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Antihistamine Structural Variations Aptly With Their Pharmacodynamics And Physicochemical Properties

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Abstract

General Background: Antihistamines targeting the histamine H1 receptor are crucial therapeutic agents for managing allergic and inflammatory conditions globally. **Specific Background:** Structural modifications among first-, second-, and third-generation antihistamines directly dictate their lipophilicity, receptor selectivity, and central nervous system penetration. **Knowledge Gap:** Comprehensive insights linking subtle chemical variations to detailed pharmacodynamics, receptor occupancy, and unexpected therapeutic applications remain fragmented. **Aims:** This review evaluates how structural diversity influences H1 receptor binding, physicochemical behavior, sedative potential, and clinical outcomes. **Results:** Non-sedating zwitterionic structures exhibit lower blood-brain barrier permeability and reduced H1 receptor occupancy compared to lipophilic, flexible first-generation compounds. **Novelty:** Recent structural insights reveal secondary binding pockets and extracellular loop interactions that facilitate novel antiparasitic and migraine therapeutic avenues. **Implications:** Understanding these structure-activity relationships guides the rational pharmacoengineering of personalized next-generation antihistamines with enhanced safety profiles.

Keywords: Antihistamine Structure, Pharmacodynamics, Physicochemical Properties, Receptor Occupancy, Inverse Agonist

Key Findings Highlights

Structural variations in functional groups dictate blood-brain barrier permeability and central nervous system sedation profiles.

Low brain H1 receptor occupancy in zwitterionic agents ensures peripheral selectivity without impairing psychomotor function.

Unique binding pocket configurations enable potential novel applications ranging from antiparasitic activity to migraine management.

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Introduction

Antihistamines, a medication class dating back to the 1940s, block histamine effects and are commonly used for allergy symptoms [1]. They work as inverse agonists by binding to the H receptor, stopping histamine-induced inflammation, according to Simmons et al. (2021) [2]. H1 and H2 antihistamines are among the most frequently prescribed medications throughout the clinical setting. H1 antihistamines work as inverse agonists, which means they stop histamines from working at the H1 receptors by binding to them and keeping them in an inactive state [3]. Moreover, H1-antihistamines show an even stronger effect as anti-allergic agents by decreasing the presentation of antigens, expressing the pro-inflammatory cytokines, and cell adhesion molecules. Furthermore, through the transcription factor nuclear factor-kB, H1 antihistamines restrain mast cell activation and histamine release in a concentration-dependent manner [4]-[6]. H1 antihistamines are widely used to treat allergic rhinitis, urticarial, and other allergic diseases. From the time of the very first antihistamine development in 1937 [7], to the production of the constant greater types with the kinds of drugs, first-generation, second-generation, and third-generation antihistamines have been through the developing stage.

To optimize the effectiveness of antihistamines, it is crucial to understand their structural diversity and how it affects their modes of action. Modifying the structure of a compound can greatly affect its affinity for histamine receptors and the selectivity of receptor subtypes. Antihistamines' pharmacological action could be significantly affected by these changes. Alterations in the chemical structure of the antihistamines may affect their physicochemical properties such as their solubility, lipophilicity, and metabolization [8]. This literature review will also outline plans for antihistamine studies, including the potential of structural variations to improve therapy, and will aim to increase our understanding of their potential therapeutic value and help design new agents that have improved efficacy and safety profiles.

Structural Variations of Antihistamines

These drugs differ in their structure, which has a great impact on their antihistamine pharmacodynamics, physicochemical properties and therapeutic effects. A detailed discussion of structural differences between 1st and 2nd generation anti-histamines, and how this can affect treatment is included in this section. Antihistamines are substances which competitively block the receptors so that histamine cannot be formed, released and act on them. They can therefore be divided into three groups: sedative mixtures, antiallergic (nonsedating) agents, and agents that can interact with H1-antihistamines but have different effects. A group of antihistamines called H1-histamine antagonists are able to stop the histamine from binding to the ego tub. The action of H2-histamine antagonists is on the parietal cells that produce acid in the stomach. New agents are being developed against illnesses of the central nervous system, using a technique known as agents called H3-receptor antagonists. H1-antihistamines have been modified to make first generation, second generation and third generation antihistamines.

First generation antihistamines (e.g. diphenhydramine, chlorpheniramine: figure 1) have been noted for their ability to penetrate the blood-brain barrier (BBB) and provide a central nervous system (CNS) effect, such as sedations. Generally, these drugs have a flexible linker and an aromatic ring structure and contain various substituents that facilitate CNS penetration and lipophilicity [9].

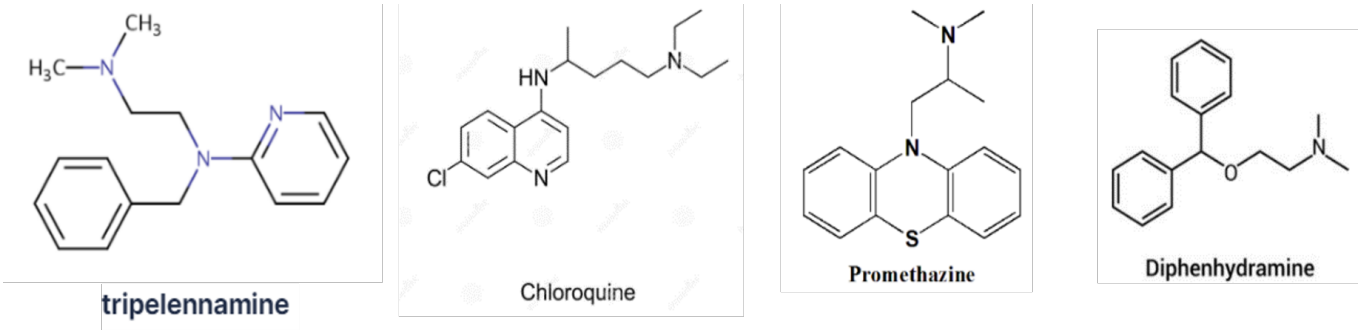

Figure 1.

Figure 1. Chemical structures of sedating antihistamines.

In contrast, second generation antihistamines such as loratadine and cetirizine have been developed with polar properties that decrease their ability to cross the CNS and hence their sedative properties. These structural changes make them more selective for peripheral H1 receptors and make them less lipophilic [10]. A piperidine ring and a carbamate group in loratadine lowers its lipophilicity and limits its ability to cross the CNS which translates to lower sedative effects [11].

Second-generation H1 antihistamines include terfenadine, imidazoline and loratadine. Apart from their strong affinity for histamine H1 receptors, they have other anti-allergic properties, such as inhibiting intercellular adhesion molecules (ICAMs) [12].

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The chemical structures of non-sedating H1 antihistamines (Figure 2) contain at least one hydrophilic functional group such as amino group (-NH2) and/or carboxyl (-COOH) group, which is believed to prevent penetration of the BBB [13].

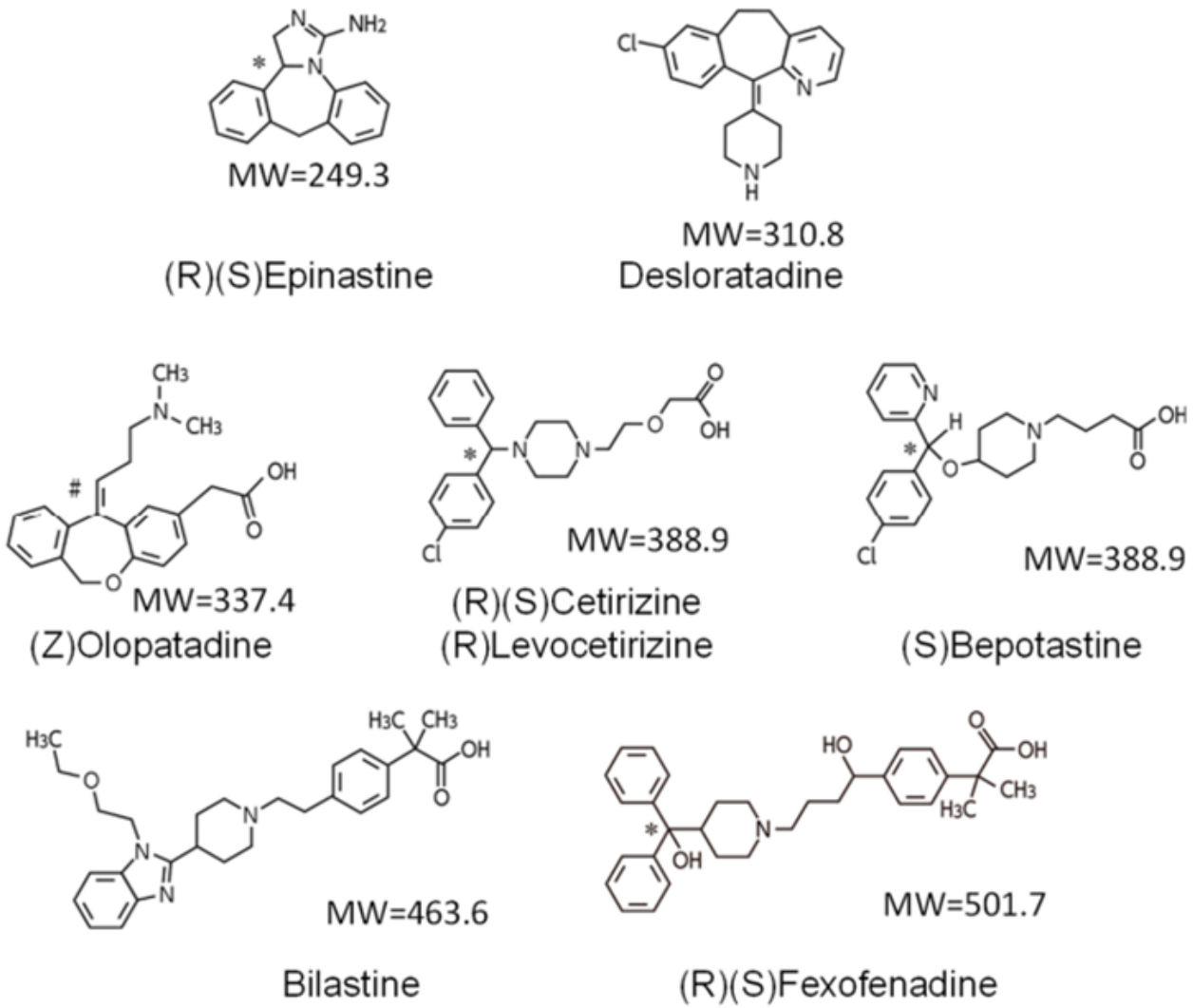

Figure 2.

Figure 2. Chemical structures of several non-sedating antihistamines.

Antihistamines and their pharmacological actions and classification

Mast cells and basophils produce and secrete histamine, a heterocyclic amine that is formed by the decarboxylation of l-histidine. It has both pro-inflammatory and anti-inflammatory properties, depending on the type of histamine receptor and cells stimulated. Histamine receptors are divided into four types: H1, H2, H3 and H4 receptors. Histamine's defense and immunoregulatory activities, as well as acute and chronic allergic inflammation, are all mediated by H1 receptors. They are found in many organs and cells such as neurons, endothelial cells, vascular smooth muscle cells, respiratory epithelium, hepatic cells, dendritic cells and lymphocytes. Histamine acts on H1 receptors on small capillary venules to produce edematous and erythematous wheals (angioedema), or skin-colored swellings. This is due to vasodilation and increased vascular permeability, leading to leakage of plasma into the interstitial space of the tissue which contains large molecular weight proteins, especially immunoglobulins, [14]. Histamine also activates sensory nerves leading to itching and recruitment of eosinophils, basophils, neutrophils and other inflammatory cells, as shown by the mixed infiltrate of cells within the wheals on histopathological examination. The word 'antihistamine' is only used for drugs that act on the H1 receptor, drugs that act on the other histamine receptors are not antihistamines. Antihistamines are inverse agonists to the constitutionally active H1 receptors. They diminish the constitutional activity of histamine at H1 receptors and neutralize the effects of histamine on H1 receptors by keeping the H1 receptor in its inactive conformation [15]. Hence, they are more

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appropriately called ‘H1-antihistamines' than ‘histamine antagonists. Antihistamines reverse the process of blood vessel dilation and permeability caused by histamine and thus can help to decrease swelling in an area. In addition, to blocking receptors on blood vessels and nerves antihistamines also play a role in reducing inflammation by preventing the buildup of inflammatory cells in tissues and dampening the immune response to allergens through their effects, on nuclear factor K beta and calcium channels [16]. The first anti-histamines were like histamine. Included an ethylamine group. Various chemical groups, with even stronger effects have since been discovered, such as ethanol amines, ethylene diamines, alkylamines, piperazines, piperidines and phenothiazines [17] (Table 1).

Table 1. antihistamines: chemical and functional classification

Chemical category	First Generation	Second Generation
Alkylamines	Brompheniramine Chlorpheniramine Dimethindene Pheniramine Triprolidine	Acrivastin
Piperazines	Buclizine Cyclizine Hydroxyzine Meclizine Oxatomide	Cetrizine Levocetrizine
Piperidines	Azatadine Cyproheptadine Diphenylpyraline Ketotifen	Astemizole Bilastine Desloratidine Ebastine Fexofenadine Levocabastine Loratadine Mezolastine Olopatadine Rupatadine Terfenadine
Ethanolamines	Carbinoxamine Clemastine Dimenhydrinate Diphenylhydramine Doxylamine Phenyltoloxamine	----
Ethylenediamines	Antazoline Pyrilamine Tripelennamine	----
Phenothiazines	Methdilazine Promethazine	----
Other	Doxepin	Azelastine Emedastine Epinastine

Figure 3.

Clinical Applications and sedative potentials of antihistamines

The structure of the antihistamines plays a key role in their therapeutic uses as well as their side effects. First generation anti-histamines have sedative properties, which makes them popular for treating acute allergic reactions and as a sleep aid. Their benefits for allergy treatment in the long term are restricted by the central nervous system side effects. Second generation antihistamines: These last longer and are less sedating and are better for chronic allergic reactions. They have been found to be effective in treating chronic urticaria, allergic rhinitis, and other conditions [2].

The second-generation antihistamines of the 1980s brought a step forward in antihistamine innovation, in terms of their ability to reach the brain with limited or no sedative effects [18]. Yanai et al. evaluated the H1RO of various first and second generation antihistamines and proposed to classify these drugs into groups according to the H1RO [19]-[21]. The importance of H1RO as a measure of non-sedative properties of the antihistamines was also reiterated at the "Consensus Group of New Generation of Antihistamines (CONGA)" expert meeting, sponsored by the British Society for Allergy and Clinical Immunology (BSACI) [22]. After a single oral dosage, antihistamines are divided into three groups according to the H1RO: non-sedating (<20%), less-sedating (20–50%), and sedating (≥50%). Based on the results of various research organizations' measurements, the non-sedating group includes the following medications: bilastine 20 mg, fexofenadine 60-120 mg, levocetirizine 5mg, epinastine 20 mg, ebastine 10 mg, loratadine 10 mg and terfenadine 60 mg. According to the results of measurements of various research groups, the non-sedating group includes levocetirizine (5 mg), epinastine (20 mg), ebastine (10 mg), loratadine (10 mg), terfenadine (60 mg), cetirizine (10 mg), olopatadine (5 mg), and bepotastine (10 mg).

One of the best measures for classify antihistamines into non-sedating, less-sedating, and sedating groups is H1 receptor

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occupancy (H1RO). The two non-sedating drugs, bilastine and fexofenadine, are classified as "non-brain-penetrating antihistamines" due to the lack of brain H1 receptor occupancy at their recommended doses. Bilastine and fexofenadine have other molecular similarities besides being zwitterions. In contrast, bilastine has a higher affinity to H1 receptor than fexofenadine. The medications are chosen for their ability to penetrate the brain and because there are no significant differences among the second generation antihistamines in their clinical efficacy, but rather in their sedative vs. non-sedative properties. In a study, the researchers recommended that the antihistaminic classification should consider both the antihistaminic action and the ability of the antihistamines to cross the blood–brain barrier as well as their effects on central nervous system functions even at a double dose, 40 mg. The study is aimed at brain H1 receptor occupancy, with a low occupancy linked to improved psychomotor function and decreased sedation, a factor of paramount importance for patients who need to be alert to carry out their daily activities. In addition, the authors recommend the objective tests of psychomotor performance like Critical Flicker-Fusion Frequency (CFF) and Simple Reaction Time (SRT) tests to be taken into account for the more precise assessment of the sedative effects of these drugs. Ultimately, it will facilitate the better treatment of allergic rhinitis by doctors and decrease side effects by helping them select the optimum antihistamine for their patients [24]. Due to their sedative qualities, first-generation antihistamines are commonly used to treat acute allergic reactions as well as sleep aids. But, the CNS side effects limit their usefulness to long-term allergy treatment. Second generation antihistamines: These work longer, and require less anaesthetic and are the preferred antihistamines for chronic/sustained allergies. Simmons et al. recommend their use in the treatment of several diseases including chronic urticaria and allergic rhinitis [2].

Daniel and colleagues (2024) performed a systematic review of all clinical antihistamines against the nematode Angiostrongylus cantonensis of particular interest to vertebrate hosts, including humans. The first-stage larvae (L1) of A. cantonensis collected in the infected rats' feces were used and tested for activity with 21 anti-H1 antihistamines. Standard drug use of anthelmintics (ivermectin and albendazole) was introduced. Four active compounds were found: promethazine (EC50 = 31.6 µM), cinnarizine, desloratadine and rupatadine. Promethazine (EC50 = 31.6 µM) was the most potent compound. In addition, the morphological study revealed that there were significant changes in the morphology of the larvae induced by these anti-histamines. The antimuscarinic effect, defined as the average pKi values of human muscarinic receptor (mAChR) subtypes, was an important effect of the tested compounds. Moreover, there was no direct correlation between the antihelminthic activity of antihistamines and their activity on H1 receptors, the researchers also observed. The present work is the first report on the anthelmintic activity of anti-histamines against A. cantonensis which will give a lot of information for developing new drugs which can be used against the zoonotic helminthes [25]. Chen et al. (2008) have reviewed this extensively on the physicochemical, pharmacological and pharmacokinetic properties of cetirizine and its enantiomer, levocetirizine. These second generation anti-histamines have the following zwitterionic property and this gives them efficacy in the treatment of seasonal allergic rhinitis," the authors write. The molecular structure of cetirizine and its binding with the H1 receptor are highlighted, in view of the importance of this interaction for the clinical activity of these compounds, while reducing undesirable side effects commonly seen with the first-generation antihistamines.

Recently Second generation H1 Antihistamines are regarded as the backbone of the treatment of allergic diseases because they have less side effects and contraindications when compared with the first generation (old) antihistamines (South African Family Practice, 2015). First generation anti-histamines are still used in a number of ways, but are no longer recommended as the first choice for treating allergic reactions. Topical decongestants, corticosteroids and second generation antihistamines are also important therapies for the effective management of allergic rhino conjunctivitis in clinical practice. H1 antihistamines are generally good and applicable drug therapeutic classes with wide spectrum of application in clinical practice [8].

Farzam, et al. (2024) talks about the negative effects of H-1 and H-2 receptor antihistamines. H1 antihistamines are first generation antihistamines which cross the blood brain barrier and can have central nervous system side effects such as drowsiness, dizziness, dry mouth, sedation, impaired co-ordination and delirium, particularly at high doses, with cardiotoxicity (due to central nervous system side effects) and QTc prolongation. Second generation H-1 antihistamines, on the other hand, are not as readily absorbed by the blood-brain barrier and thus have fewer side effects, making them safer to take for extended periods of time. The antihistamine agents that block the H-2 receptors are very well tolerated and have few side effects, but may have some gastrointestinal side effects and cause dizziness. However, cimetidine is also antiandrogenic, resulting in gynecomastia in males and galactorrhea in females, it may also be a liver enzyme inhibitor and drug interacting agent. Ranitidine has been removed from the market because it became contaminated with a cancer-causing agent. The article highlights the need for careful selection of antihistamines, taking into account the patient's health to prevent aggravation of any underlying illnesses, and to reduce side effects [27].

Currently, the issue of drug response variability, especially adverse reaction risks, is a common problem in the field of pharmacotherapy. Advances in pharmacogenomics, including exome or genome sequencing, offer new tools to gain insight into and control over this variability. So far, studies on antihistamine pharmacogenomics are limited in number, but have helped to rationalize antihistamine use in clinical practice. Thus, most studies have been conducted on the genes of metabolic enzymes, while attention has been less on the genes that encode drug-binding receptors, drug-transport-related membrane channels, and signal transduction proteins. To optimize the clinical application of anti-histamines, avoid adverse clinical effects associated with genetic variability [28] and to further develop precision medicine. Almost all antihistamines have unfavorable side effects when taken in large enough dosages; the frequency and intensity of these symptoms vary depending on the patient as well as the characteristics of the particular medication. Adults who have adverse effects most frequently are sleepy. Headache, dry mouth, impaired eyesight, and stomach discomfort are some other adverse effects. If the patient fails to improve after 3 days of antihistamine treatment, then the antihistamine will not be effective. The digestive system readily absorbs antihistamines and most are metabolized by liver enzymes called monoamine oxidase.

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Pharmacokinetics and Pharmacodynamics of Antihistamines

Antihistamines are the most common agents in allergy treatment. Therefore, a central branch of research in allergy management is the pharmacodynamics of antihistamines, which includes their mechanisms of action and effects in the treatment of allergies. Perhaps the best way to understand antihistamine pharmacokinetics is to realize that an antihistamine has four main pharmacokinetic features, namely, absorption, distribution, metabolism, and excretion. All these components are closely related to pharmacodynamics. As a result, scientists should strive to communicate high pharmacodynamics knowledge at a clinical level to maximize the application of antihistamines. Drug response varies among individuals due to disease heterogeneity, environmental and genetic factors: doses that are effective in some patients inevitably become ineffective or cause adverse drug reactions (ADRs) in others. Gene polymorphism can influence the pharmacokinetics and pharmacodynamics of drugs, leading to changes in local and systemic drug exposure and/or changes in drug target function that alter drug responses. For patients. After oral administration, antihistamines usually start to work one to two hours later, reaching their peak plasma concentrations in a few hours. Antihistamines range in how long they take to take effect; some can relieve symptoms for up to 24 hours, which means they can be used once daily [29]. In clinical studies, the ability of antihistamines to inhibit the wheal and flare response to histamine is a common method of assessing the effectiveness of an antihistamine. Second generation anti-histamines have been shown to be much less likely to cause these reactions and do not appear to cause the drowsiness seen with first generation anti-histamines. Their extensive usage in the treatment of allergic disorders is a result of this. Hindmarch, I., Shamsi, Z. (1999) [30]. Antihistamines are known to act on the H1 receptors, blocking histamine binding and so easing symptoms such as itching and rhinorrhea, according to Kuna et al. (2016). The discovery of second-generation antihistamines has made a significant leap forward the field, as they have better safety, and are more effective in alleviating urticaria and allergic rhinitis symptoms. Interestingly, the recommendations highlight the importance of these second generation non-sedative antihistamines in the management of allergic diseases, with the addition of recommending them as first and second line treatment in the urticaria treatment algorithm [31].

Moreover, current studies have demonstrated the range of antihistamines' abilities to inhibit the production of the histamine H1 receptor gene. The field of antihistamine research has progressed significantly over the past few years, with increased knowledge about the histaminergic system and its association with diseases such as migraine. There are multiple histamine receptors (H1, H2, H3, and H4) within the body. Little is known about the H4 receptor. The fact that histamine may effectively cause migraines is particularly intriguing, and this has drawn further attention to the importance of the histaminergic system in migraine prevention. Although there is currently little and low-quality research on the impact of antihistamines on migraine, there are encouraging findings on the H3 receptor agonist Nα-methylhistamine as a possible therapy for migraine. This emphasizes the necessity of investigating the histaminergic system more thoroughly in order to find novel targets for the treatment of migraines [32].

Wang et al. studied the structural characteristics of the histamine H1 receptor (H1R) complexed with desloratadine, mepyramine, and astemizole in this work. The study concludes that while there are synthetic activities in all four histamine receptors, the ligands associated with these receptors have different pharmacological profiles. In their role as inverse agonists, H1R receptor antagonists often contain a phenyl group that hinders critical residues (W428), preventing receptor activation. The selective effect of these antihistamine drugs is explained by the differences in binding pockets between H1R receptors and other histamine receptors. Furthermore, the study indicates that secondary binding pockets have a lower level of conservation, providing opportunities for the development of more targeted antihistamines. These new understandings of H1R receptor processes and their regulation provide a foundation for the development of more effective and selective antihistamines [33].

Daniel A. McNaught-Flores et al.'s research done in the year 2023 is about the recognition of the structural and pharmacodynamic features of the zebrafish histamine H1 receptor (zf H1R). On the molecular side, it was observed that zf H1R has a remote connection between human H1 receptors (21%–23%) but a sharp sequence similarity (41%–43%) with the neighbor H1 receptor orthologs. The preservation of many of the key amino acid patterns linked to receptor activation and folding may indicate that they have a role in the process of histamine. The binding of the zf H1R was carefully studied with [3H]-mepyramine through binding experiments. The effect of the reference compound on the receptor is similar in the human receptor, but there are clear variations among histamine binding. The results indicated that the zf H1R (zebrafish histamine H1 receptor) binds with Gaq/11 proteins and at the same time transmits a myriad of reporter genes, which is in line with its signaling role in cellular activity. The study reveals that the primary characteristic of histamine binding intensity is the flipping of electrostatic charges in the second extracellular loop (ECL2), offering a new insight into the pharmacological distinctions among histamine receptors. It draws attention to the fact that distinct species' histamine receptors react differently to medications, as evidenced by the differences between zebrafish and human histamine receptor structural protein alterations. According to the study, these findings make it possible to identify the molecular structure's contribution to therapeutic efficacy more accurately. They eventually create additional possibilities for the creation of more targeted and potent medications [34].

Conclusion

In this review the evidences confirm nexus between antihistamine chemistry and pharmacology, reflecting receptor binding to systemic biodistribution related to structural chemistry, perhaps structural modifications can decouple the target therapeutic effects from undesirable side effects, this open the path for pharmacoengineering of next generation of antihistamines to be tailored for better pharmacokinetic and pharmacodynamic demands of individual patients.

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References

1. R. Sharma, S. K. Jaiswal, S. Kumar, and M. Yadav, "Structural insights into the binding modes of antihistamines to histamine H1 receptor: Molecular dynamics simulations and free energy calculations," Journal of Biomolecular Structure and Dynamics, vol. 38, no. 10, pp. 2884–2894, 2020.
2. F. E. R. Simons, K. J. Simons, and E. M. Frith, "The pharmacology and use of H1-receptor-antagonist drugs: Advances and perspectives," New England Journal of Medicine, vol. 384, no. 5, pp. 275–285, 2021.
3. R. Leurs, M. K. Church, and M. Taglialatela, "H1-antihistamines: Inverse agonism, anti-inflammatory actions and cardiac effects," Clinical & Experimental Allergy, vol. 32, no. 4, pp. 489–498, 2002.
4. R. A. Bakker, S. B. Schoonus, M. J. Smit, H. Timmerman, and R. Leurs, "Histamine H(1)-receptor activation of nuclear factor-kappa B: Roles for G beta gamma- and G alpha(q/11)-subunits in constitutive and agonist-mediated signaling," Molecular Pharmacology, vol. 60, no. 5, pp. 1133–1142, 2001.
5. R. A. Bakker, K. Wieland, H. Timmerman, and R. Leurs, "Constitutive activity of the histamine H(1) receptor reveals inverse agonism of histamine H(1) receptor antagonists," European Journal of Pharmacology, vol. 387, no. 1, pp. R5–R7, 2000.
6. K. Weller and M. Maurer, "Desloratadine inhibits human skin mast cell activation and histamine release," Journal of Investigative Dermatology, vol. 129, no. 11, pp. 2723–2726, 2009.
7. M. B. Emanuel, "Histamine and the antiallergic antihistamines: A history of their discoveries," Clinical & Experimental Allergy, vol. 29, no. S3, pp. 1–11, 1999.
8. S. Linton, L. Hossenbaccus, and A. K. Ellis, "Evidence-based use of antihistamines for treatment of allergic conditions," Annals of Allergy, Asthma & Immunology, vol. 131, no. 5, pp. 572–580, 2023.
9. H. Kawauchi, K. Yanai, D. Y. Wang, K. Itahashi, K. Okubo, and C. Kamei, "Antihistamines for allergic rhinitis treatment from the viewpoint of nonsedative properties," International Journal of Molecular Sciences, vol. 21, no. 5, p. 213, 2020.
10. F. E. R. Simons, K. J. Simons, and E. M. Frith, "The pharmacology and use of H1-receptor-antagonist drugs: Advances and perspectives," New England Journal of Medicine, vol. 365, no. 14, pp. 1275–1285, 2011.
11. P. Paśko, T. Rodacki, R. Domagała-Rodacka, K. Palimonka, M. Marcinkowska, and D. Owczarek, "Second generation H1-antihistamines interaction with food and alcohol—A systematic review," Biomedicine & Pharmacotherapy, vol. 93, pp. 27–39, 2017.
12. G. Ciprandi, M. A. Tosca, C. Cosentino, A. M. Riccio, G. Passalacqua, and G. W. Canonica, "Effects of fexofenadine and other antihistamines on components of the allergic response: Adhesion molecules," Journal of Allergy and Clinical Immunology, vol. 112, no. 4, pp. S78–S82, 2003.
13. Papi, N. G. Papadopoulos, L. A. Stanciu, K. Degitz, S. T. Holgate, and S. L. Johnston, "Effect of desloratadine and loratadine on rhinovirus-induced intercellular adhesion molecule 1 upregulation and promoter activation in respiratory epithelial cells," Journal of Allergy and Clinical Immunology, vol. 108, no. 2, pp. 221–228, 2001.
14. N. Schellack, G. Schellack, and M. Janse van Rensburg, "An overview of anti-allergic drug therapy and the histamine-1 antihistamines," South African Family Practice, vol. 57, no. 1, pp. 43–49, 2015.
15. K. Hiraoka, M. Tashiro, T. Grobosch, M. Maurer, K. Oda, J. Toyohara, K. Ishii, K. Ishiwata, and K. Yanai, "Brain histamine H1 receptor occupancy measured by PET after oral administration of levocetirizine, a non-sedating antihistamine," Expert Opinion on Drug Safety, vol. 14, no. 2, pp. 199–206, 2015.
16. D. A. McNaught-Flores, A. J. Kooistra, Y. C. Chen, J. A. Arias-Montano, P. Panula, and R. Leurs, "Pharmacological characterization of the zebrafish (Danio rerio) histamine H1 receptor reveals the involvement of the second extracellular loop in the binding of histamine," Molecular Pharmacology, vol. 104, no. 5, pp. 242–253, 2023.
17. F. E. R. Simons and K. J. Simons, "H1 antihistamines: Current status and future directions," World Allergy Organization Journal, vol. 1, no. 9, pp. 145–155, 2008.
18. K. Yanai, T. Watanabe, H. Yokoyama, J. Hatazawa, R. Iwata, K. Ishiwata, K. Meguro, M. Itoh, T. Takahashi, and T. Ido, "Mapping of histamine H1 receptors in the human brain using [11C]pyrilamine and positron emission tomography," Journal of Neurochemistry, vol. 59, no. 1, pp. 128–136, 1992.
19. K. McDonald, L. Trick, and J. Boyle, "Sedation and antihistamines: An update. Review of inter-drug differences using proportional impairment ratios," Human Psychopharmacology: Clinical and Experimental, vol. 23, no. 7, pp. 555–570, 2008.
20. K. Yanai, D. Zhang, M. Tashiro, T. Yoshikawa, F. Naganuma, R. Harada, T. Nakamura, K. Shibuya, and N. Okamura, "Positron emission tomography evaluation of sedative properties of antihistamines," Expert Opinion on Drug Safety, vol. 10, no. 4, pp. 613–622, 2011.
21. K. Yanai and M. Tashiro, "The physiological and pathophysiological roles of neuronal histamine: An insight from human positron emission tomography studies," Pharmacology & Therapeutics, vol. 113, no. 1, pp. 1–15, 2007.
22. S. T. Holgate, G. W. Canonica, F. E. R. Simons, M. Taglialatela, M. Tharp, H. Timmerman, and K. Yanai, "Consensus Group on New-Generation Antihistamines (CONGA): Present status and recommendations," Clinical & Experimental Allergy, vol. 33, no. 9, pp. 1305–1324, 2003.
23. K. Yanai, T. Yoshikawa, A. Yanai, T. Nakamura, T. Iida, R. Leurs, and M. Tashiro, "The clinical pharmacology of non-sedating antihistamines," Pharmacology & Therapeutics, vol. 178, pp. 148–156, 2017.
24. K. Hiraoka, K. Yanai, and D.-Y. Watanabe, "Antihistamines for allergic rhinitis treatment from the viewpoint of nonsedative properties," International Journal of Molecular Sciences, vol. 20, no. 2, p. 213, 2019.
25. D. B. Roquini, B. L. Lemes, A. L. B. Kreutz, S. C. Spoladore, M. C. Amaro, F. B. Lopes, J. P. S. Fernandes, and J. de Moraes, "Antihistamines H1 as potential anthelmintic agents against the zoonotic parasite Angiostrongylus cantonensis," ACS Omega, vol. 9, no. 28, pp. 31159–31165, 2024.
26. C. Chen, "Physicochemical, pharmacological and pharmacokinetic properties of the zwitterionic antihistamines cetirizine and levocetirizine," Current Medicinal Chemistry, vol. 15, no. 21, pp. 2173–2191, 2008.

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27. K. Farzam, S. Sabir, and M. C. O'Rourke, "Antihistamines," in StatPearls, Treasure Island, FL, USA: StatPearls Publishing, 2024.
28. L. Li, R. Liu, C. Peng, X. Chen, and J. Li, "Pharmacogenomics for the efficacy and side effects of antihistamines," Experimental Dermatology, vol. 31, no. 7, pp. 993–1004, 2022.
29. M. K. Church, "Comparative inhibition by bilastine and cetirizine of histamine-induced wheal and flare responses in humans," Inflammation Research, vol. 60, no. 12, pp. 1107–1112, 2011.
30. Hindmarch and Z. Shamsi, "Antihistamines: Models to assess sedative properties, assessment of sedation, safety and other side-effects," Clinical & Experimental Allergy, vol. 29, no. S3, pp. 133–142, 1999.
31. P. Kuna, D. Jurkiewicz, M. Czarnecka-Operacz, R. Pawliczak, J. Woroń, M. Moniuszko, and A. Emeryk, "The role and choice criteria of antihistamines in allergy management – Expert opinion," Postępy Dermatologii i Alergologii, vol. 33, no. 6, pp. 397–410, 2016.
32. Worm, K. Falkenberg, and J. Olesen, "Histamine and migraine revisited: Mechanisms and possible drug targets," The Journal of Headache and Pain, vol. 20, no. 1, p. 30, 2019.
33. D. Wang, Q. Guo, Z. Wu, M. Li, B. He, Y. Du, K. Zhang, and Y. Tao, "Molecular mechanism of antihistamines recognition and regulation of the histamine H1 receptor," Nature Communications, vol. 15, no. 1, p. 84, 2024.
34. D. A. McNaught-Flores, A. J. Kooistra, Y. C. Chen, J. A. Arias-Montano, P. Panula, and R. Leurs, "Pharmacological characterization of the zebrafish (Danio rerio) histamine H1 receptor reveals the involvement of the second extracellular loop in the binding of histamine," Molecular Pharmacology, vol. 105, no. 2, pp. 84–96, 2024.

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