

Histamine: A mediator of inflammation

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Histamine and its receptors, including the recently discovered receptors (H₃ and H₄), novel sources of histamine, and the place of histamine in mediator networks continue to be areas of great interest. The 4 major subtypes of histamine receptors, H₁ to H₄, differ in their location, second messengers, and histamine-binding characteristics. In addition, it would appear that different histamine receptor agonists and antagonists bind to different portions of the receptor complex. A fifth receptor subtype, the intracellular H_{IC}, has only been defined by its location within cell types that are not traditionally associated with histamine. In airway tissue, most cells express at least 1 subtype of histamine receptor; however, blockade of these receptors does not completely abolish the inflammatory response. In addition, some H₁-antihistamines might also exert anti-inflammatory effects by pathways independent of H₁-receptor binding. Studies of selected second-generation H₁-antihistamines have shown that these agents inhibit the release of certain cytokines from basophils, acting at a point downstream from the calcium signaling pathway. It has not yet been determined whether this action represents a class effect. (*J Allergy Clin Immunol* 2003;112:S53-9.)

Key words: Antihistamines, receptors, cytokines, mast cells, basophils, calcium signaling

In an evolutionary sense, histamine is probably an ancient mediator, and it is likely that biologic systems have been using molecules such as histamine, catecholamines, and other simple chemical mediators derived from amino acids to communicate among cells for long time periods. The synthesis of histamine in 1907 and its characterization in 1910 by Barger and Dale¹ as a substance ("beta-1") capable of constricting guinea pig ileum were the result of a century of exploration into the notion that simple chemicals could mediate complex biologic reactions. This notion was also the starting point for the formation of the pharmaceutical industry that had been developing during the 19th century. However, it required another 17 years to demonstrate the presence of histamine in normal tissues, with Best et al² noting its marked concentration in lung tissue. The connection between histamine and anaphylactic reactions was made rapidly by Dale³ in 1929, whereas the link to mast cells was not made until 1952⁴ and the link to basophils in 1972.⁵

The development of the receptor theory paralleled the progress in chemical mediator research. From the side-chain theory of immunity put forth by Ehrlich in 1897 to

Abbreviations used

cAMP: Cyclic adenosine monophosphate
GTP: Guanosine triphosphate
HDC: Histidine carboxylase
LT: Leukotriene

the modern view of ligands and receptors, both on the cell surface and within the cell, the pharmaceutical industry has successfully treated many medical conditions by adhering to the idea that a ligand's receptor is a target for therapy. The search for antihistamines began at the Pasteur Institute during the 1930s, and a variety of compounds based on the ethylenediamine structure were found to partially block the effects of histamine. By 1942 the first antihistamine, antergan, was being used in humans.⁶ By 1950 there were 20 compounds clinically available to block the effects of histamine.

LOCALIZATION OF HISTAMINE

With such a long history, it is easy to conclude that there is not much to learn about histamine or its receptors. Indeed, *PubMed* lists more than 53,000 articles for the key word *histamine*; some 8,000 articles explore histamine receptors, and another 9,000 articles discuss antihistamines since 1966 alone. However, there remain some important aspects in this field that are yet to be fully appreciated. These include the nontraditional sources of histamine, a new receptor (with others still possible), and the particularly thorny issue of mediator networks.

The role of histamine in biologic reactions could be reduced to the phrase, "follow the histidine decarboxylase (HDC)." This might be a good approach because mast cells are widely distributed and can contaminate most tissues with fairly high concentrations of histamine. Thus, measuring histamine in a particular tissue always carries with it the potential risk that a few difficult-to-exclude mast cells are being measured rather than a novel source of histamine. This is also true in the study of histamine in nonbasophilic leukocytes. In addition, if the concentrations of histamine found in nontraditional sources are any indication, then measuring and localizing histamine itself can be difficult without sophisticated technology. Instead, "following HDC" allows one to use sensitive molecular biologic techniques (which might arguably be better for localizing a protein) at least to determine the possibility of the presence of histamine.

There are 3 well-described sources of histamine in humans: mast cells and basophils, gastric enterochromaffin-like cells, and histaminergic nerves in the brain. Remarkably, if all the mast cells dispersed throughout the human body were assembled into a discrete organ, it

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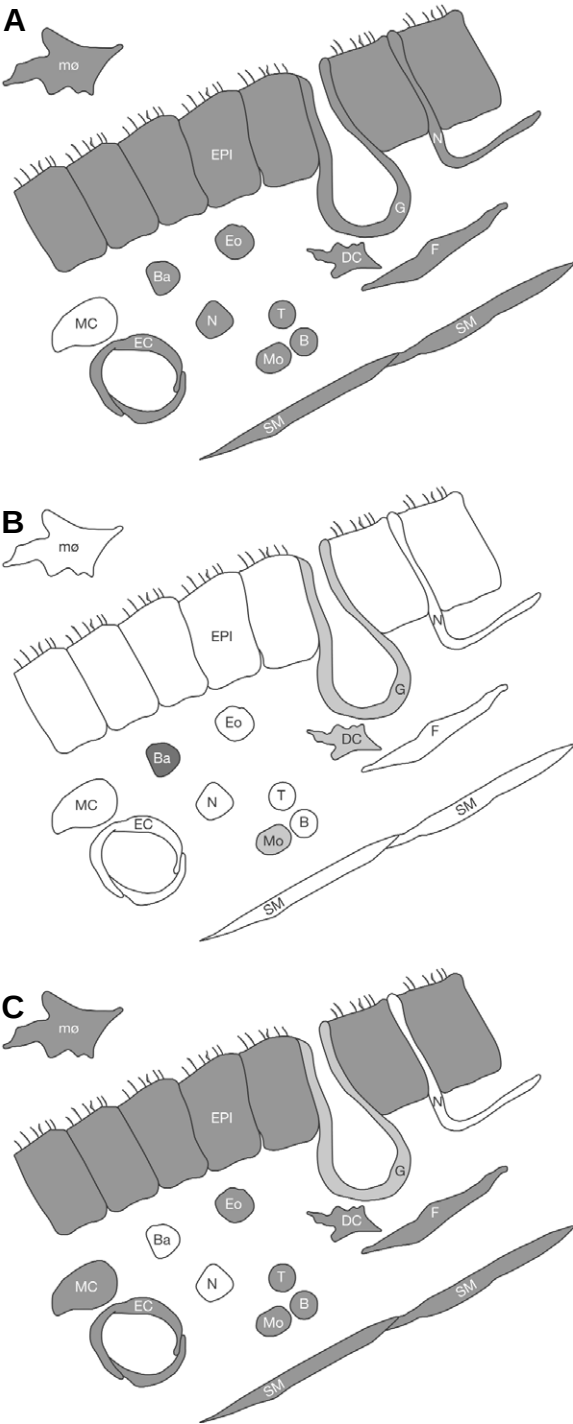


FIG 1. Tissue and inflammatory cells in the airway. A simplified representation of a tissue mucosal interface is shown, including both resident cells and migrating leukocytes. **A**, Distribution of histamine receptors (any subclass, H_1 - H_4); **B**, receptors for IL-3; and **C**, receptors for IL-4. *Dark gray* signifies the presence of a receptor (for human cells only); *white* signifies no current evidence of a receptor; *light gray* signifies either that it has not yet been examined or that it might be induced. *Mφ*, Macrophage; *EPI*, epithelial cell; *MC*, mast cell; *EC*, endothelial cell; *Ba*, basophil; *Eo*, eosinophil; *N*, neutrophil; *Mo*, monocyte; *T*, T cells; *B*, B cells; *DC*, dendritic cells; *F*, fibroblasts; *SM*, smooth muscle cells; *G*, gland cells (undefined); *N*, nerves.

TABLE I. Sources of histamine

	Relative to basophils
Platelets	1/100,000 (1/1,000 for equivalent cell volume)
Monocytes	1/100
Lymphocytes	1/100–1/1,000

would be about the size of a child's fist (~100 mL). Basophils could be assembled into a volume of approximately 1 mL; although this is considerably smaller, it is also a significantly more mobile source of histamine. For many years there have been persistent observations of histamine in other, nonbasophilic, circulating cells; lymphocytes, monocytes, and platelets appear to contain very low levels of histamine (Table I).⁷⁻¹⁰ The significance of this observation will be covered in more detail later.

In addition to reports of histamine in circulating cells, several studies suggest that a variety of tissue cells might be affected by histamine in an ill-defined way.^{11,12} Particularly intriguing are reports that HDC levels increase in the skeletal muscle of mice after exercise.¹³ These changes occur in W/Wv mice, which should lack mast cells. Again, there remains a great deal of work to be done to validate these observations and to understand their significance, but it should be noted that this line of investigation is motivated by "following the HDC." Furthermore, it remains to be determined whether HDC in these situations is acting solely on histidine or whether other substrates are involved.

HISTAMINE RECEPTORS

The significance of histamine as a mediator can be derived from cataloging the cell types that express histamine receptors (Fig 1). With the exception of the mast cell, every cell type expresses one type of histamine receptor. In this context, it should be noted that the figure represents human tissue and, whereas rodent mast cells appear to express histamine receptors,^{14,15} expression of a histamine receptor has not been adequately demonstrated on human mast cells to date.¹⁶ However, this is likely a highly qualified statement because the search for a histamine effect has been minimal and it would not be expected that human mast cells do express a histamine receptor.

Histamine receptors are among the thousands of members (when including olfactory receptors) of the 7-transmembrane-spanning family of receptors that couple ligand binding to intracellular reactions through interactions with another large family of guanosine triphosphate (GTP)-binding heterotrimeric proteins. H_1 -receptors mediate a host of intracellular events most readily characterized by changes in free cytosolic calcium levels, whereas H_2 -receptors mediate an intracellular response most readily characterized by elevations in cyclic adenosine monophosphate (cAMP). The 2 newer family members, H_3 and H_4 , operate by a variation on these 2 themes but have the additional effect of decreasing cAMP levels (Table II).

TABLE II. Histamine receptor subtypes

Receptor type (classified)	Cloned	K _d	Location	Second messenger
H ₁ (1966)	1991	~10 μmol/L	Widely distributed	Ca ²⁺
H ₂ (1972)	1991	~30 μmol/L	Widely distributed	cAMP
H ₃ (1983)	1999	~10 nmol/L	Brain	cAMP/Ca ²⁺
H ₄ (1994)	2000	20-40 nmol/L	Hematopoietic, intestines	Ca ²⁺
H _{1C} (circa 1992)		~μmol/L	Hematopoietic	Is a second messenger?

K_d, Equilibrium constant for dissociation.
For H₃-receptors, inhibition of cAMP occurs. For H_{1C} “receptors,” the affinity is not entirely clear and histamine is presumably the second messenger.

Cloning receptors is a necessary step in understanding how they work, but there have been no x-ray crystallography studies of ligand binding performed for these receptors. Mutation studies have demonstrated some of the characteristics of histamine binding to H₁-receptors. Although this kind of approach must be interpreted cautiously, histamine appears to interact with amino acids located in the TM3 and TM5 transmembrane segments of the receptors, which is similar to the binding of catecholamine to its receptors. For example, mutation of lysine 200 to alanine in the TM5 region, located in the alpha helix loop proximal to the outer leaflet of the membrane, results in a 100-fold shift in histamine potency.¹⁷ Curiously, different histamine agonists and antagonists appear to use portions of the receptor for interaction, suggesting that there are many possible ways of inducing a functional conformational change in the receptor.¹⁸

Several groups have cloned a similar protein that, in cell lines, has the properties of a histamine receptor; this has been identified as the H₄-receptor.¹⁹⁻²³ Similar to the H₃-receptor but unlike H₁ and H₂, the K_d for histamine of the H₄-receptor is quite high (between 30 and 40 nmol/L). The H₄-receptor is particularly intriguing because it has similar properties to those of a previously characterized receptor. For example, one previous study showed that when histamine was applied to eosinophils, an elevation in intracellular calcium occurred.²⁴ However, unlike H₃-receptors, R-α-methyl histamine was 17-fold less potent than histamine as an agonist. This and other properties are shared with the cloned H₄-receptor (Table II). Given that H₁- and H₂-receptor antagonists have been successful therapeutic tools, the characterization of a new histamine receptor with primary expression outside the brain is an exciting development. However, the role of this receptor in modulating an immunologic reaction (or other unknown functions) has yet to be determined.

There is also a fifth category including ill-defined histamine receptors such as an intracellular receptor currently labeled H_{1C}. Its existence has thus far only been inferred by the presence of low amounts of histamine in cells not traditionally thought to contain histamine, as described above. Despite the fact that the levels of histamine in these cells are only 1/100 to 1/1000 of those found in basophils, the cytosolic concentration appears to be in the order of 100 μmol/L. This is much higher than the K_d of H₁- and H₂-receptors for histamine and 4 orders of magnitude above the concentrations required to activate H₃- or H₄-receptors.

The importance of histamine in regulating the function of lymphocytes, monocytes, or platelets has been inferred from previous studies.^{10,25,26} Because HDC is necessary for the synthesis of histamine, the use of α-fluoro-methyl histidine provides a relatively specific means with which to inhibit its production. The compound N,N-diethyl-2-4-(phenylmethyl) phenoxyethan-amine-HCl has been characterized as an inhibitor of the H_{1C} “receptor” and as a cell permanent antagonist that can be used in conjunction with α-fluoro-methyl histidine to define the functional role of intracellular histamine. Surprisingly, cells such as lymphocytes also express extracellular-oriented H₁-receptors,²⁷⁻²⁹ and studies appear to show that histamine on the outside of the lymphocyte inhibits its proliferation, whereas histamine on the inside augments proliferation. Clearly, a great deal of additional work is needed to understand the specifics of this reaction and its application to intracellular signaling in a potential host of other cell types.

NETWORKS

During the last 2 decades, investigators have been assembling a picture of the complexity of the intercellular communication network. This complexity results from a plethora of mediators and a great redundancy in their actions. Recent research efforts have focused attention on the identification of cytokines and chemokines; the resulting network of cellular interactions mediated by these molecules is not fully understood. Although this network is daunting in its complexity, it is made more so by the inclusion of smaller chemical mediators like histamine.

It is a useful exercise, if only to gain some perspective, to enumerate the various types of receptors on tissue cells and the hematopoietic cells that migrate into these tissues. As noted above, Fig 1 shows a simple representation of airway tissue. Although nearly every cell type expresses histamine receptors, the receptor for IL-3 (a cytokine with known importance in allergic inflammatory reactions) appears far more restricted in its distribution. Other simple chemical mediator receptors might be broadly expressed, but this characteristic is not exclusive to simple molecules. Remarkably, another mediator of allergic inflammation, IL-4, also has a wide variety of targets (Fig 1, C).

With the large number of histamine antagonists available, one might think that it would be easy to study the general role of histamine in the evolution of an inflammatory

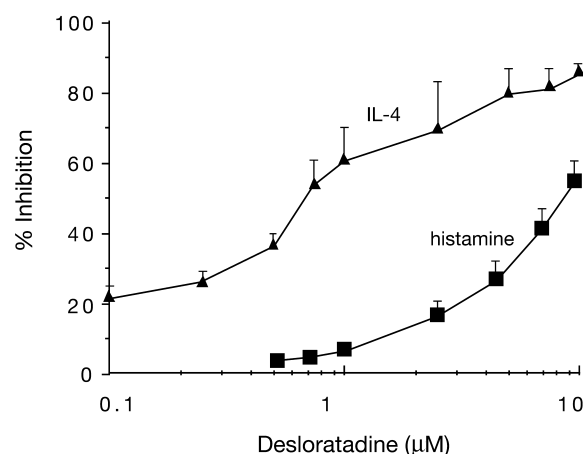


FIG 2. Effect of desloratadine on IL-4 and histamine secretion from human basophils stimulated with an optimal concentration of anti-IgE antibody ($n = 5$). Histamine release in the absence of drug was $40\% \pm 6\%$, and IL-4 release was 403 ± 207 pg/ 10^6 basophils. Cells were incubated with or without drug for 15 minutes before stimulation. Adapted with permission from Schroeder JT, Schleimer RP, Lichtenstein LM, Kreutner W. Inhibition of cytokine generation and mediator release in human basophils treated with desloratadine. *Clin Exp Allergy* 2001;31:1369-77.⁴³

reaction by using histamine antagonists that are specific for each receptor subtype. However, it is increasingly being recognized that many H_1 -antihistamines alter cellular functions by means that do not involve H_1 -receptor binding.

PHARMACOLOGY OF THE H_1 -ANTIHISTAMINES UNRELATED TO RECEPTOR BINDING

It was noted 25 years ago that first-generation H_1 -antihistamines could inhibit IgE-mediated secretion of histamine from basophils.³⁰ Because these cells do not appear to express the H_1 -receptor, these effects were likely due to alterations in signal processing in the cells. Since then, both first- and second-generation compounds have been found to demonstrate a wide variety of effects not attributable to H_1 -receptor binding; Table III summarizes some of these effects studied for basophils and mast cells.³¹⁻⁴² The list would be much longer if effects on other cell types were considered. In general, however, inhibition of cellular functions occurs at antihistamine concentrations that are significantly higher than their ability to saturate H_1 -receptors and outside the therapeutic range (typical inhibitory concentration of 50% values, 10 to 50 $\mu\text{mol/L}$). This has probably slowed down the search for altered signaling pathways, as well as a more serious discussion of the potential therapeutic benefits of this aspect of antihistamine pharmacology. However, the number of functional end points used to study inflammatory cell function is steadily increasing, opening up the possibility of selective inhibition of these functions by H_1 -antagonists.

One example can be found in a recently published study of cytokine secretion from human basophils.⁴³ A Schering-Plough supported study found that desloratadine was

significantly more potent at inhibiting IgE-mediated IL-4 and IL-13 secretion from human basophils than histamine or leukotriene C_4 (LTC_4) release. Fig 2 shows that the inhibition of IL-4 secretion appears to be biphasic. The inflection point between the 2 apparent superimposed inhibition curves is ~ 1 $\mu\text{mol/L}$. The higher end of this unusual curve appears to be similar to that for the inhibition of histamine release. Notably, 20% inhibition of IL-4 secretion occurred with 100 nmol/L desloratadine.

In 1988 we examined the ability of azelastine to inhibit both histamine release and the cytosolic calcium elevation that follows stimulation through the IgE receptor. Fig 3 shows the results for both human basophils and human lung mast cells stimulated with an optimal concentration of anti-IgE antibody. Notably, inhibition of either histamine release or the cytosolic calcium response was similar and typical of the many studies with this class of compound. IL-4 secretion is a process that appears very sensitive to changes in cytosolic calcium, but the azelastine results, if found similar for desloratadine, would suggest that the lower concentrations required to inhibit IL-4 secretion are not a result of inhibition of the cytosolic calcium response. Supporting this interpretation, Schroeder et al⁴³ also found that desloratadine was a very effective inhibitor of ionomycin-induced IL-4 secretion from basophils; 0.1 $\mu\text{mol/L}$ desloratadine inhibited stimulation of IL-4 secretion induced by 0.5 $\mu\text{g/mL}$ ionomycin by 40%. Because this stimulus bypasses all the normal means of elevating cytosolic calcium, inhibition of signaling by desloratadine probably occurs downstream of the calcium signal. Desloratadine also inhibited IL-13 secretion induced by either anti-IgE antibody or IL-3. This is particularly interesting because IL-13 secretion involves a non-FK506-sensitive pathway, whereas secretion of IL-4 is very sensitive to FK506.

The conclusion from this result is less clear, but it suggests that the point of action of the drug lies downstream in the cytokine-signaling pathway. Although it has not been firmly established that IgE-mediated IL-4 secretion results from increased transcription of the IL-4 gene, indirect evidence supports such a conclusion. Therefore, it is interesting to note that desloratadine also markedly inhibits accumulation of mRNA for IL-4, which would then suggest that it inhibits IL-4 gene transcription. These results indicate that at concentrations of drug that could be found under therapeutic conditions, there is partial inhibition of cytokine secretion from basophils. It should also be kept in mind that these studies were done under conditions of optimal stimulation. Studies by Tung and Lichtenstein⁴⁴ demonstrated clearly that at levels of suboptimal stimulation—levels that might better represent the average situation in vivo—most drugs are significantly more efficacious inhibitors.

Similarly, it should be noted that fexofenadine has been shown to reduce cytokine release from ex vivo human macrophage cultures and from an in vivo mouse model of airways hyperresponsiveness and inflammation (refer to articles by Marone et al and Gelfand et al, respectively, in this supplement for more details).

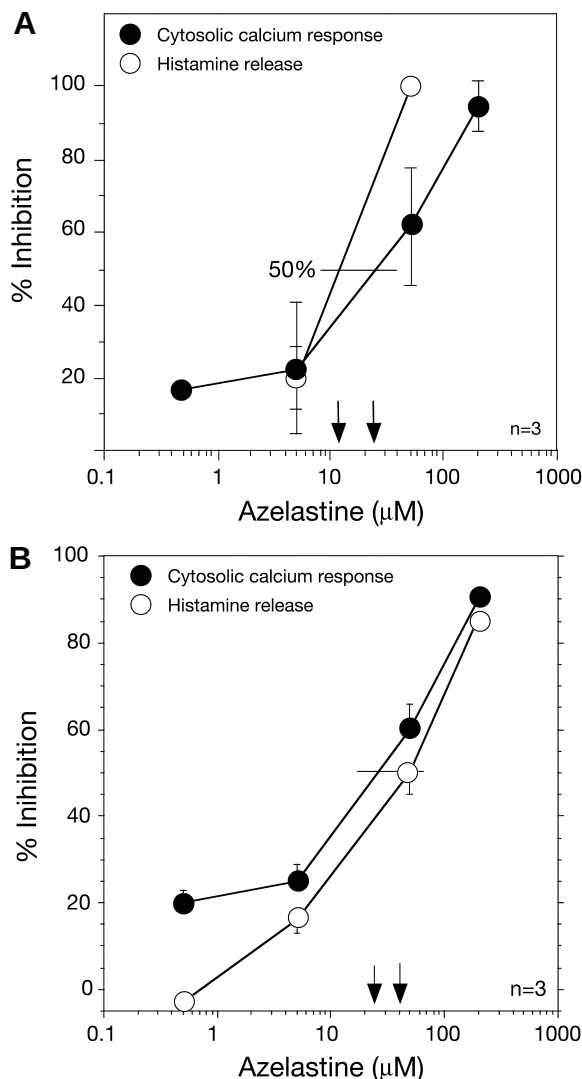


FIG 3. Effect of azelastine on the cytosolic calcium response or on histamine release from basophils or mast cells stimulated with an optimal concentration of anti-IgE antibody. Cells were labeled with fura-2 and analyzed for free cytosolic calcium by digital microscopy. The average net calcium elevation for the first 15 minutes of the reaction was determined from a field of 30 to 100 cells. For cells treated without azelastine, dimethyl sulfoxide at a relevant concentration was used as a control. Histamine release was determined from the supernatants obtained from the microscope chamber from which the calcium measurements were made. **A**, Basophil studies (0.5 µg/mL anti-IgE antibody); **B**, purified human lung mast-cell studies (3 µg/mL anti-IgE antibody).

One important issue that needs to be addressed is whether these anti-inflammatory properties represent a class effect. The literature is unclear on this point when considering the inhibitory effects of antihistamines at higher concentrations. There are indications that isolated H_1 -receptor antagonists do not display strong inhibitory effects.⁴¹ Therefore, this aspect needs to be explored in the context of cytokine secretion. Given the nature of the effect, it would not be surprising to find that this was not a class effect and that a particular attribute of some of these H_1 -receptor antagonists alters a signaling step by a

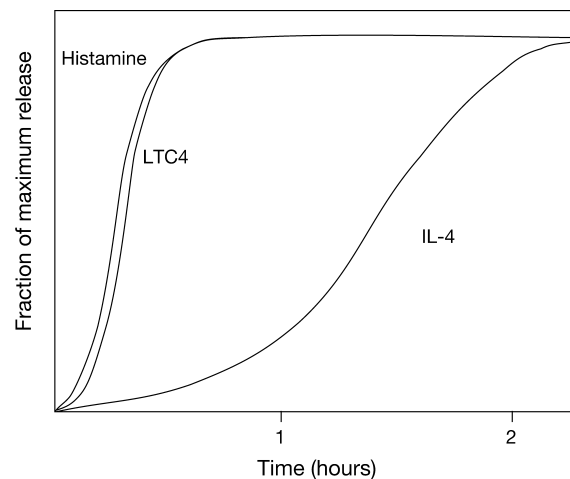


FIG 4. Idealized representation of mediator release kinetics from human basophils. The 3 major classes of mediators are represented: histamine (preformed), LTC_4 (newly generated without protein synthesis), and IL-4 (newly generated with protein synthesis).

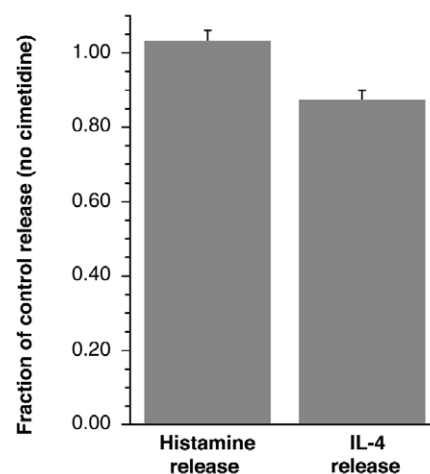


FIG 5. Effect of cimetidine (10 µmol/L) on histamine or IL-4 secretion from human basophils stimulated with an optimal concentration of anti-IgE antibody (n = 2). Cimetidine (or control vehicle) was added 10 minutes before stimulation. IL-4 and histamine were measured 4 hours later.

novel mechanism that could be exploited by further pharmaceutical chemistry. Indeed, under normal circumstances some antihistamines might be considered lead compounds for the inhibition of cytokine secretion.

FEEDBACK INHIBITION BY H_2 -RECEPTORS

In the context of IL-4 secretion from human basophils, it should be noted that there is a possibility that basophil-secreted histamine acts in a negative feedback loop through the cell's surface H_2 -receptors to downregulate IL-4 secretion if the cell density is high enough. Bourne et al⁴⁵ and Lichtenstein and Gillespie⁴⁶ showed that the addition of histamine only minutes after the onset of an IgE-mediated reaction has little effect on the ongoing reaction (whereas it inhibits release by 40% to 70% if

TABLE III. Studies of H₁-receptor antagonists on effects unrelated to receptor binding

Cell type	Drug	Effect	Publication
Basophils	Loratadine	Inhibit H, LTC ₄	Miadonna et al, 1994 ³¹
		Inhibit LTC ₄ , not H	Ramachers et al, 1994 ³²
	Azelastine	Inhibit H	Little et al, 1989 ³³
	Astemizole	±LTC ₄ , not H	Ramachers et al, 1994 ³²
	Oxatamide	Inhibit H, LTC ₄	Patella et al, 1996 ³⁵
Lung tissue		Inhibit LTC ₄ , not H	Ramachers et al, 1994 ³²
	Ketotifen	Inhibit H	Ramachers et al, 1994 ³²
	Loratadine	Inhibit LTC ₄ , not H	Temple et al, 1988 ³⁶
	Azelastine	Inhibit H	Little et al, 1989 ³⁴
	Astemizole	±H	Awouters et al, 1983 ³⁷
	Cetirizine	Inhibit H	Church et al, 1996 ³⁸
		Inhibit H, LTC ₄ , prostaglandin D ₂	Fabre et al, 1995 ³⁹
Lung or skin mast cells	Ketotifen	Inhibit H	Church et al, 1996 ³⁸
	Loratadine	Inhibit H, LTC ₄	Genovese et al, 1997 ⁴¹
	Azelastine	Inhibit H	Bolsmann et al, 1996 ⁴²
	Cetirizine	Inhibit H	Church et al, 1996 ³⁸
	Oxatamide	Inhibit H, LTC ₄ , prostaglandin D ₂	Patella et al, 1996 ³⁵
	Terfenadine	Inhibit H	Church et al, 1996 ³⁸

applied before the stimulus). However, as Fig 4 shows, IL-4 secretion is a late event, occurring long after histamine and LTC₄ secretions are complete. Furthermore, it has been shown that, despite the fact that histamine and LTC₄ secretions are complete, there remains a requirement for aggregated FcεRI on the cell surface for secretion of IL-4 to occur.⁴⁷ This implies a requirement for early signaling events to sustain the pathway leading to IL-4 secretion. Because H₂-receptor occupancy results in elevation of cAMP and an elevation in cAMP results in the downregulation of cytosolic calcium response,⁴⁸ it remains possible that secreted histamine could feed back to partially inhibit IL-4 secretion. Studies in rat peritoneal mast cells support such a hypothesis, in which addition of ranitidine enhances IgE-mediated TNF-α release.⁴⁹ A similar experiment in basophils pretreated with 10 μmol/L cimetidine did not significantly alter either histamine or IL-4 release induced by anti-IgE antibody (Fig 5).

SUMMARY

It is evident that some interesting issues remain regarding histamine and its receptors. The wide distribution of receptors for histamine, as well as the wide distribution of mast cells and mobile basophils within the body, suggest that histamine is an important regulator of a wide variety of functions. As with other aspects of the complex regulatory network involving cytokines and chemokines, the exact meaning of the extensive presence of histamine receptors has yet to be determined.

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