Histamine Receptors and Antihistamines: From Discovery to Clinical Applications

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Abstract

The synthesis and the identification of histamine marked a milestone in both pharmacological and immunological research. Since Sir Henry Dale and Patrick Laidlaw described some of its physiological effects in vivo in 1910, histamine has been shown to play a key role in the control of gastric acid secretion and in allergic disorders. Using selective agonists and antagonists, as well as molecular biology tools, four histamine receptors (H\textsubscript{1}R, H\textsubscript{2}R, H\textsubscript{3}R and H\textsubscript{4}R) have been identified. The Nobel Prize in Physiology and Medicine was awarded to Daniel Bovet in 1957 for the discovery of antihistamines (anti-H\textsubscript{1}R) and to Sir James Black in 1988 for the identification of anti-H\textsubscript{2}R antagonists. Anti-H\textsubscript{1}R and anti-H\textsubscript{2}R histamine receptor antagonists have revolutionized the treatment of certain allergic disorders and gastric acid-related conditions, respectively. More recently, anti-H\textsubscript{3}R antagonists have entered early-phase clinical trials for possible application in obesity and a variety of neurologic disorders. The preferential expression of H\textsubscript{4}R by several immune cells and its involvement in the development of allergic inflammation provide the rationale for the use of anti-H\textsubscript{4}R antagonists in allergic and in other immune-related disorders.

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logical properties continue to accumulate day by day. In the present chapter, we will review this extraordinary story with a special emphasis on its implications in allergy and clinical immunology.

### The Discovery of Histamine

In 1907, Windaus and Vogt [1] chemically synthesized and, in 1910, Ackermann [2] isolated histamine as a metabolite of bacterial histidine fermentation. Henry Dale, a young pharmacologist at Sir Wellcome’s research laboratories in London, was working on ergot fungi extracts that were used for the treatment of postpartum bleeding. Dale’s mission was to identify the active ingredient(s) responsible for this activity [3]. Dale had the intuition that a novel substance could have a much higher contractant activity on the uterus than all those identified so far. Watching a demonstration of the new in vitro assay for uterus contraction developed by Kehrer, a German obstetrician, he realized that the so-called ‘ergotinum dialysatum’ of Wernich was much more potent than ergot itself. With the help of the chemist George Barger, Dale isolated a new base from ergotinum dialysatum that could replicate the effect of the dialysatum on a cat uterus [4, 5].

In 1910, Dale and Laidlaw reported the first physiological characterization of β-imidazolyl ethylamine, the chemical formula of histamine [6]. This work remains a milestone in pharmacology for its exhaustive experimental approach and for the tremendous impact it had on future research. They demonstrated that this molecule caused vasodilatation, the contraction of smooth muscles in the airways, uterus and the intestine, stimulated heart rate and contractility, and induced a shock-like syndrome when injected into animals.

During the following decade, the effects of histamine administration were intensively investigated. In 1920, Popielski [7] reported that histamine also affects the activity of the stomach by potently stimulating hydrochloric acid secretion in the dog. In 1924, Lewis and Grant [8] described the classic ‘triple response’ elicited by the subcutaneous injection of histamine consisting of a red spot due to vasodilatation, a wheal which was the consequence of increased permeability and flare due to an axon reflex.

During the first 20 years after the synthesis of histamine, it was unclear whether this mediator could have any physiological role. In 1927, C.H. Best et al. [9] isolated crystalline histamine from liver and lungs, providing formal evidence that histamine is physiologically present in the body. Later, W. Feldberg and coworkers [10–12] provided compelling evidence that histamine is a mediator of experimental anaphylaxis. In 1952, J.F. Riley and G.B. West [13, 14] demonstrated that mast cells are the predominant cellular source of histamine. Subsequently, basophil leukocytes were identified as the main source of histamine among blood cells [15].

### The Synthesis of the First Antihistamines and the Identification of H1R

In 1937, while working in the laboratory of Ernest Fournier at the Institut Pasteur in Paris, Daniel Bovet started a research program aiming to identify new drugs that could block the actions of histamine. Bovet tested several compounds that were part of the large collection of molecules previously synthesized by Fournier [16]. He described two benzodioxanes, compound 883 F and compound 933 F, which were slightly effective in preventing histamine shock in guinea pig [17–19]. Based on these results, twenty congeners of these compounds were synthesized leading, in 1937, to the identification of the first potent histamine antagonists, thymoxyethyldiethylamine (929 F) [20] and N,N’-diethyl-N’-phenyl-N’-ethylene diamine (1571 F) [21]. Unfortunately, these compounds proved to be too toxic for clinical development. More effective and better-tolerated compounds were soon developed by chemical modification of their structure. Bernard Halpern [22] first used N’-dimethylethyldiamine clinically, which matched the requirements of safety and efficacy for clinical development in humans. It has been marketed since 1942 by Rhone-Poulenc under the brand name of Antergan. This compound was soon replaced by its derivative, mepyramine, which was marketed under the brand name of Neo-Antergan and for years represented the gold standard of histamine H1R antagonists.
The Identification of H₂R and the Synthesis of the First H₂ Blockers

In the late 1940s, it became clear that some of the actions of histamine were refractory to inhibition by classical antihistamines. In particular, mepyramine did not block the effects of histamine on heart rate and on gastric hydrochloric acid secretion [23, 24]. In 1948, Folkow et al. [25] first suggested that two different classes of histamine receptors should exist because the antihistamine blocker Benadryl could block the vasodilator effect of low, but not of high concentrations of histamine. A limitation of those studies was the absence of a mathematical model to analyze the interactions between increasing concentrations of agonists (e.g. histamine) and antagonists (e.g. antihistamines). In 1947, Hans Schild [26] described a mathematical method for the evaluation of drug antagonism (the pA² value). In particular, he evaluated the effects of two antihistamines (Neo-Antergan and Benadryl) on histamine-induced ileum contraction. By applying the pA² method, Ash and Schild [27] showed that H₁R antagonized by meperidine and diphenhydramine mediate the effects of histamine on intestinal and uterine tone. Whilst not specifically stated in their 1966 paper, the results implied that other receptor(s) could be responsible for the histamine effects insensitive to classical antihistamines.

The discovery of histamine H₂R is linked to the name of the Nobel Laureate Sir James Black [28]. He hypothesized that anti-H₂ drugs should be more similar to histamine because anti-H₁ compounds were significantly different to histamine. Therefore, the idea behind the project was to modify the molecule of histamine. This approach led to the identification of burimamide that blocked histamine effects on both the beating guinea pig atrium and the rat gastric acid secretion [29]. These findings, communicated in a classical paper in Nature in 1972 [29], provided the first pharmacological demonstration of H₂R distinct from H₁R. After burimamide, several other H₂R antagonists were developed that revolutionized the treatment of peptic ulcer [28, 30, 31].

Evidence that histamine acting through H₂R induces both a Gₛ-dependent increase in intracellular cAMP concentrations and a G₉-dependent increase in [Ca²⁺], was obtained in different tissue and cell preparations, including gastric mucosal cells, vascular smooth muscle cells, brain slices and adipocytes [32]. In 1973, Lichtenstein and Gillespie [33] reported that H₂R are functionally present on human basophils. Subsequently, H₂R were found on rodent mast cells [34], human eosinophils [35, 36] and human neutrophils [37].

Histamine in the Brain

When Antergan entered clinical use, it was reported that it induced marked sedation. It soon became clear that this characteristic was typical of the entire class of the first generation of anti-H₁ drugs. In 1943, Kwiatkowski found small amounts of histamine in different brain regions. With the development of antibodies directed against histidine decarboxylase, different groups mapped histaminergic neurons and their projections in the brain [38–41]. Histaminergic neurons are localized in the tuberomammillary nucleus of the hypothalamus, project to all major areas of the brain, and are involved in several functions including the regulation of sleep/wakefulness, feeding and memory processes. The presence of histaminergic neurons and H₁R in the brain underlies the sedative effects of the classical H₁ antagonists. There are also H₂R in the brain, but their functions are more limited compared to H₁R and H₃R [42].

In 1983, Jean-Charles Schwartz and colleagues [43] reported that histamine does inhibit its own release in the isolated rat brain cortex. This histamine inhibitory activity was mimicked with a higher potency by Nα- and Nα,Nα-methylhistamine, two compounds weakly effective on H₁R and H₂R; in addition, H₁R or H₂R agonists, as well as H₁R antagonists, were ineffective [43]. Conversely, several H₂ blockers, like burimamide, and the H₂R partial agonist impromidine, antagonized histamine release autoinhibition [43]. These effects were observed at concentrations much higher than those required to block H₂R. Importantly, Schild plot analysis demonstrated that these effects could not be explained as an action on H₂R [43]. Based on these findings it was proposed that an H₃R could exist in the brain. The
same group reported the synthesis of selective ligands for \( H_3 \)R, including the agonist \((R)-\alpha\)-methylhistamine and the antagonist thioperamide [44]. Using selective \( H_3 \)R agonists and antagonists it was shown that signal transduction by the \( H_3 \)R is mediated by pertussis toxin-sensitive \( G_i/G_o \) proteins leading to a decrease in intracellular cAMP concentrations [45, 46] and to a decrease in extracellular Ca\(^{2+}\) influx in neurons [47].

The group of Manfred Göthert showed that \( H_3 \)R also inhibit the release of other neurotransmitters, including noradrenaline and serotonin [48–52]. Thus, histamine \( H_3 \)R modulate neurotransmitter release acting as presynaptic autoreceptors or heteroreceptors.

There is compelling evidence that \( H_3 \)R could be involved in several neurological diseases like sleep-wake disorders, Alzheimer’s disease and cognitive disorders, as well as in obesity [53]. Several \( H_3 \)R agonists and inverse agonists/antagonists have been synthesized and some of these compounds are now being tested for therapeutic use in neurological disorders and obesity [53, 54].

Cloning of \( H_1 \)R, \( H_2 \)R and \( H_3 \)R, and Generation of Histamine Receptor Knockout Mice

Molecular biology entered the field of histamine pharmacology in the 1990s with the cloning of histamine receptors and the generation of histamine receptor knockout mice. In 1991, Gantz et al. [55] cloned the canine \( H_2 \)R gene. Molecular biologists in different laboratories were rapidly successful in cloning the \( H_2 \)R gene from other species, including human [56], rat [57] and guinea pig [58]. Once the \( H_2 \)R cDNAs were cloned, detailed studies on the tissue distribution of these receptors became possible, confirming and extending previous functional data showing that these receptors are highly expressed in a variety of tissues and immune cells [59–61].

Cloned \( H_2 \)R were heterologously expressed for signal transduction and structure-activity studies. The group of Henk Timmerman [62] demonstrated that recombinant rat \( H_2 \)R heterologously expressed in CHO cells have a spontaneous activity that can be inhibited by \( H_2 \) antagonists. This observation was made when the allosteric theory of receptor activity was rapidly becoming popular after the seminal work on mutant adrenergic receptors by Robert Lefkowitz et al. [63]. Following the publication of Timmerman’s paper, \( H_2 \) antagonists became the paradigmatic example of inverse agonists in pharmacology. It should be noted that, similar to the Schild plot analysis, another fundamental concept in pharmacology found a relevant application in histamine research.

In 2000, Kobayashi et al. [64] generated \( H_2 \)R knockout mice. Homozygous mutant mice were phenotypically normal and, unexpectedly, showed normal basal gastric pH. A marked hypertrophy of gastric mucosa and high circulating levels of gastrin were found in these mice, suggesting that when the histamine-dependent major regulatory system of hydrochloric acid secretion is genetically destroyed, compensatory mechanisms are activated to maintain normal gastric secretion. Interestingly, these mice showed a dysregulated T lymphocyte activity. \( H_2 \)R knockout mice display upregulation of both Th1 and Th2 cytokines and decreased OVA-specific IgE production compared with wild-type and \( H_1 \)R knockout mice [65].

\( H_2 \)R gene expression increased in human interleukin (IL)-4+ T cells upon bee venom exposure of non-allergic beekeepers [66] and in basophils during the first hours of ultra-rush venom immunotherapy [67]. \( H_2 \)R upregulation was responsible for the inhibition of IL-4 and the stimulation of IL-10 secretion by IL-4+ T cells [66] as well as the inhibition of histamine release and cytokine secretion from basophils [33, 67]. In addition, activation of \( H_2 \)R inhibits histamine release from rodent mast cells [34], neutrophil activation [37], eosinophil chemotaxis [35] and degranulation [36], \( \gamma\delta \)T cell-mediated cytotoxicity [68], and reduces the inflammatory response of dendritic cells (DCs) to microbial ligands [69, 70].

Owing to the inhibitory effect exerted on several immune cells, \( H_2 \)R may play a role in the development of allergy and possibly other immune-mediated disorders. Interestingly, the use of histamine dihydrochloride (a salt of histamine) in conjunction with low-dose IL-2 has been proposed as a relapse-preventive immunotherapy for patients with acute myeloid leukemia [71, 72]. It is thought that myeloid
cell-derived reactive oxygen species inhibit natural killer (NK) cell-mediated killing of human acute myeloid leukemia blasts. Histamine via H1R protects NK cells from myeloid cell-dependent inactivation, probably through inhibition of reactive oxygen species production [73].

In 1991, Yamashita et al. [74] cloned the H1R gene. Thanks to H1R cDNA cloning, the tissue distribution of these receptors could be studied by Northern blot analysis. The expression of H1R was found to be high in the lung and small intestine, moderate in the adrenal medulla and uterus, and low in the cerebral cortex and spleen [74]. The H1R was later cloned in other species including mouse [75], rat [76] and human [77]. Heterologously expressed H1R triggered the activation of phospholipase C, the accumulation of IP3 and an increase in [Ca2+]i via Gq proteins [78, 79].

Studies on recombinant H1R also helped to clarify the apparent paradox of the increase in intracellular cAMP concentration blocked by H1 blockers that had been reported since the end of the 1970s in different native preparations [80, 81]. Working on heterologously expressed human H1R in CHO cells, Maruko et al. [82] demonstrated that adenylate cyclase is indirectly activated upon H1R activation via Gβγ subunits released from Gq proteins.

In 1996, Inoue et al. [75] produced knockout mice for the H1R. The study of these animals confirmed and extended previous knowledge on the physiological roles of H1-mediated histamine effects. H1R knockout mice have an impairment in locomotor activity and exploratory behavior, and a decrease in aggression and anxiety [83]. The study of the behavioral effect of H1R raised great interest because of its possible implications in the pharmacological activity of antipsychotic drugs, a class of compounds also acting on H1R [84]. In addition, studies performed on these knockout mice provided evidence that histamine via H1R could be involved in the neurotensin anorexic effect [85]. H1R knockout mice also showed a significant impairment in nociception and an enhancement in the sensitivity to the analgesic effect of morphine, confirming the role of these receptors in pain perception [83, 86, 87].

H1R knockout mice showed lower percentages of IFN-γ-producing T cells and produced more OVA-specific IgG1 and IgE compared with wild-type mice [65]. Interestingly, although allergen-stimulated T cells from H1R knockout mice exhibited an enhanced production of Th2 cytokines, allergen-challenged H1R knockout mice showed reduced lung Th2 cytokines associated with lower airway inflammation, goblet cell metaplasia and airway hyperresponsiveness. These conflicting results can be explained, at least in part, considering that histamine promotes T cell chemotaxis. Thus, defective T cell trafficking could be responsible for reduced lung inflammation in allergen-challenged H1R knockout mice [88].

The effects of histamine acting via H1R on the immune system extend well beyond those described for T cells. Human lung macrophages (HLM), monocyte-derived macrophages (MDM) and monocyte-derived DCs express higher levels of H1R compared with precursor monocytes. Histamine induces the release of pro-inflammatory mediators (β-glucuronidase, IL-8 and IL-6) by MDM and HLM through the activation of H1R [89–91].

Interestingly, gene variability of the H1R can influence the risk of developing specific disorders. Bphs, one of the first non-major histocompatibility complex-linked genes associated with the susceptibility of murine models to autoimmune diseases, was identified with the H1R [92]. In addition, polymorphisms of the H1R were associated with the risk of developing Parkinson’s disease [93].

Despite the intense efforts of several laboratories, H3R cloning proved a formidable task. It was not until 1999 that Lovenberg et al. [94] attained this important result by a reverse approach. They were working at R.W. Johnson Pharmaceutical Research Institute on the identification of orphan GPCR. Among the almost 30 different orphan receptors they identified GPCR97, which was highly expressed in the brain and showed a significant structural homology with several members of the biogenic amine receptor superfamily. When heterologously expressed in different cell lines this receptor conferred a high responsiveness to the inhibitory action of histamine on adenylate cyclase activity, thus behaving as a new histamine receptor: it was dubbed the H3R [94, 95]. Recombinant H3R showed a pharmacological profile indistinguishable from H3R [94]. Impor-
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stantly, as observed for H₂R, H₃R also showed a relevant constitutive activity in heterologous expression systems [96, 97]. Evidence that these receptors are also constitutively activated in native preparations was reported, suggesting that they could also regulate neurotransmitter release in the absence of histamine [98].

Different isoforms of the H₃R were identified both in humans [99] and in rodents [95, 100]. Evidence was reported for isoform-specific differences in signal transduction as some isoforms, but not all, activated the MAPK cascade and caused arachidonic acid release [95, 100]. Once the H₃ gene was cloned, the tissue distribution of this receptor was explored by RT-PCR and in situ hybridization. These studies confirmed its preferential localization in the brain with minor expression in other tissues, including stomach, intestine, skin and thymus [100, 101].

In 2002, Toyota et al. [102] reported the generation of H₃R knockout mice. Unexpectedly, these mice showed a decrease in locomotor activity, wheel-running behavior and body temperature, which was interpreted as the consequence of compensatory mechanisms, such as H₁R downregulation, triggered by the increased availability of histamine in the synapse. Similarly, a mild obesity [103] and a reduction in anxiety [104] were reported in these mice.

Identification and Cloning of H₄R

At the end of 2000, both Oda et al. [105] and Nakamura et al. [106] reported the cloning of a new histamine receptor that they designated H₄R. This result was attained by screening the human genome database for sequences similar to that of H₃R. The newly cloned receptor showed a very limited homology with all the known histamine receptors (approximately 31% with H₁R and only 23% and 22% with H₁R and H₂R, respectively). The existence of similar receptors was confirmed in other animal species, including mouse, rat, monkey, pig and guinea pig [107–109]. With the discovery of the H₄R gene, the pharmacology of these receptors could be accurately defined in heterologous expression systems. It was established that whereas the pharmacological profile of H₄R is different from that of H₁R and H₂R, some overlap does exist with H₃R. Specifically, thioperamide acts as an inverse agonist both on H₃R and on H₄R and (R)-α-methylhistamine, immepip and imetit activate both these classes of receptors [110]. Conversely, clobenpropit and burimamide block H₃R and activate H₄R [111]. These initial pharmacological data showed that no available drug could distinguish between H₄R and H₃R, and prompted the development of selective H₄R-acting drugs. To this aim, Jablonowski et al. [110], working at the Johnson & Johnson pharmaceutical research laboratories, started a high-throughput screening program to identify in the company compound collection new molecules acting on recombinant H₄R. This effort led to the identification of several indolylpiperazine whose SAR analysis provided useful information needed for the synthesis of the first selective H₄R blocker, compound JNJ 7777120 [110, 112].

H₄R is preferentially expressed on immune cells, namely eosinophils [113, 114], basophils [115], mast cells [112, 116, 117], NK cells, DCs, monocytes [118] and T cells [68, 119–122]. The activation of this receptor is emerging as an important mechanism for the modulation of chemotaxis as well as several other functions of these cells [59].

Hofstra et al. [117] demonstrated that H₄R modulates mast cell chemotaxis by a Gᵢ/o-dependent PTX-sensitive mechanism. Mast cells from wild-type and H₃R-deleted mice migrated in response to histamine, while mast cells from the H₃R-deleted mice did not. Conversely, no role for H₄R could be demonstrated in IgE-dependent mast cell degranulation [117]. Compound JNJ 7777120 prevented histamine-induced [Ca²⁺]ᵢ increase as well as mast cell chemotaxis and submucosal mast cell accumulation in the trachea of mice after histamine inhalation [112]. By using siRNAs directed against H₄R, Godot et al. [116] showed that histamine acting through H₄R enhanced CXCL12-induced chemotaxis of mast cell precursors, but not mature mast cells. A role for H₄R was also demonstrated in the modulation of eosinophil chemotaxis [113, 114]. Recently, it was shown in a mouse model of allergic rhinitis that histamine released from mast cells recruits H₄R-expressing basophils to the nasal cavity, an event that...
was required for the development of early- or late-phase nasal responses following allergen challenge [115].

A role in the control of lymphocyte activity was also proposed based on the evidence that H_{4}R blockers prevent histamine-induced IL-16 release by human CD8 T cells [119]. This could be of particular importance because IL-16 induces the chemotaxis of several immune cells (CD4 T lymphocytes, eosinophils and DCs) [123–125] and has been found in the bronchoalveolar fluid of allergen- or histamine-challenged asthmatics [126–128]. In addition, this cytokine is highly expressed by eosinophils and mast cells [129] in the bronchial mucosa of atopic asthmatics [130]. H_{4}R is also expressed by CD4 T cells and intratracheal administration of an H_{4}R agonist mitigated airway inflammation in a murine model of allergic asthma. This anti-inflammatory effect was associated with an increase in IL-10 and IFN-γ, and a decrease in IL-13 in the bronchoalveolar lavage fluid as well as the recruitment of FoxP3+ T cells. In vitro data confirmed that, among T lymphocytes, a specific H_{4}R agonist preferentially induces the chemotaxis of CD4+CD25+FoxP3+ cells [122].
Although the latter study suggests that H₄ receptor activation protects from allergic airway inflammation, it should be noted that H₄R agonists were administered intratracheally and before antigen challenge. In addition, possible discrepancies between human and mouse cells should be taken into account. For example, conversely to what has been observed in mice, H₄R is highly expressed by Th2 cells or CD4 T cells stimulated with IL-4. Moreover, polyclonally activated peripheral blood mononuclear cells or Th2 cells stimulated with H₄R agonists upregulated IL-31 mRNA, a cytokine involved in skin allergic inflammation and the induction of pruritus. Specific H₄ agonists have been shown to induce itch, whereas pretreatment with H₄R antagonists reduced the itch response to either H₄ agonists or histamine. Interestingly, the effects of H₄R antagonists on pruritus are enhanced by the concurrent blockade of H₁R [131–133]. Thus, H₄R might contribute to skin allergic inflammation by activating Th2 cells and inducing pruritus via IL-31 [120].

In summary, although the balance between pro-inflammatory and anti-inflammatory effects of H₄R needs to be fully elucidated and requires further investigation, these findings suggest that H₄R could play a role in allergic inflammation and could, therefore, be a potential target for drug intervention.

H₄R has also been involved in the pathogenesis of non-allergic disorders. H₄R blockade decreased neutrophil accumulation in experimental models of peritonitis [112] and pleurisy [134]. Moreover, H₄R activation induces chemotaxis of IL-2-activated NK
cells, DCs, THP-1 cells (a human acute monocytic leukemia cell line) [118] and γδ T cells [68], and enhances cytokine secretion from invariant NK T cells [121] (fig. 1). Recently, a role for H₄R has also been proposed in diabetes, cancer, neuropathic pain and vestibular disorders [135].

Collectively, these results provide the rationale for the development of a new generation of selective antagonists of H₄R [136]. A first oral H₄R antagonist, compound UR-63325 synthesized by Palau Pharma, has entered clinical trials [137]. In addition, dual H₁R/H₄R antagonists and/or the combination of H₁R and H₄R antagonists could pave the way for the development of new therapeutic strategies for certain inflammatory and immunological disorders.

Closing Thoughts

Since the discovery of histamine almost 100 years ago, several breakthroughs have marked this field of research (fig. 2). Four histamine receptors have been characterized so far (H₁R, H₂R, H₃R and H₄R), and an important role for histamine has been identified in several physiological and pathological responses. In particular, histamine acting through H₁R or H₂R plays a fundamental role in the development of allergic disorders and in the regulation of gastric acid secretion, respectively. Although all histamine receptors are expressed in the brain, the preferential expression of H₃R in the central nervous system underlies its pivotal role in the regulation of basic homeostatic and higher functions, including cognition, arousal, circadian and feeding rhythms. Finally, the role of H₄R in the modulation of several aspects of the immune response is now increasingly being appreciated.

Several histamine receptor antagonists/agonists have been synthesized over the last century, some of them already used for the treatment of allergic and gastric acid-related disorders (anti-H₁R and anti-H₂R, respectively), and others being tested in clinical trials for neurologic and immune-mediated disorders (anti-H₃R and anti-H₄R, respectively).

Despite these great advances, several questions remain to be answered. First of all, we cannot exclude the existence of histamine receptors beyond the four currently known. Moreover, the sequential activation of histamine receptors on immune cells and their roles in chronic inflammatory diseases as well as therapeutic procedures (e.g. vaccines and venom immunotherapy) remains to be fully elucidated. Further examination of this important immunoregulatory network will likely lead to new advances in our understanding of immune-mediated disorders and could pave the way for a more thoughtful clinical exploitation of histamine receptor agonists/antagonists.

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