CURRENT OPINION

Ophthalmic antihistamines and H_1–H_4 receptors

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Purpose of review
Antihistamines exert pharmacologic effects by binding to four histamine receptors (H_1–H_4) at different affinities, producing variable effects depending on the receptor they predominantly bind to. This review's purpose is to determine the relative potency of antihistamines by comparing their binding affinities to these receptors. Studies on binding affinities of antihistamines to histamine receptors were reviewed and the dissociation constant for inhibitor binding (Ki) analyzed to determine the most and least potent antihistamine for each receptor.

Recent findings
We retrieved the binding affinities for nineteen antihistamines. For H_1 receptors, pyrilamine exhibited the highest affinity (Ki = 0.8 nM), and thioperamide the lowest (Ki = 280 000 nM). For H_2 receptors, ranitidine exhibited the highest affinity (Ki = 187 nM), and olopatadine the lowest (Ki = 100 000 nM). For the recently discovered H_3 and H_4 receptors, thioperamide exhibited the highest affinity (Ki = 1.1 nM), and olopatadine exhibited the lowest (Ki = 79 400 nM), to H_3. Data on binding affinities to the H_4 receptor exist for: ketotifen, pheniramine, ranitidine, cimetidine and thioperamide. Of these, thioperamide exhibited the highest affinity (Ki = 27 nM), whereas cimetidine and ranitidine exhibited the lowest affinity (Ki = >10 000 nM) for H_4 receptors.

Summary
This review summarizes the relative potency of antihistamines based on their binding affinities to the four histamine receptors. Although data on binding affinities of antihistamines to the H_4 receptor are sparse, it is apparent that further research on these histamine subtypes may open new venues for more direct treatment with a higher therapeutic efficacy on allergic disorders including those affecting the ocular surface.

Keywords
allergic conjunctivitis, antihistamine, histamine, histamine receptors, ophthalmic

INTRODUCTION

Allergic conjunctivitis, associated with ocular symptoms such as itching, redness and swelling of the conjunctiva and increased tear production, affects up to 40% of the population, with an increase in incidence over the past 10 years [1▪]. Antihistamines act as an inverse agonist on the histamine receptor, and thus primarily block the acute phase allergic response, but differ due to their affinity and preference for each of the various histamine receptors, and their efficacy depends largely on their ability to bind to the receptor responsible for that symptom. Mast cell stabilizers prevent the release of inflammatory mediators associated with the late phase of the allergic response. Topical ophthalmic drugs that work both as antihistamines and mast cell stabilizers have become a preferred treatment because of their dual action and, at times, multiple actions. Even among antihistamines that bind preferentially to the same receptor, there is variation in binding affinity. The purpose of this review is to determine the relative potency of different antihistamines by comparing the binding affinity of each antihistamine to each of the four histamine receptors [2].

ANTIHISTAMINE VARIATION

The efficacy of an antihistamine depends mostly on four factors: the drug's binding affinity for each of the different histamine receptors, the rate of onset of the drug binding to the receptor, the duration of binding and maintenance of the drug-receptor complex. The additive qualities of each of these factors determine how useful a specific drug will be at

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KEY POINTS

- A relative potency of marketed antihistamines to each of the four known histamine receptors (H_1–H_4) can be determined by comparing the binding affinity of a drug to each receptor.
- The ideal antihistamine would have high affinity for the targeted histamine receptor (high efficacy), with low affinity for muscarinic receptors (low incidence of side effects).
- Alcaftadine, a novel topical antihistamine used for the treatment of allergic conjunctivitis, has antagonistic activity against both the H_1 and H_4 histamine receptor types.
- Further research into the activity of various antihistamines and their activity at the H_4 receptor is needed to determine what future place this receptor may have in the treatment of allergic and inflammatory disease states.

antagonizing the histamine receptor, including its efficacy, length of duration of histamine blockade, and relief of symptoms while minimizing side effects.

BINDING AFFINITY

Antihistamines are believed to work by binding to the active site of the receptor, thereby blocking access of histamine. In order to achieve inhibition, enough of the drug has to be present to prevent the activation of the receptor. If a drug has poor binding affinity, a higher concentration of drug is needed to achieve inhibition compared with a drug that has high binding affinity. Additionally, if a drug has a lower binding affinity for the receptor than histamine itself, theoretically it might require large amounts of drug to outcompete histamine for the receptor site. A comparison of a drug's binding affinity for the targeted histamine receptor in relation to other antihistamines is useful to predict how potent its antihistaminic effect will be [3].

RATE OF ONSET OF DRUG-RECEPTOR INTERACTION/DURATION OF DRUG-RECEPTOR COMPLEXES

The competition between drug and histamine is a dynamic process through time. Both drug and histamine constantly bind to and release from the receptor. The sum total of which compound spends more time 'occupying' the binding site will determine whether the overall effect on the receptor will be stimulation (by histamine) or inhibition (by drug). Two properties that could enhance the efficacy of an antihistamine are: rapid equilibrium and onset of action, and slow dissociation rate from the receptor.

SIDE-EFFECT PROFILE

Many antihistamines are known to have anticholinergic effects that may cause ocular drying through muscarinic receptor inhibition. In some cases, anticholinergic side effects are used favorably for symptomatic relief, such as the case of diphenhydramine in the treatment of insomnia or excessive allergic rhinorrhea.

HISTAMINE RECEPTOR TYPES

Histamine affects nearly every human organ and has a broad range of biological functions that are mediated through the distribution of four types of G-coupled histamine receptors. The effects of histamine binding to different histamine receptors vary based on the location of the receptor and the physiological responses with which it is associated. All four receptors have some constitutive (ongoing) activity, even without histamine bound. The histamine H_1 and H_2 receptors are much more widely expressed throughout the body than H_3 and H_4.

All histamine receptors are heptahelical transmembrane molecules that transduce extracellular signals by way of G proteins to intracellular second messenger systems. These second messenger systems include Ca^{2+}, cGMP in H_1 receptors, cAMP in H_2 receptors and Ca^{2+} and MAP kinase for H_3 and H_4 receptors. The effect histamine has is largely dependent on the expression of specific histamine receptors on different cell types and the location of these receptors in different physiological locations [2]. A summary of histamine receptor types and related effects is shown in Table 1.

Table 1. Histamine receptor types and associated effects

	H_1	H_2	H_3	H_4
Immunomodulatory effects	●	●	●	●
Itching	●			●
Swelling	●			●
Erythema	●	●		
↑ Vascular permeability	●	●		
Pain	●			
Vasodilation		●		
Nasal congestion			●	

H_1 RECEPTOR

H_1 histamine receptors are located in the bronchi, central nervous system (CNS), arterial and intestinal smooth muscle and the heart. Stimulation of H_1 receptors is associated with effects such as inflammation, prostaglandin production, pain, headache, hypotension, tachycardia and bronchoconstriction. The H_1 receptor is the only histamine receptor associated with itching. Studies have shown that H_1 antagonism can prevent the cytokine release and ocular itching associated with allergic conjunctivitis. Further studies demonstrated that vascular permeability is controlled by the H_1 receptor subtype. H_1 receptors are extensively involved in CNS and smooth muscles that underlie some of the side effects seen with oral antihistamines, such as somnolence and cardiac side effects [2]. The signature sedative effect of first generation of oral antihistamines, including compounds such as diphenhydramine and chlorpheniramine, was due to their ability to cross the blood–brain barrier and exert H_1 blocking effects in the CNS [4].

H_2 RECEPTOR

H_2 receptors are located in the parietal cells of the gastric mucosa and are most well known for their role in gastric acid secretion. Members of a class of medications for gastric acid reflux disease, including cimetidine and famotidine, are H_2 receptor inhibitors. H_2 histamine receptors are also located in the heart, uterus, and CNS. When stimulated, H_2 receptors are involved with cytokine production, an increase in vascular permeability, flushing, bronchial smooth muscle relaxation, secretion of gastric acid and various inflammatory effects. The H_2 receptor shares with the H_1 receptor an involvement in vasodilation. A study [5] of stimulated vasodilation in the conjunctiva found this effect was prevented with prior administration of an H_2 antagonist.

H_3 RECEPTOR

The H_3 histamine receptors are primarily found in neurons located in the CNS and peripheral nervous system, in the heart and in bronchioles. These receptors are located presynaptically, and their stimulation inhibits the release of histamine and other neurotransmitters, as well as enhances modulation of the blood–brain barrier. Stimulation of H_3 receptors leads to a decrease in gastric acid production, bronchial relaxation, inhibition of sympathetic neurotransmission and control of vasoactive mediators. Drugs that affect the H_3 receptor are currently being studied for the treatment of insomnia, obesity, inflammatory diseases, schizophrenia and other disease states impacted by neurotransmitter release [6]. There are currently no H_3 agonists or antagonists in clinical use.

Animal models suggest the H_3 receptor also has involvement in nasal congestion, and H_3 blockade may provide relief of congestion symptoms. Combination H_1 antagonism with chlorpheniramine and H_3 antagonism with either chlobenpropit or thioperamide showed significant decongestive effects, although avoiding the common side effect of hypertension seen with most sympathomimetic decongestants [7]. Another study [8] combined fexofenadine, an H_1 receptor antagonist, with a novel H_3 blocking agent and found that superior symptomatic relief was achieved when H_3 receptors were also antagonized. Statistically significant relief of subjective rhinorrhea, itching and sneezing was greater with the addition of an oral H_3 antagonist, and fexofenadine and an H_3 blocker significantly lowered congestion symptom scores compared with placebo. These results support the notion that H_3 receptors are involved in sympathetic transmission and also suggest that oral H_3 antagonists, in combination with H_1-blocking agents, may be of use for the treatment of allergic rhinitis symptoms. These symptoms include nasal congestion, which is not relieved with present antihistamine-only treatment options.

H_4 RECEPTOR

H_4 receptors are found in leukocytes, mast cells and peripheral hematopoietic cells. The stimulation of H_4 receptors leads to mast cell activation, eosinophil recruitment and differentiation of myelocytes and promyleocytes. The H_1 receptor antagonists have little affinity for H_4 receptors, but H_3 antagonists, and some H_2 antagonists, have some affinity for the H_4 receptor. H_4 receptors are involved in autoimmune reactions, allergies, and with the specific symptom of pruritus. Due to its proposed immunomodulating effects, the H_4 receptor is being investigated as a potential target for antiallergy therapy, and experimental compounds that antagonize the H_4 receptor are currently being examined as possible treatments for immune-related disease states such as asthma [9,10]. Antagonists at the H_1 receptor are largely ineffective in asthma, but studies have suggested that blocking the H_4 receptor may control asthmatic symptoms. One study [11] found that H_4-receptor knockout mice had statistically significant decreases in cytokine release and airway inflammation than wild-type mice.

The H_4 receptor is also believed to be involved in itching, and in a murine model, H_4-receptor knockout mice given a dose of histamine or an H_4-receptor

agonist exhibited fewer bouts of scratching compared with wild-type animals [12]. Following injection of histamine or an H_4 agonist, itching was significantly prevented in both groups by pretreating with an experimental H_4-receptor antagonist. No itch relief was seen, if mice were pretreated with H_2-receptor or H_3-receptor antagonists, and significantly less symptom relief was shown with diphenhydramine than with the H_4 antagonist.

It is hypothesized that synergistic control and prevention of symptoms such as itching and inflammation related to allergic disease states can be achieved with combination H_1/H_4 receptor antagonism [4]. The study [12] in murine models with induced pruritus showed statistically significant decreases in scratching when the H_1 antagonist diphenhydramine was administered concurrently with an H_4 blocker, as compared with either agent alone, and scratching that did occur in H_4-receptor knockout mice was eliminated by administering diphenhydramine.

METHODS

We searched the literature for studies regarding binding affinities of antihistamines to the different histamine receptors. A comparison of 19-marketed antihistamines shows differences in receptor affinity and drug potency. A lower binding affinity value (Ki) corresponds to stronger binding affinity of the drug for the receptor. If the binding affinity for the receptor is strong, less of that drug is needed to achieve inhibition of that receptor [2]. The Ki values for each antihistamine, as determined by the studies examined, were compared to determine relative potency among the agents. Comparative potencies of marketed antihistamines for muscarinic receptor inhibition were also examined to determine the likelihood of these agents to cause anticholinergic side effects. It should be emphasized that these binding affinities are from different studies so are not direct comparisons, but some general trends emerge.

DIFFERENTIAL AFFINITIES FOR THE H_1 RECEPTOR

For perspective, the binding affinity of histamine itself for the H_1 receptor is 180 000 nM. Many of the antihistamine drugs evaluated have a much greater binding affinity for the H_1 receptor than does histamine. Thioperamide had the lowest affinity for the H_1 receptor, with a Ki value of 280 000 nM.

Of the antihistamines compared, pyrilamine showed the highest affinity for the H_1 receptor, with a Ki value of 0.8 nM. The first-generation drug diphenhydramine is very potent (Ki = 12.5 nM), but potency is variable among the second-generation compounds. Desloratadine and cetirizine showed the most affinity (Ki = 4 and 6.3 nM, respectively), followed by loratadine (Ki = 35 nM). Fexofenadine had the lowest binding affinity of the second-generation antihistamines and of the H_1 receptor antagonists in general, with a binding affinity value of 83 nM [2].

Among those drugs most recently introduced as topical ophthalmic formulations in the United States (azelastine, epinastine, ketotifen, olopatadine), potency is generally high, with olopatadine having the lowest binding affinity of the group (Ki = 31.6) [13]. Ketotifen and emedastine showed the greatest affinity among the topical antihistamines, with binding affinity values of 1.3 nM for both drugs [2,14].

DIFFERENTIAL AFFINITIES FOR THE H_2 RECEPTOR

The dynamics of drug to H_2 receptor binding may well be different from drug to H_1 receptor interactions. When you compare H_2 binding affinities with H_1 binding affinities, drug affinities for the H_2 receptor are two to four orders of magnitude weaker than for the H_1 receptor.

As with the H_1 receptor, there are substantial differences in the binding affinities of various compounds for the H_2 receptor. Of the antihistamines compared, ranitidine showed the greatest affinity for the H_2 receptor (Ki = 187 nM) [2]. The weakest binding affinity for the H_2 receptor occurred with olopatadine (Ki = 100 000 nM) [13]. Of the various antihistamines compared, only diphenhydramine, azelastine, epinastine and ketotifen exhibited binding affinities in the range of cimetidine, which is a well characterized H_2-receptor antagonist [2].

The binding affinity of a drug in comparison to histamine can predict the drug's ability to compete for the receptor site and produce an antihistamine effect. Histamine's affinity for the H_2 receptor is 18 350 nM. Two drugs, emedastine (Ki = 49 067 nM) nM) and olopatadine (Ki = 100 000 nM), appear to have lower binding affinities for the H_2 receptor compared with histamine, suggesting that a very high concentration of either drug might be required simply to outcompete histamine for binding to the receptor [13,14]. The clinical significance of this is not known.

DIFFERENTIAL AFFINITIES FOR THE H_3 AND H_4 RECEPTORS

The H_3 and H_4 share the most similarities to each other of all the histamine receptors [10]. Of the

compared antihistamines, the highest affinity for the H3 receptor was shown with thioperamide (Ki = 79 400 nM). Olopatadine exhibited the lowest affinity for the H_3 receptor (Ki = 79 400 nM) [13].

Limited data exist regarding binding affinities for the H4 receptor. Only five antihistamines were compared: ketotifen, pheniramine, ranitidine, cimetidine and thioperamide. Affinity for the H_4 receptor was greatest with thioperamide (Ki = 27 nM). Cimetidine and ranitidine exhibited relatively low affinity for H_4 ($Ki \geq 10\,000$ nM) [2]. More study of various drugs and their activity at the H_4 receptor is needed to determine their utility as agonists or antagonists for this receptor and their place, if any, in the treatment of allergic and inflammatory disease states.

DIFFERENTIAL AFFINITIES FOR MUSCARINIC RECEPTORS

Comparison of marketed antihistamines was examined for the M_1 and M_3 muscarinic receptor types as a percentage of the inhibition of intracellular calcium mobilization via acetylcholine activation of the receptor. Antihistamines were tested for anticholinergic activity. For the M_1 receptor, the greatest anticholinergic activity was shown with desloratadine. The ideal antihistamine should have high antihistamine potency against the H_1 receptor, combined with low antimuscarinic activity. See Fig. 1 [15].

SELECTED OPHTHALMIC PREPARATIONS FOR THE TREATMENT OF ALLERGIC CONJUNCTIVITIS

There are several topical options for treating allergic conjunctivitis; below we discuss a selection of ophthalmic antihistamines.

KETOTIFEN

Ketotifen is a strong H_1 receptor antagonist and mast cell stabilizer with leukotriene inhibition. It is, as of this publication, the only antihistamine/mast cell stabilizer topical ophthalmic agent available without a prescription in the United States (Alaway). It is available in a 0.025% formulation and administered twice daily. Ketotifen was found to be effective in prevention of itching, redness and other symptoms of allergic conjunctivitis compared with placebo [16]. A randomized, double-masked, placebo-controlled study [17] compared ketotifen fumarate and emedastine difumarate (an H_1 receptor antagonist) and found they both statistically decreased the incidence of itching compared with

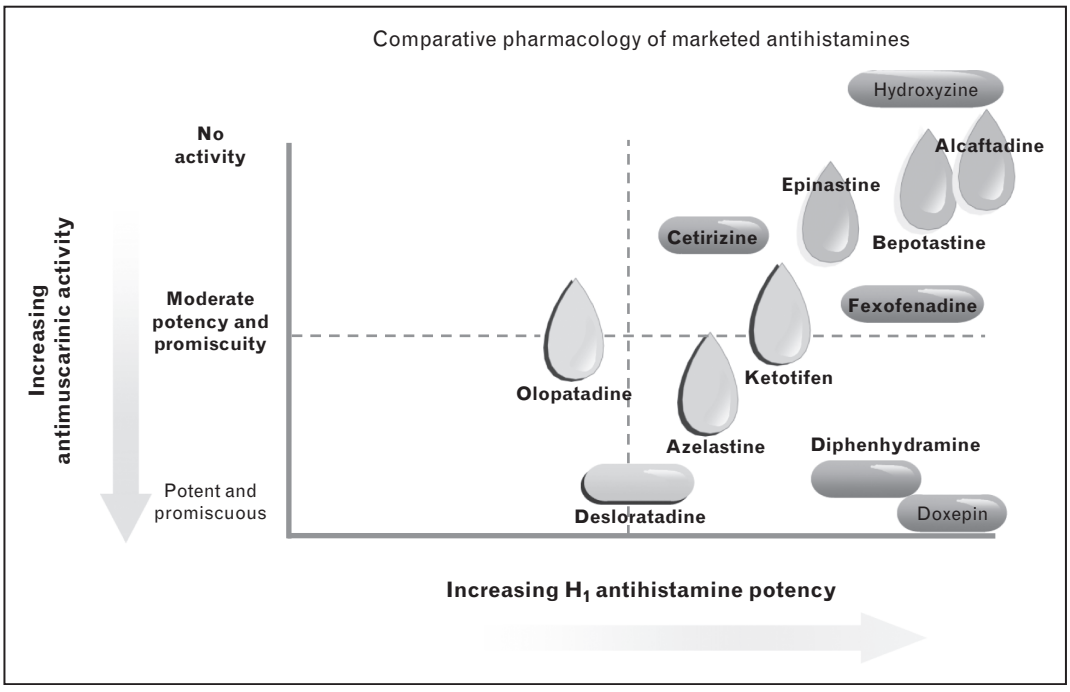

FIGURE 1. Comparative pharmacology of marketed antihistamines. The ideal antihistamine should have high antihistamine potency against the H_1 receptor, combined with low antimuscarinic activity. Note that the Y-axis on this chart displays drug potency and affinity for muscarinic receptor subtypes M1 through M5. The most promiscuous compounds displayed are Clarinex and Zaditor, which interact with all five muscarinic receptor subtypes. Adapted from [15].

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