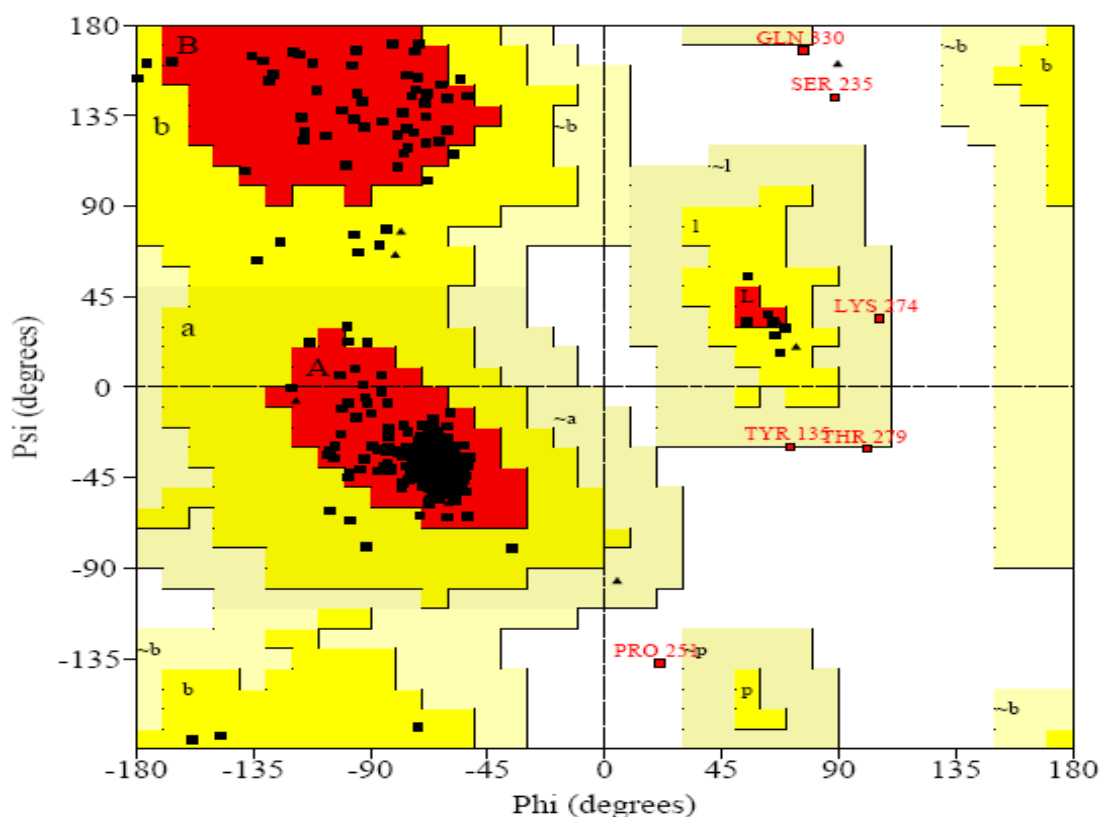**Figure 4.** Homology model of histamine H1 receptor.

Figure 5. Ramachandran plot for the model of Histamine H1 receptor.

initiated to construct the 3D model for Histamine H1 receptor.

In order to understand the binding characteristics as well as the structural and molecular level properties of the Histamine H1 receptor homology, modeling is carried out based on the structure of human B2-adrenergic G protein-coupled receptor (ExPDB ID: 1rh1A) as the template. The structure of Histamine H1 receptor was modeled using the program SWISSPDBVIEWER - SWISSMODEL (Figure 4).The modeled structure has 27 helices, 6 strands and 37 turns.

Refinement and evaluation of the quality of the model

The stereochemistry of the theoretical model of Histamine H1 Receptor is done by subjecting it into energy minimization in SWISSPDBVIEWER. The model was subjected to structure verification and evaluation using PROCHECK. The Ramachandran plot for the model showed 92.5% residues in most favored regions and other parameters for PROCHECK was in the allowed range (Figure 5). A good quality model would be expected to have over 90% in the most favored regions.
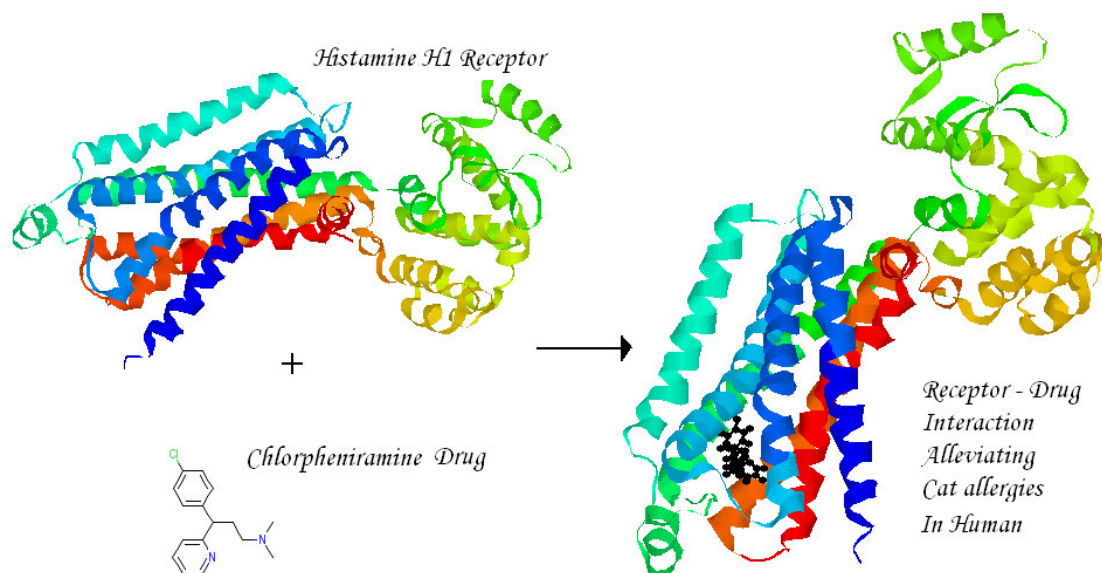
Figure 6. Representation of interaction between Histamine H1 (Receptor) and chlorpheniramine (Drug). Receptor is represented in ribbons format and drug is represented in ball and sticks format. The Docking is performed in Patch Dock software.

The theoretical model is a good quality model since 92.5% of the residues are in most favored region.

Interaction of histamine H1 receptor with chlorpheniramine

The drug chlorpheniramine is downloaded in PDB format from Drug Bank. Downloaded drug is then subjected to molecular docking (Figure 6) with the model of Histamine H1 Receptor using PatchDock program. Receptor–Drug complex has a complementarity score of 4846, Atomic Contact Energy (ACE) of -139.35.

Conclusion

The work involved the homology modeling of Histamine H1 Receptor, and molecular docking studies of modeled structure of Histamine H1 Receptor with the drug chlorpheniramine. The docking studies which involves the interaction of Histamine H1 Receptor with the drug chlorpheniramine provided valuable insight into the role of chlorpheniramine having anti histamine activity and in alleviating cat allergies produced by the cat allergen namely Fel d 1 protein.

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http://www.drgreene.com/.

http://www.expasy.org/uniprot.

http://www.felixpets.com.