G&I Genomics & Informatics

pISSN 1598-866X eISSN 2234-0742
Genomics & Informatics 2012;10(2):128-132
http://dx.doi.org/10.5808/GI.2012.10.2.128

ARTICLE

Characteristics in Molecular Vibrational Frequency Patterns between Agonists and Antagonists of Histamine Receptors

S. June Oh*

Department of Pharmacology, Inje University College of Medicine, Busan 614-735, Korea

To learn the differences between the structure-activity relationship and molecular vibration-activity relationship in the ligand-receptor interaction of the histamine receptor, 47 ligands of the histamine receptor were analyzed by structural similarity and molecular vibrational frequency patterns. The radial tree that was produced by clustering analysis of molecular vibrational frequency patterns shows its potential for the functional classification of histamine receptor ligands.

Keywords: corralled intensity of molecular vibrational frequency, G protein-coupled receptors, histamine receptors, molecular vibration-activity relationship

Introduction

G protein-coupled receptors (GPCRs) are regarded to take up more than one-fourth of marketed human medicines [1, 2]. Drugs targeting GPCRs account for the majority of the best-selling drugs and about 40% of all prescription pharmaceuticals in the marketplace [3].

Histamine receptors belong to one family of rhodopsin-like class A GPCRs, and four subtypes are named in chronological order as H_1, H_2, H_3, and H_4. Histamine exerts its effects through the activation of these four histamine receptors. Each type of histamine receptor reacts to subtype-specific ligands into an active or inactive form.

GPCRs are integral membrane proteins that consist of 7 transmembrane segments connected by 3 intracellular and 3 extracellular loops of variable length. The crystal structures of GPCRs with their binding ligands have revealed the features of the ligand binding pockets and extracellular loops [4-6]. A ligand of GPCR activates the receptor by changing the receptor structure to the active form.

The biogenic amine histamine [2-(1H-imidazol-5-yl) ethanamine] (Fig. 1) is produced by decarboxylation of L-histidine and acts as a chemical mediator and neurotransmitter in central and peripheral tissues. It acts as an important pharmacological modulator involved in the processes of allergy, inflammation, neurophysiology, and cancer [7-10].

The molecular understanding of ligand-receptor interactions of GPCR remains unclear and is still the subject of investigations. There are several theories explaining the ligand-receptor interaction mechanism, such as shape theory, binding theory, and vibration theory [11, 12]. The structures of histamine receptor ligands are so variable that we can not easily classify the pharmacological function of the ligand. To find any other characteristic in the molecular patterns between agonists and antagonists of histamine receptors, a computational approach to molecular vibration was carried out in an attempt to find a bit of the molecular interaction mechanisms.

Methods

Dataset

The simplified molecular-input line-entry system (SMILES) and 3-dimensional structure data format (SDF) files of the dataset were downloaded from the PubChem Compound Database in National Center for Biotechnology Information (NCBI) and used in the further analyses. All 47

Received April 18, 2012; Revised May 22, 2012; Accepted May 23, 2012

***Corresponding author:** Tel: +82-51-893-3569, Fax: +82-51-797-8569, E-mail: o@biophilos.org

ligand molecules in the dataset, comprising 9 histamine agonists and 38 histamine antagonists, are shown in Table 1.

Structure comparison of histamine receptor ligands

The molecular similarities between histamine and other 46 chemicals were calculated from SMILES of the chemicals. The structural similarity was calculated and represented as the Tanimoto distance of each molecule from histamine. The Tanimoto coefficient for pairwise comparison of molecules is the most widely used measure of molecular structural similarity. This coefficient is defined as $Tc = N_{ab}/(N_a + N_b - N_{ab})$, with N_{ab} being the number of common bits, N_a the unique bits in molecule a, and N_b the unique bits in molecule b, using a molecular fingerprint [13]. In this study, the molecular similarity was calculated as the Tanimoto coefficient using the 38-bit set.

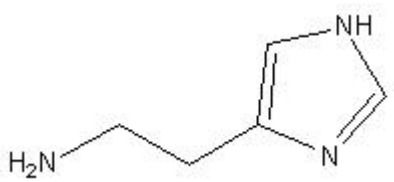

Fig. 1. The chemical structure of histidine.

Geometry optimization and calculation of molecular vibrational frequency

In order to calculate molecular vibrational frequency, the structure of a chemical must first be geometrically optimized. Since each provided theoretical 3-D conformer SDF is not at an energy minimum and may not represent the lowest energetic form in a vacuum, solvent, or a binding pocket, each SDF file of a ligand molecule underwent conversion to a single low-energy conformation using the general atomic and molecular electronic structure system (GAMESS) program package [14]. Restricted Hartree-Fock (RHF) calculations using Becke's exchange and Lee-Yang-Parr's correlation functionals (BLYP) density functional theory (DFT) method with 6-31G basis set were performed to optimize the geometries of the molecules. Each result was taken as the representative conformation of the molecule, although the calculation of molecular vibrational frequency has some dependence on conformation. Each geometry optimization result was subjected to the calculation step for the vibrational frequency with RUNTYP of HESSIAN in the GAMESS program.

Table 1. List of agonists and antagonists used in the present study

PubChem ID	Compound name	Receptor	Function type	PubChem ID	Compound name	Receptor	Function type
87653	2-Thiazoleethanamine	HRH1	Agonist	3957	Loratadine	HRH1	Antagonist
2366	Betahistine	HRH1	Agonist	4034	Meclozine	HRH1	Antagonist
75919	Demethylbetahistine	HRH1	Agonist	4761	Pheniramine	HRH1	Antagonist
7741	Betazole	HRH2	Agonist	4927	Promethazine	HRH1	Antagonist
3077	Dimaprit	HRH2	Agonist	5002	Quetiapine	HRH1	Antagonist
3692	Imetit	HRH3	Agonist	3032915	Burimamide	HRH2	Antagonist
126688	Amthamine	HRH3,H4	Agonist	2756	Cimetidine	HRH2	Antagonist
41376	Impromidine	HRH4	Agonist	5282136	Lafutidine	HRH2	Antagonist
5227	SKF91488	HR	Agonist	3033637	Nizatidine	HRH2	Antagonist
2267	Azelastine	HRH1	Antagonist	5282450	Pibutidine	HRH2	Antagonist
2678	Cetirizine	HRH1	Antagonist	3001055	Ranitidine	HRH2	Antagonist
2725	Chlorpheniramine	HRH1	Antagonist	5105	Roxatidine	HRH2	Antagonist
26987	Clemastine	HRH1	Antagonist	50287	Tiotidine	HRH2	Antagonist
6726	Cyclizine	HRH1	Antagonist	9954017	A-349821	HRH3	Antagonist
124087	Desloratadine	HRH1	Antagonist	9818903	ABT-239	HRH3	Antagonist
33036	Dexchlorpheniramine	HRH1	Antagonist	2366	Betahistine	HRH3	Antagonist
21855	Dimetindene	HRH1	Antagonist	6422124	Ciproxifan	HRH3	Antagonist
3100	Diphenhydramine	HRH1	Antagonist	3035746	Iodophenpropit	HRH3	Antagonist
667477	Doxepin	HRH1	Antagonist	9948102	Pitolisant	HRH3	Antagonist
3162	Doxylamine	HRH1	Antagonist	3035905	Thioperamide	HRH3,H4	Antagonist
3191	Ebastine	HRH1	Antagonist	2790	Clobenpropit	HRH3	Antagonist
19105	Embramine	HRH1	Antagonist	4908365	JNJ-7777120	HRH4	Antagonist
3348	Fexofenadine	HRH1	Antagonist	10446295	VUF6002	HRH4	Antagonist
1549000	Levocetirizine	HRH1	Antagonist				

Hierarchical clustering of the corralled intensity of molecular vibrational frequency (CIMVF)

For the simplified molecular comparison, the calculated vibrational frequencies of a molecule were then sorted in increasing order and taken into the corrals, the step size of which was 5. The intensities of each frequency in the same corral were summed up as the representative of the corral in the frequency range of 0-5,000 cm^{-1}. As a final outcome, this potential molecular descriptor of each molecule was displayed in a 1-dimensional vector containing 1,000 elements. Finally, the similarity matrix, comprising the descriptors of 47 ligands of histamine receptor, was then subjected to hierarchical clustering in the agglomerative manner. In this study, the similarity matrix was finally clustered to make an unrooted tree of 47 vertices. The calculations of CIMVF were performed by in-house scripts, written in Python.

Results and Discussion

The Tanimoto coefficients between histamine and other ligand molecules are shown in Table 2. Typically, a Tanimoto coefficient $>$ 0.85 is considered highly similar, and a coefficient $>$ 0.75 is considered similar for the purpose of clustering molecules that may have similar biological activity profiles [15]. The highest Tanimoto coefficient among agonists was 0.45 (imetit), and this is not high enough to be considered a molecule that has potential agonist efficacy. Moreover, the lowest value of Tanimoto coefficient among agonists was 0.08 (dimaprit and SKF91488) and is also a lower value as an antagonist. It seems that there is no related pattern between Tanimoto coefficients and the functional types of molecules in the case of histamine receptor agonists or antagonists.

To search for a novel characteristic for the classification of histamine receptor ligands, a kind of molecular calculation using agglomerative hierarchical clustering was adopted in this work. The result of the hierarchical clustering of the similarity matrix from CIMVF is shown in Fig. 2. As shown in the figure, eight agonists were located nearby (the part in the dotted circle), except impromidine, and all antagonists were clustered close to each other in the radial tree. We can tell the regional difference between agonists and antagonists in the tree and also find that the information from the molecular vibrational frequency may play a role in the classification of agonists/antagonists for histamine receptor as a possible molecular descriptor. For these methods, clustering with CIMVF shows the more proper result in the

Table 2. The molecular similarity between histamine and each ligand molecule in Tanimoto coefficient

Compound	Tanimoto coefficient	Function type	Compound	Tanimoto coefficient	Function type
Histamine	1	Agonist			
Imetit	0.45	Agonist	Loratadine	0.13	Antagonist
Burimamide	0.43	Antagonist	JNJ-7777120	0.13	Antagonist
Thioperamide	0.41	Antagonist	Pitolisant	0.12	Antagonist
Iodophenpropit	0.3	Antagonist	Embramine	0.12	Antagonist
Demethylbetahistine	0.3	Agonist	Cyclizine	0.11	Antagonist
Ciproxifan	0.3	Antagonist	Dimetindene	0.11	Antagonist
Impromidine	0.29	Agonist	Meclozine	0.11	Antagonist
Clobenpropit	0.29	Antagonist	Nizatidine	0.1	Antagonist
Betahistine	0.27	Antagonist	Promethazine	0.1	Antagonist
Amthamine	0.25	Agonist	Azelastine	0.1	Antagonist
2-Thiazoleethanamine	0.25	Agonist	Cetirizine	0.1	Antagonist
Cimetidine	0.24	Antagonist	Levocetirizine	0.1	Antagonist
Betazole	0.22	Agonist	Tiotidine	0.09	Antagonist
VUF6002	0.19	Antagonist	ABT-239	0.09	Antagonist
Doxylamine	0.18	Antagonist	Doxepin	0.09	Antagonist
Pheniramine	0.18	Antagonist	Dimaprit	0.08	Agonist
Chlorpheniramine	0.18	Antagonist	A-349821	0.08	Antagonist
Dexchlorpheniramine	0.18	Antagonist	Pibutidine	0.08	Antagonist
Fexofenadine	0.16	Antagonist	SKF91488	0.08	Agonist
Desloratadine	0.14	Antagonist	Roxatidine	0.08	Antagonist
Diphenhydramine	0.14	Antagonist	Ranitidine	0.07	Antagonist
Clemastine	0.13	Antagonist	Lafutidine	0.07	Antagonist
Ebastine	0.13	Antagonist	Quetiapine	0.07	Antagonist

The Tanimoto coefficients between histamine and other ligand molecules are listed in descending order.

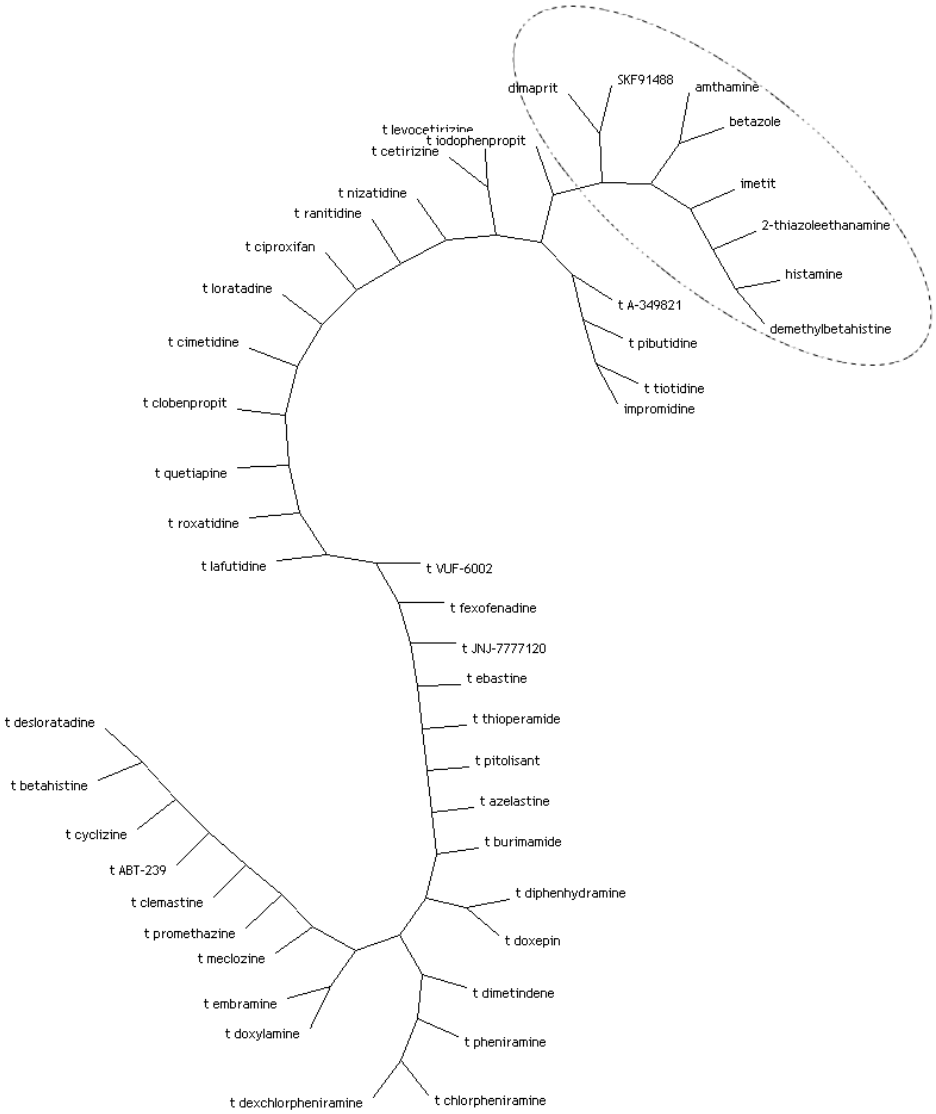

Fig. 2. Radial tree of corralled intensity of molecular vibrational frequency (CIMVF) clustering using the complete linkage method. Antagonists are tagged with "t" to their chemical names as a prefix, whereas agonists are not. Agonists of histamine receptors except impromidine are located in a cluster (the part in the dotted circle).

case of histamine receptor ligands. With a more concentrated study on the relationship between the molecular vibrational frequency and pharmacological function of a ligand, the vibrational spectrum of a molecule may shed light on the field of ligand-receptor interaction mechanisms.

Acknowledgments

The author would like to express sincere appreciation to Prof. C. H. Choi for the use of his cluster computer and his valuable advice. This work was supported by the 2010 Inje University research grant.

References

1. Bleicher KH, Bohm HJ, Müller K, Alanine AI. Hit and lead generation: beyond high-throughput screening. *Nat Rev Drug Discov* 2003;2:369-378.
2. Zheng CJ, Han LY, Yap CW, Ji ZL, Cao ZW, Chen YZ. Therapeutic targets: progress of their exploration and investigation of their characteristics. *Pharmacol Rev* 2006;58:259-279.
3. Drews J. Drug discovery: a historical perspective. *Science* 2000;287:1960-1964.
4. Cherezov V, Rosenbaum DM, Hanson MA, Rasmussen SG, Thian FS, Kobilka TS, *et al*. High-resolution crystal structure of an engineered human beta2-adrenergic G protein-coupled receptor. *Science* 2007;318:1258-1265.
5. Chien EY, Liu W, Zhao Q, Katritch V, Han GW, Hanson MA, *et al*. Structure of the human dopamine D3 receptor in complex with a D2/D3 selective antagonist. *Science* 2010;330:1091-1095.
6. Shimamura T, Shiroishi M, Weyand S, Tsujimoto H, Winter G, Katritch V, *et al*. Structure of the human histamine H1 receptor

complex with doxepin. *Nature* 2011;475:65-70.
7. Medina VA, Rivera ES. Histamine receptors and cancer pharmacology. *Br J Pharmacol* 2010;161:755-767.
8. Schwartz JC, Arrang JM, Garbarg M, Pollard H, Ruat M. Histaminergic transmission in the mammalian brain. *Physiol Rev* 1991;71:1-51.
9. Hill SJ. Distribution, properties, and functional characteristics of three classes of histamine receptor. *Pharmacol Rev* 1990;42:45-83.
10. Hill SJ, Ganellin CR, Timmerman H, Schwartz JC, Shankley NP, Young JM, *et al*. International Union of Pharmacology. XIII. Classification of histamine receptors. *Pharmacol Rev* 1997;49:253-278.
11. Keller A, Vosshall LB. A psychophysical test of the vibration theory of olfaction. *Nat Neurosci* 2004;7:337-338.
12. Takane SY, Mitchell JB. A structure-odour relationship study using EVA descriptors and hierarchical clustering. *Org Biomol Chem* 2004;2:3250-3255.
13. Godden JW, Xue L, Bajorath J. Combinatorial preferences affect molecular similarity/diversity calculations using binary fingerprints and Tanimoto coefficients. *J Chem Inf Comput Sci* 2000;40:163-166.
14. Schmidt MW, Baldridge KK, Boatz JA, Elbert ST, Gordon MS, Jensen JH, *et al*. General atomic and molecular electronic structure system. *J Comput Chem* 1993;14:1347-1363.
15. Keseru GM, Makara GM. The influence of lead discovery strategies on the properties of drug candidates. *Nat Rev Drug Discov* 2009;8:203-212.