Histamine, Histamine Receptors, and their Role in Immunomodulation: An Updated Systematic Review

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Abstract: Histamine, a biological amine, is considered as a principle mediator of many pathological processes regulating several essential events in allergies and autoimmune diseases. It stimulates different biological activities through differential expression of four types of histamine receptors (H1R, H2R, H3R and H4R) on secretion by effector cells (mast cells and basophils) through various immunological or non-immunological stimuli. Since H4R has been discovered very recently and there is paucity of comprehensive literature covering new histamine receptors, their antagonists/agonists, and role in immune regulation and immunomodulation, we tried to update the current aspects and fill the gap in existing literature. This review will highlight the biological and pharmacological characterization of histamine, histamine receptors, their antagonists/agonists, and implications in immune regulation and immunomodulation.

Keywords: Histamine, histamine receptors, H4-receptor, antagonists, agonists, immunomodulation.

I. INTRODUCTION

In historical evolution, histamine (biogenic amine) is probably one of the most important phlogistic ancient mediator, and even one of the most intensely studied molecules in biological systems which have been using histamine, catecholamines and other chemical mediators to communicate among cells [1]. Histamine was synthesized in 1907 and characterized in 1910 as a substance ("beta-1") [2], owing to its significant competence to constrict guinea pig ileum, and its cogent vasodepressor action. However, it took 17 years to demonstrate its presence in normal tissues [3]. The relation between histamine and anaphylactic reactions was made rapidly in 1929, and was identified as a mediator of anaphylactic reactions in 1932 [4, 5], whereas its connection to mast cells was not made until 1952 [6], and also its connection to basophils in 1972 [7]. The search for compounds being potent to neutralize the pathological effects of histamine began at the Pasteur Institute in Paris during the 1930s, and these compounds were found to partially block the effects of histamine based on the ethylenediamine structure. The first antihistamine compound was the adrenolytic benzodioxan, piperoxan (933F), reported by Ungar, Parrot and Bovet in 1937 and was shown to block the effect of histamine on the guinea-pig ileum [8]. It followed shortly by the report of Bovet and Staub [9] that structurally related to aryl ethers such as the thymol ether (929F) [8]. The latter antihistamine compound proved to be highly toxic for clinical development; however, the replacement of ether oxygen by an amino group led to the search of aniline ethylene diamine derivatives. For this noble research on antihistamines and curare, Bovet was awarded the Nobel Prize in 1957 [8]. It was being documented that histamine played an important role as a mediator of allergic reactions indicated by a series of compounds with antihistamine activity which protected guinea pigs from anaphylaxis. However, the clinical use of these compounds in humans was precluded due to their toxicity [9]. The first antihistamine, Antergan™ (phenbenzamine, RP 2339) was being used in humans [10], but this compound was subsequently replaced by Neoantergan™ (mepyramine, pyrilamine, RP 2786), which is still in use to counteract the uncomfortable effects of histamine release in the skin. Many other antihistamines such as diphenhydramine (Benadryl™), tripelennamine, chlorpheniramine and promethazine are also used in similar manner to counteract the adverse effects of histamine [8]. Subsequently, after 1945, these antihistamines were widely used in the treatment of various allergic diseases such as hay fever, urticaria, and allergic rhinitis. However, the side effects were not uncommon and the sedation was a drawback to their use. A very few side effects were put to their good use; therefore, some antihistamines such as cyclizine (Marzine™) and diphenhydramine in the form of its 8-chlorotheophyllinate (Dramamine™) are being used as an antiemetics for travel sickness [8]. By 1950 there were only 20 compounds clinically available to block the effects of histamine [1], but advances in histamine receptors (HRs) ligands have ever attracted many researchers for pharmaceutical developments and are still highly topical [11].

Histamine (2-(imidazol-4-yl) ethylamine) is one of the monoamines and was coined after the Greek word for tissue *histos,* with the broadest spectrum of activities in various physiological and pathological conditions including the cell proliferation, differentiation, hematopoiesis, embryonic development, regeneration, wound healing, aminergic neuro-

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transmission and numerous brain functions (sleep/nociception, food intake and aggressive behavior), secretion of pituitary hormones, regulation of gastrointestinal and circulatory functions, cardiovascular system (vasodilatation and blood pressure reduction), as well as inflammatory reactions, modulation of the immune response, energy of endocrine and homeostasis [1, 12-18]. It is being documented by several studies which highlighted the evidence of histamine that it elicits immune-modulatory and pro-inflammatory effects by the differential expression of histamine receptors (H1R, H2R, H3R, and H4R) that is easily modulated the diverse effects of histamine on immune regulation and distinct intracellular signals. All these four receptors are members of the 7-transmembrane (heptahelical) spanning family of receptors, are G protein-coupled (GPCR), are expressed on various histamine responsive target tissues and cells and suggest an important critical role of histamine in immunomodulation and allergic diseases [1, 8, 11-14].

In the present review, we will discuss biology of histamine including synthesis, regulation and metabolism; histamine receptors including H1-, H2-, H3-, and H4-receptors and their cellular distribution, functional characterization, structural biology, and signaling mechanisms; non-classical histamine-binding sites such as cytochrome P450; and histamine transporters; as well as immune regulation by histamine in immunomodulation and allergic inflammation; effects of histamine in immune cells in respect to allergic diseases; implication of histamine on cytokines production; significance of histamine in autoimmunity and allergic diseases and also in malignancies; and finally the relation of histamine-cytokine during hematopoiesis.

II. BIOLOGY OF HISTAMINE

Histamine exhibits two main important basic functionalities such as primary aliphatic amine (pK_{a1} 9.4) and imidazole (pK_{a2} 5.8). These make the monocation with different tautomers; the preferred form at physiologic pH value (96%) with a minor dicationic fraction (3%) and a very small amount of the neutral form [19]. The nomenclature for histamine positions may be highly significant for histamine biology including synthesis, regulation, metabolism, and also histamine derivatives (Fig. **1**).

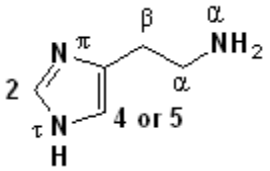


Fig. (1). Specific nomenclature for histamine positions.

A. Synthesis of Histamine

Histamine was first identified as an autocoid having potent vasoactive properties. It is a low molecular weight amine synthesized from L-histidine exclusively by L-histidine decarboxylase (HDC) (E.C. 4.1.1.22 or E.C. 4.1.1.26), which is dependent on the cofactor pyridoxal-5′-phosphate to a putative binding site (TFNPSKW) on the protein. Histamine cannot be generated by another enzymatic pathway [8, 14]. Histidine decarboxylase (HDC) is an enzyme that is expressed in various cells through out the body, including central nervous system, neurons, gastric-mucosa, parietal cells, mast cells(~3 pg/cell histamine), and basophils(~1 pg/cell histamine). Histamine has an important role in human health, and exerting its diverse biologic effects by 4 types of receptors [1, 13, 20-22]. Histamine is also produced by enterochromaffin-like cells (ECL) in the stomach and plays an important role in secretion of gastric acid [14]. Only basophils and mast cells can store the amine in specific granules, in the hematopoietic system, where histamine is closely associated with anionic proteoglycans heparin (in mast cells) and chondroitin-4-sulfate (in basophils). In this specific form, histamine can be released in large amounts during degranulation in response to various immunological (immunoglobulin E, or cytokines) or non-immunological (compound 48/80, calcium ionophore, mastoparin, substance P, opioids, or hypo-osmolar solutions) stimuli [14]. Histamine synthesis in Golgi apparatus can be inhibited by α-fluoromethylhistidin [23].

Recently, many myeloid and lymphoid cell types that do not store histamine show more HDC activity and are capable of synthesis of high amounts of histamine [24]. This so called "neo synthesized histamine," has been shown in various cells, including hematopoietic progenitors, macrophages, neutrophils, platelets, dendritic cells (DCs) and T cells [14, 25-28]. Histamine synthesis in non-mast cells was first confirmed using W/W^V mice, which genetically lack mature mast cells, upon stimulation with a phorbol ester [29]. HDC activity is demonstrated *in vitro* through cytokines, such as IL-1, IL-3, IL-12, IL- 18, GM-CSF, macrophage-colony stimulating factor, TNF-α, and calcium ionophore [30, 31]. Histidine decarboxylase (HDC) activity has been modulated in conditions such as LPS stimulation, inflammation, infection, and graft rejection, *in vivo* [32].

It is being demonstrated that the generation of HDC-knockout mice provides histamine-free system and it is more beneficial to study the role of endogenous histamine in a broad range of normal and disease processes. Such mice demonstrate diminished numbers of mast cells and significantly decreased granule content, which suggests that histamine might affect the production of mast cell granule proteins [33]. In a recent study, interleukin-3 (IL-3)-dependent bone marrow derived mast cells (BMMCs) have been found to be activated by certain immunoglobulin-E (IgE) clones in absence of specific antigen, leading to their survival, cytokine secretion, histamine production, adhesion, and migration [34]. In addition to this study, Tanaka *et al.* [35] has shown a drastic and transient induction of HDC (~ 200-fold in activity) in BMMCs stimulated by IgE alone, which was found much higher than that upon antigen stimulation. Thus, this induction resulted in the increase in stored histamine. Another study suggested that the anti-apoptic effects of monomeric IgE on BMMCs were mediated by interleukin-3 (IL-3) in an autocrine fashion [36]. Although Schneider *et al.* [30] found the potential role of IL-3 to induce HDC in bone marrow cells, it is clearly indicated that monomeric IgE-induced histamine synthesis may not be mediated through IL-3 [36]. Since stimulation of histamine synthesis occurs upon IgE-mediated antigen induction, and this remains controversial if these two modes of FcεRI activation share a common signal transduction pathway. However, many recent studies have demonstrated the qualitative differences between both modes: such as monomeric IgE-induced Ca^{2+} influx is mediated by a distinct channel from that activated

upon antigen stimulation [37], and protein kinase C beta-II (PKCβII) plays a significant role in monomeric IgE-induced histamine synthesis in mast cells, but not upon antigen stimulation [38]. Since, only small levels of increase in histamine synthesis were found by monomeric IgE both in purified rat peritoneal mast cells and *in vitro* maturated BMMCs, inducing effects of monomeric IgE on mast cells may be limited to immature mast cells [37]. However, Tanaka and Ichikawa [39] has suggested that monomeric IgE-induced histamine synthesis exacerbates the symptoms of chronic allergy, while drastic increases in the levels of serum IgE are often observed in such diseases.

B. Regulation of Histamine

Histamine is synthesized only by HDC enzyme. Therefore, histamine regulation is dependent on the gene of HDC enzyme, which is expressed in the cells throughout the body. It has been shown that complementary deoxyribonucleic acids (cDNAs) of HDC enzyme have been isolated from mouse mastocytoma, fetal rat liver, erythroleukemia cells and human basophil leukemia cells. Based on structural studies, mouse and human genes are composed of 12 exons spanning nearly 24 kb. The 2.4 kb single transcript is produced by mouse gene, whereas two splice variants of 3.4 kb and 2.4 kb exist in humans, and latter encode the functional HDC [40]. HDC gene is found on chromosome 2 in mice and chromosome 15 in human and their expression is controlled by lineage-specific transcription factors. These factors interact with a promoter region consisting of GC box, four GATA consensus sequences, a c-Myb-binding motif and four CACC boxes [41]. It has been demonstrated in several studies that the HDC transcription is regulated by various factors in gastric cancer cells such as gastrin, oxidative stress and phorbol 12-myristate 13-acetate (PMA), through a Ras-independent, Raf-dependent mechanism, MAP kinase/ERK and a protein kinase C (PKC) pathways functioning on three overlapping cisacting elements (GASRE 1, GAS-RE 2 and GAS-RE3) known as gastrin response elements [42, 43]. The negative control on HDC expression in gastric epithelial cell line is exerted by expression of the transcription factors GATA-4 and GATA-6 [44]. It is well known that the expression of HDC in basophils and mast cells seems to be a consequence of the state of CpG methylation in the promoter region [45]. Many studies on the mast cell line HMC1 and the pluripotent hematopoietic cell line UT7D1 have demonstrated that HDC-gene expression is subject to post-transcriptional control. Therefore, the chromosomal configuration and methylation of the HDC-promoter is likely to account for its cell-specific expression [46, 47]. It has also been reported that PMA stimulates a strong increase in HDC activity in UT7D1, which is affected by actinomycin D, and that is not paralleled by enhanced HDC mRNA expression. Similar effect was noted in cell lines (HEL and CMK) with megakaryocyte/basophil differentiation potential [48]. In addition to this effect, a mechanism that accounts for the strong enhancement of HDC activity in ECL cells in response to gastrin is explained by a translation control of HDC expression [49]. Two essential mechanisms of translational control have been explained in hematopoietic cells: (i) a rapamycin dependent pathaway that is linked to phosphoinositide 3-kinase (PI3K), FRAP/mTOR and phosphorylation/dephosphorylation of repressor of translation 4E-binding protein (4E-Bps) and (ii) ERK- and p38-dependent pathway that control the 4E-BP expression by the induction of Egr-1 [50]. The multiple carboxy-truncated isoforms are formed due to post-translational processing of HDC gene; the gene is initially translated 73-74 kDa protein in mammals, and originally it was assumed that enzymes purified from native sources corresponded to a dimer of two processed isoforms of 53 and 55 kDa. According to Fleming and Wang [51], the biosynthesis of histamine involves primarily the 55 kDa isoform and it is being acknowledged that many other isoforms generated from 74 kDa primary translation product can also be active. It is also being documented that enhancing the histidine decarboxylase activity might cause reduction in messenger RNA (mRNA) degradation by amino acid carboxyl-terminal PEST domains [52]. Here is a need to completely understand the negative feed back regulation of histidine decarboxylase activity that differs from one cell type to another. This activity has been shown in AGS-B cells that over expression of the HDC protein inhibited histidine decarboxylase promoter activity by down regulation of ERK signals [53].

However, in gastrin-stimulated ECL cells, this type of feed back mechanism was not observed. It was also demonstrated that in the hematopoietic cells, as well as in the stomach, negative feed back signals could be produced through high cytosolic histamine concentration [50]. Histamine reuptake mechanism comparable to that of the other aminergic neurotransmitters has not been observed [54].

C. Metabolism of Histamine

It is noteworthy that only a small amount of released histamine (2 to 3%) is excreted unchanged. The remaining histamine (more than 97%) is controlled *via* two major pathways for the metabolizing enzymes: histamine N^{τ}-methyltransferase (HMT) (EC 2.1.1.8) and diamine oxidase (DAO) (EC1.4.3.6) before excretion [23, 55]. Histamine N^{τ}-methyltransferase metabolizes the majority of histamine (50 to 80%) to *N*-methyl histamine, which is further metabolized to the primary urinary metabolite *M*-methylimidazole acetic acid by monoamine oxidase. Diamine oxidase metabolizes the histamine (15 to 30%) to imidazole acetic acid [20]. The study of the former pathway was greatly facilitated by the availability of a potent and highly specific inhibitor of diamine oxidase, aminoguanidine. HMT appears to be the most important enzyme contributing to the degradation of histamine in the airways, because blockers of HMT (such as SKF 91488) increase the bronchoconstricting action of histamine *in vitro* and *in vivo*, whereas diamine oxidase inhibition remained uneffected [56]. HMT is expressed in airway epithelial cells and may therefore be responsible for the local metabolism of histamine released from airway mast cells. Mechanical removal of airway epithelium enhances the bronchoconstriction response to histamine *in vitro* [57-59]; this might be the result, in part, of loss of the metabolizing enzyme. Furthermore, experimental viral infections resulted in reduced epithelial HMT activity in association with increased responsiveness to inhaled histamine [60]. The half-life of pharmacologically active doses of histamine is less than 10s in the rat and 20-30s in the dog. In earlier studies, histamine levels were measured by bioassay, but subsequently fluorometric and radio-enzymatic techniques were employed [8].

III. HISTAMINE RECEPTORS

Histamine is an important biogenic amine and has multiple effects that are mediated through specific surface receptors on specific target cells. Four types of histamine receptors have now been identified. In 1966, histamine receptors were first differentiated into H1 and H2 [61], and it was reported that some responses to histamine were inhibited by low doses of mepyramine (pyrilamine), whereas others were unsympathetic. In 1999, a third histamine receptor subtype was cloned and termed as H3 [22]. Subsequently in 2000, the fourth histamine receptor subtype was reported which was termed as H4 [21] and introduced a significant chapter in the story of histamine effects.

A. Histamine H1-Receptor

1. Cellular Distribution and Functional Characterization

In different mammalian tissues, the study of the distribution of histamine H1-receptors (H1Rs) has been significantly helped by the development of specific radioligands for this subtype. In 1997, [3H]mepyramine a selective radioligand was developed (Table **1**) [62], and since then it has been used to identify H1-receptors in a wide variety of tissues such as gastrointestinal tract, central nervous system, airways and vascular smooth muscle cells, mammalian brain, hepatocytes, nerve cells, endothelial cells, chondrocytes, monocytes, neutrophils, dendritic cells, T and B lymphocytes (Table **2**), the cardiovascular system and genitourinary system, endothelial cells and adrenal medulla in which H1-receptor mediates different biological properties of allergic responses such as typical immediate responses of allergic reaction type I like redness, itching and swelling ("triple response"). In many pathological processes of allergy, including allergenic rhinitis, atopic dermatitis, conjunctivitis, urticaria, asthma, and anaphylaxis, H1-receptors are involved. The receptors also mediate bronchoconstriction and enhanced vascular permeability in the lung [17, 63-65]. It has been noticed that [3H]mepyramine binds to secondary non-H1-receptor sites in various tissues and cells [66-70]. In addition to [3H]mepyramine, which predominantly binds to a protein homologous with debrisoquine 4-hydroxylase cytochrome P450 in rat liver [71], this nonspecific binding can be blocked by quinine. This investigation led to the demonstration that quinine may be used to block binding to other lower affinity sites [72], and it was thus proved that all secondary binding sites for [3H]mepyramine were not sensitive to inhibition through quinine [69]. Many researchers have shown that a 38 to 40 kDa protein was isolated from DDT1MF-2 cells, that binds H1R antagonists with specific K_D values in the μM range, but that was not sensitive to inhibition through quinine and also that DDT1MF-2 cells possess [3H]mepyramine binding sites which have the characteristics of histamine H1-receptors (i.e., K_D values in the nM range) to mediate functional responses, and those were produced by H1R activation [69, 73, 74]. Other radioligands that have been demonstrated to study histamine H1-receptors are [3H]mianserin, [3H]doxepin, [125I]iodobolpyramine, [125I] iodoazidophenpyramine, and [3H](1)-N-methyl-4-methyldiphenhydramine [75-80]. [125I]Iodobolpyramine has been successfully used for autoradiographic localization of H1Rs in the brain of guinea pig, whereas, it was used with lower success for localization in rat brain (Table **1**) [78, 81]. Slow dissociation of [3H]mepyramine from H1Rs has been shown at low temperature (i.e., 4°C) and this denotes that [3H]mepyramine can also be used for autoradiography (Ta-

Table 1. Characterization of Histamine Receptors Agonist, Antagonist and Radioligand

Receptor Subtypes	Agonists with Potency	Antagonists with Potency	Radioligands with Equilibrium Constant for Dissociation (Kd)
H1	Histamine(100)[a, b], Dimethylhistaprodifen (240)[a], Methylhistaprodifen (340)[a], Histamine-trifluoromethyltoluidine (HTMT)[c], 2-(3-trifluoromethylphenyl) histamine (128)[a, b], 2-Thiazolylethylamine (26)[a], 2-Pyridylethylamine (6)[a]	Mepyramine (pA_2 9.4)[a], (+)-Chlorpheniramine (pA_2 9.4)[a], (-)-Chlor-pheniramine (pA_2 6.7)[a], *Trans*-triprolidine (pA_2 10.0)[a], Temelastine (pA_2 9.5)[a], Promethazine (pA_2 8.9)[a], Diphenhydramine (pA_2 9.0)[a], Tripelennamine (pA_2 8.5)[a], Chlorpromazine (pA_2 8.9)[a]	[^{3}H]-Mepyramine (Kd 0.8nM: guinea-pig brain, ileum)[a,b], [^{125}I]-Iodobolpyramine (Kd 0.01nM, guinea-pig brain)[a], [^{125}I]-Iodoazidophen-pyramine (Kd 0.01nM, guinea-pig cerebellum)[a, b]
H2	Histamine(100)[a, b], Arpromidine (10230)[a, b], Impromidine (4810)[a, b], Sopromidine (740)[a, b], Amthamine (150)[a, b], Dimaprit (71)[a, b], 4-Methylhistamine (43)[a, b]	Cimetidine (pA_2 6.1)[a], Ranitidine (pA_2 6.7)[a], Famotidine (pA_2 7.8)[a], Zolantidine (pA_2 7.6)[a], Mifentidine (pA_2 7.6)[a], Titotidine (pA_2 7.8)[a], Iodoaminopotentidine (pA_2 8.6)[a]	[^{3}H]-Tiotidine (25nM)[a, b], [^{125}I]-Iodoaminopotentidine (Kd 0.3nM)[a, b], [^{125}I]-Iodoazido-potentidine (Kd 10nM)[a, b] (all guinea-pig brain membrains)
H3	Histamine(100)[a, b], Imetit (6200)[a, b], Immepip (2457)[a, b], R-α-methylhistamine (1550)[a, b]	*Thioperamide (pA_2 8.4)[a], Iodophenpropit (pA_2 9.6)[a], *Clobenpropit (pA_2 9.9)[a], Ciproxifan (pA_2 9.3)[a], Impentamine (pA_2 8.4)[a], GR174737 (pA_2 8.1)[a,b], Impromidine (pA_2 7.2)[a]	[^{3}H]-R-α-methylhistamine (Kd 0.5nM)[a, b], [^{3}H]-N^α-methylhistamine (Kd 2.0nM)[a, b], [^{125}I]-Iodophenpropit (Kd 0.3nm)[a, b], [^{125}I]-Iodoproxyfan (Kd 0.065nM)[a, b], [3H]-GR168320 (Kd 0.1nM)[a, b] (all rat cerebral cortical membranes in Tris buffer)
H4	Imetit (pA_2 8.6)[c], Immepip (pA_2 8)[c], *Clobenpropit (pA_2 7.9, partial agonist)[c], 4-Methylhistamine (pA_2 7.3)[c]	JNJ 10191584 (7.6)[c], *Thioperamide (7.6)[c]	None to date

[11[a], 23[b], 221[c]]; *These compounds act as agonist/antagonist for different histamine receptors at variable potencies.

Table 2. Characteristics of the Histamine Receptor Subtypes

Characteristics	H_1-Receptor	H_2-Receptor	H_3-Receptor	H_4-Receptor
[a, b]Receptor described, human gene cloned (years)	1966, 1993	1972, 1991	1983, 1999	1994, 2000
[a]Receptor proteins in human	487 amino acids, 56 kD	359 amino acids, 40 kD	445 amino acids,70 kD; splice variants	390 amino acids
[a,c]Chromosomal location in human	3p25, 3p14-21	5, 5q35.3	20, 20q13.33	18q11.2
[b]Equilibrium constant for dissociation (Kd)	~10 μmol/L	~ 30 μmol/L	~ 10 nmol/L	20-40 nmol/L
[a]Receptor expression	Widespread, including neurons, smooth muscle (e.g., airways, vascular), and other types of cells.*	Widespread, including gastric mucosa parietal cells, smooth-muscle, heart, and other types of cells.*	High expression in histaminergic neurons, low expression elsewhere.	High expression in bone marrow and peripheral hematopoietic cells, low expression elsewhere.
[c]Gene Structure	Intronless	Intronless	Three introns	Two introns
[a]G-protein coupling	Gαq/11	Gαs	Gi/o	Gi/o
[a,b]Activated intracellular signals (principal signaling effector molecules)	Ca^{2+}↑, cGMP, NF-κB, PLC↑, phospholipase A2, and D, cAMP, NOS	cAMP↑, Ca^{2+},protein kinese C, c-fos, phos- pholipase C	Ca^{2+}↑, MAP kinase↑; inhibition of cAMP↓	Ca^{2+}↑, MAP kinase↑; Inhibition of cAMP↓

Abbreviations: cAMP = cyclic adenosine monophosphate, cGMP = cyclic guanosine monophosphate, MAP = mitogen-activated protein, NF-κB = nuclear factor-κB, NOS = nitric oxide synthase, PLC = phospholipase C.
*Other types of cells: epithelial, endothelial cells, neutrophils, eosinophils, monocytes, dendritic cells, T-cells, B cells, hepatocytes, and chondrocytes.
[a][399], [b][1], [c][14].

ble **1**) [82, 83]. [125I]Iodoazidophenpyramine (Table **1**) is a very potent H1-receptor antagonist that can bind irreversibly to H1-receptors following irradiation with ultraviolet light [79]. The existence of H1Rs in the living human brain has been proved by specific ligands [11C]Mepyramine and [11C]doxepin [84, 85]. H1Rs have widely been studied in blood vessels [86-88], and also in smooth muscles [61, 88, 89]. In smooth muscles, such as the guinea pig ileum, which freely generate muscle action potentials, modulation of action-potential discharge by low concentrations of histamine is an important mechanism by which tension is increased [90] and there is evidence that the contractile response to histamine is produced by inositol 1, 4, 5-triphosphate-induced mobilization of intracellular calcium (Ca^{2+}) [91, 92]. Its further effects have been seen in non excitable smooth muscles including airways and vascular smooth muscles, and the contractile H1R stimulation initially involve mobilization of calcium (Ca^{2+}) from intracellular stores such as inositol phospholipids hydrolysis [93-96]. H1-receptor stimulation causes various cellular responses in vascular endothelial cells such as: it is responsible for changes in vascular permeability as a result of endothelial cell contraction [97, 98]; in synthesis of prostacyclin [99, 100]; in platelet-activating factor synthesis [99]; in release of Von Willebrand factor [101], and in nitric oxide release [102].

The study of H1R on human T lymphocytes has been characterized by use of [125I]iodobolpyramine [103] (see also Table **1**) and is shown to increase (Ca^{2+})i [104]. It is being documented that H1R-deficient mice display both strong systemic T cell and efficient B cell responses to antigen [105]. The relationship of H1Rs to adrenal medulla which elicit the release of catecholamines has been established many years ago [106-108]. Thus, histamine can stimulate the release of both adrenaline and noradrenaline [108], and also induce phosphorylation of the catecholamine biosynthesis enzyme tyrosine hydroxylase by a mechanism which mediates release of intracellular calcium from cultured bovine adrenal chromaffin cells [109].

The effects of histamine are also seen to elicit the release of leucine- and methionine- enkephalin [110]. Furthermore, many investigators have demonstrated a marked increase in mRNA-encoding proenkephalin A after prolonged exposure to histamine [110, 111]. Its negative inotropic effects have been observed in human atrial myocardium and also in guinea pig ventricle [112, 113].

Genovese *et al.* [113] suggested that the negative inotropic response of histamine in human myocardium is associated with inhibitory effects on heart rate. This can be unmasked when the positive responses of histamine on the heart rate, and force of contraction (due to histamine H2-receptors) are mediated through conjoint administration of adenosine or adenosine A1-receptor agonists. However, histamine produces a positive inotropic effect in guinea pig left atria and rabbit papillary muscle by a specific mechanism which is not related with a rise in adenosine 3c, 5c-cyclic monophosphate (cAMP) levels [90, 114, 115]. It is being documented that the distribution of H1Rs in mammalian brain with higher densities are found in neocortex, hippocampus, nucleus accumbent, thalamus, and posterior hypothalamus [90, 116], however, cerebellum and basal ganglia denotes lower densities [76, 85, 117]. The distribution of H1Rs in rat and guinea pig is very similar to each other [78, 82, 83, 118]. H1-receptor binding sites and mRNA levels were overlapped in most areas of brain except in hippocampus and cerebellum in which the inconsistency is mostly to reflect the presence of exuberance H1Rs in dendrites of pyramidal and Purkinje cells [119]. The activation of H1R inhibits the firing and hyperpolarization in hippocampal neurons [120] and also an apamine sensitive outward current in olfactory bulb interneurons [121], and these effects are mostly generated by intracellular Ca^{2+} release. However,

H1R excite various notable factors such as vegetative ganglia [122], hypothalamic supraoptic [23], brainstem [123], thalamic [124], and human cortical neurons [125] through a block of potassium conductance.

The functional characterization of H1R has benefited from the use of many potent and specific antagonists (see Tables **1** and **3**) [63, 126]. H1-receptor antagonists are the oldest therapeutic tools of the modern medicine due to their sedative side effects, and the anti-allergic drugs which were developed initially, have now been abandoned. Indeed, H1-receptor involves the disturbance of circadian rhythms and locomotor activities as well as the impairment of the exploratory behavior by histamine in the brain, and this is why so-called "non-sedating" H1 antagonists which cannot cross the blood-brain barrier have been designed. H1-receptor agonists are not readily available because they enhance rather than prevent the onset of allergic pathologies. Histaprodifens are very potent H1R agonists and are more effective than histamine in activating H1R [127]. Some anti-inflammatory effects of H1R antagonists at high doses could be non-specific because of histamine and other inflammatory mediators like leukotriene and platelet activating factors released from basophils in response to certain H1Rs antagonists [1, 14]. *Bordetella pertusis*-induced histamine sensitization (Bphs) controls *Bordetella pertussis* toxin (PTX)-induced vasoactive amine sensitization elicited by histamine (VAASH) and has an established role in autoimmunity. The congenic mapping links Bphs to the histamine H_1 receptor gene (Hrh1/H1R) and that H1R differs at three amino acid residues in VAASH-susceptible and -resistant mice. Hrh1-/- mice are protected from VAASH, which can be restored by genetic complementation with a susceptible Bphs/Hrh1 allele, and experimental allergic encephalomyelitis and autoimmune orchitis due to immune deviation. Thus, natural alleles of Hrh1 control both the autoimmune T cells and vascular responses regulated by histamine after PTX sensitization. The exact mechanism through which this effect occurs remains unclear and its clinical relevance is still uncertain [128]. The chemical structure of specific H1R-antagonists and agonists are shown in Figs. (**2**, **3**).

2. Structural Biology of Receptor

H_1 receptors have been cloned from cows, rats, guinea pigs and also from humans. The H1 receptor contains 486, 488 or 487 amino acids in rat, mouse and humans, respectively. It contains the typical properties of G protein coupled receptor (GPCR), namely, seven transmembrane domains of 20-25 amino acids predicted to form an α-helice which spans the plasma membrane and an extra cellular NH_2 terminal domain with glycosylation site. H1R is encoded by a single exon gene that is located on the distal short arm of chromosome 3p25 in humans see in Fig. (**2**) and chromosome 6 in mice. Histamine binds to aspartate residues in the transmembrane domain 3 of the H1-receptor, and to asparagine + lysine residues within the transmembrane domain 5 [14].

Its structural studies done by photoaffinity binding properties using [125I]iodoazidophenpyramine (Table **1**) and subsequent sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) analysis demonstrated that the H1-receptor protein (molecular weight 56 kDa) is found under reducing conditions in the brain of rat, guinea pig, and mouse [79, 118, 129]. Similar studies have also been done by using photoaffinity ligand [3H] azidobenzamide in bovine adrenal medullar membranes and found labeled peptides in the size range 53 to 58 kDa [130]. In guinea pig heart, the specifically labeled H1R with [125I]iodoazidophenpyramine was found to contain substantially higher molecular weight, while there was no obvious difference in the characteristics of the H1R in tissues (Table **1**) [131]. In 1991, H1R was cloned from the bovine adrenal medulla by expression cloning in the *Xenopus* oocyte system. Interestingly, 491 amino acid protein with a calculated molecular weight of 56 kDa was represented by the deduced amino acid sequence [130]; this protein has the seven transmembrane domains expected of a G-protein coupled receptor (GPCR) and contains N-terminal glycosylation sites. The main feature of the proposed H1R structure is the very large 3rd intracellular loop with 212 amino acids and relatively short intracellular C terminal tail with 17 amino acids. The availability of the bovine sequence and lack of introns has enabled the H1-receptor to be cloned from several species including rat [132], guinea pig [129, 133], mouse [134], and human [135, 136]. The human H1-receptor gene has now been localized to chromosome 3 bands 3p14-p21 (Table **2**). These clones should be regarded as true species homologues of the H1-receptor, while there are notable variations amongst them in some antagonist potencies [23]. Nevertheless, it is clear that the stereoisomers of chlorpheniramine show marked differences between species. For example, the guinea pig H1-receptor has a K_D of 0.9 nM for (1)-chlorpheniramine, whereas for the rat H1-receptor, the value is nearly 8 nM [23]. Similar variations for chlorpheniramine and other compounds (mepyramine and triprolidine) have been shown in guinea pig and rat brain, respectively [23, 67, 89]. On this basis the species differences may explain why compound [125I]iodobolpyramine can label guinea pig CNS H1-receptors, but it is unable to identify H1Rs in the brain of rat [78, 81]. In brain membranes of both guinea pig and rat the native H1-receptor protein has been solubilized [137, 138], and the solubilized receptor retains similar differences in H1-antagonist potency for (1)-chlorpheniramine as that detected in membranes [137]. It is important to note that mepyramine seems to be potent antagonist of the recombinant rat H1-receptor (i.e. expressed in C6 cells) than of the native histamine H1-receptor in the brain membrane of rat [23, 67, 132].

In addition, the recombinant studies performed in rat C6 cells [132] are complicated by the presence of a low level of endogenous histamine H1-receptors (H1Rs) [139], but in the functional studies in untransfected C6 cells, a high affinity for mepyramine (K_D 51 nM) has been deduced [23, 139]. The amino acid sequence alignment of the cloned histamine H1- and H2-receptors led to the suggestion that the third and fifth transmembrane domains (TM3 and TM5 respectively) of receptor proteins are responsible for histamine binding [140, 141]. In third transmembrane (TM3) of the human H1-receptor, Aspartate (107) that is conserved in entire aminergic receptors, has appeared to be essential for the histamine binding, and also H1-receptor antagonists to the H1-receptor [142]. In H1-receptor, the amino acid residues corresponding to Asparagine (198) and Threonine (194) are in corresponding positions in 5th transmembrane domain (TM5) of the human H1-receptor, while the substitution of an Alanine for

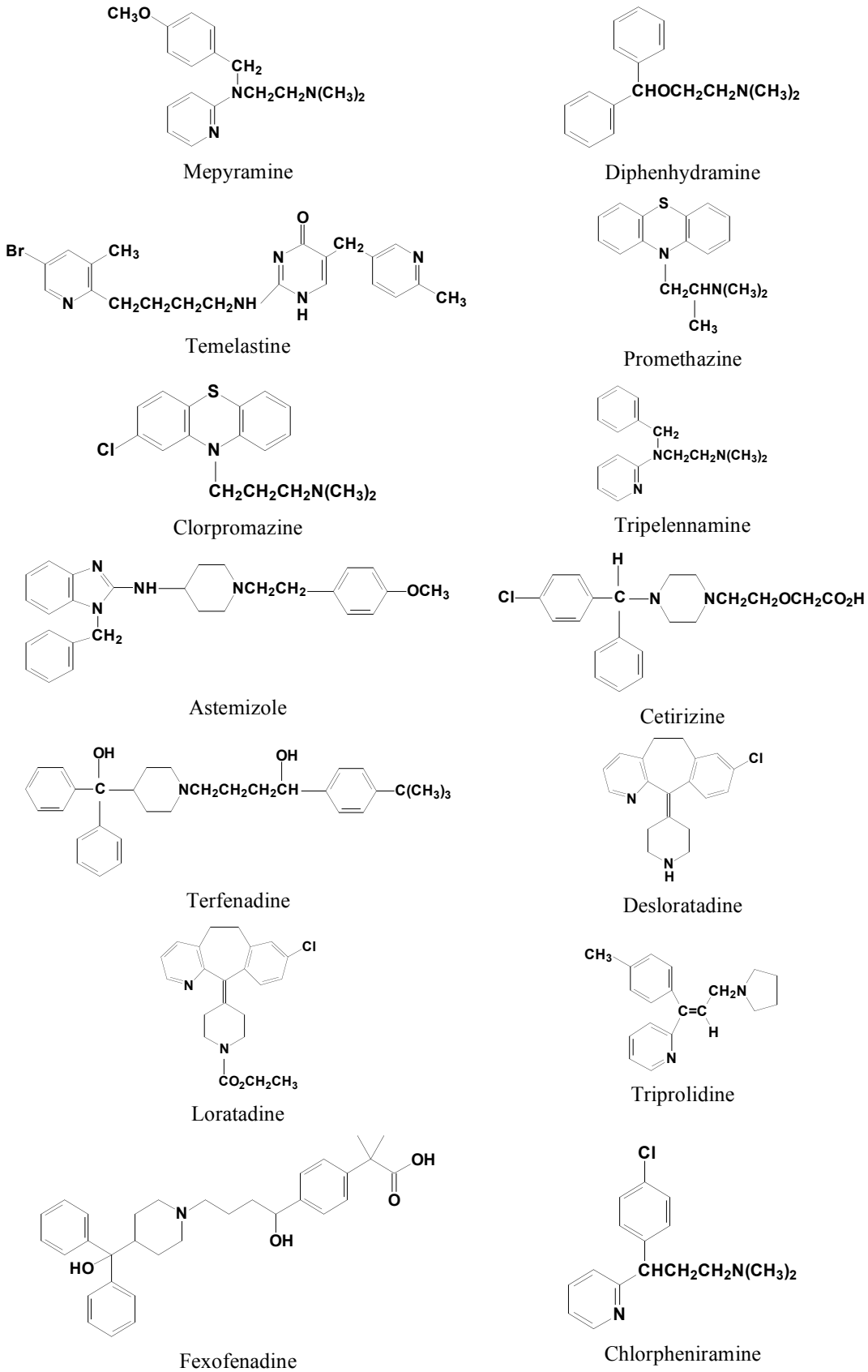
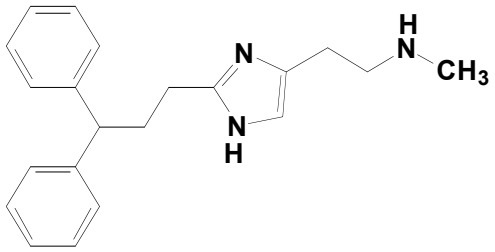
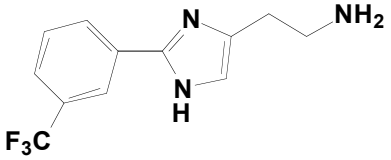


Fig. (2). Chemical structures of some histamine H1-receptor-antagonists.

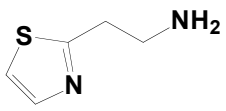
Threonine (194) did not influence the binding properties of either agonist or antagonist [142, 143]. However, the substitution of Alanine (198) for Asparagine (198) decreased agonist affinity, while the affinity of antagonist remained un-



Methylhistaprodifen



2-[3-(Trifluoromethyl)phenyl]histamine



2-(Thiazol-2-yl)ethanamine

Fig. (3). Chemical structures of some histamine H1-receptor-agonists.

changed [142, 143]. Similar results have been seen in the mutations to the corresponding residues Threonine (203) and Asparagine (207) in the guinea pig-H1R sequence [144]. In addition to these mutations 2-methylhistamine is affected by the Asparagine (207) Alanine mutation, and H1-selective agonists 2-thiazolylethylamine, 2-pyridylethylamine, and 2-(3-bromophenyl) histamine are much less influenced through this mutation [144, 145]. This suggested that Asparagine (207) interacts with the Nt-nitrogen of histamine imidazole ring.

However, it has been shown that Lysine (200) interacts with the Np-nitrogen of histamine ring, and that it is important for the activation of the H1R by histamine and the nonimidazole agonist, 2-pyridylethylamine [63]. Furthermore, Leurs *et al*. [70] has demonstrated that the Lysine (200) Alanine mutation did not alter the binding affinity of 2-pyridylethylamine to H1R of guinea pig. Thus, the studies on the organization, genomic structure and promoter function of the human H1R revealed a 5.8 kb intron in the 50 flanking region of this gene, different binding sites for various transcription factors, and the absence of TATA and CAAT sequences at the appropriate locations [146].

3. Signaling Mechanisms

H1-receptor is a Gαq/11-coupled protein with a very large third intracellular loop and a relatively short C-terminal tail see in Fig. (**4**). The main signal induced by ligand binding is the activation of phospholipase C-generating inositol 1, 4, 5-triphosphate and 1, 2-diacylglycerol (DAC) leading to increased cytosolic Ca^{2+}. The enhanced intracellular Ca^{2+} levels appear to account for the different pharmacological properties promoted through the receptor including nitric oxide (NO) production, liberation of arachidonic acid from phospholipids, contraction of smooth muscles, dilatation of arterioles and capillaries, vascular permeability in vessels as well as stimulation of afferent neurons, and increased cAMP, and also cGMP levels [64, 147] (see also Table **2**). This receptor also stimulates nuclear factor kappa B (NFκB) by Gαq/11 and Gβγ upon binding of agonist, while stimulation of NFκB occurs only *via* Gβγ leading to (pro)inflammatory mediators [70, 89, 148]. The number of tissues and cell types in which a H1R-mediated signals increases in either inositol phosphate accumulation or intracellular calcium mobilization has been described extensively and further details are provided in several comprehensive reviews [89, 149, 150]. In Chinese hamster ovary (CHO) cells Ca^{2+} mobilization and [3H]inositol phosphate accumulation has been observed due to stimulation by histamine when CHO cells are transfected with H1R-complementary deoxyribonucleic acid (cDNA) of the human, bovine, and guinea pig [150, 151]. It is worth demonstrating that in some tissues histamine can stimulate inositol phospholipid hydrolysis independently of H1Rs. Thus, in the longitudinal smooth muscle of guinea pig ileum and neonatal rat brain [92, 152], a component can be identified in response to histamine that is resistant to inhibition by H1R-antagonists. It is yet to be established whether these effects are due to "tyramine-like" effects of histamine on neurotransmitter release or direct effects of histamine on the associated G-proteins [153, 154]. In addition to well known effects on the inositol phospholipid signal transduction systems, several other signal transduction pathways can lead to stimulation of H1R and it seems to be secondary to changes in intracellular Ca^{2+}concentration or protein kinase C (PKC) activation. Thus, nitric oxide synthase activity (*via* a Ca^{2+}/calmodulin-dependent pathway), and subsequent stimulation of soluble guanylyl cyclase in a wide variety of various cell types can be activated by histamine [155-158]. The H1R can stimulate the arachidonic acid release and arachidonic acid metabolites synthesis such as prostacyclin and thromboxane [150, 159]. It is being interestingly demonstrated that the histamine-stimulated release of arachidonic acid is partially inhibited (~ 40%) by pertussis toxin, when CHO-K1 cells transfected with the guinea pig H1R and the same response is also shown in HeLa cell possessing a native H1R to resist pertussis toxin treatment [150]. The substantial changes in the intracellular levels of cAMP can be produced by H1-receptor activation, but in most tissues, H1R activation does not stimulate adenylyl cyclase directly, and acts for the amplification of cAMP effects to histamine H2-, adenosine A2-, and also vasoactive intestinal polypeptide receptors [160-162]. The role of both intracellular Ca^{2+} ions and protein kinase C has been demonstrated in various cases in this augmentation response [161]. H1R stimulation can also lead to both cAMP responses and to an increasement of forskolin-activated cAMP formation when CHO cells are transfected with the bovine or guinea pig H1R [150, 163].

B. Histamine H2-Receptor

1. Cellular Distribution and Functional Characterization

The H2R is located on chromosome 5 in humans. Similar to what has been demonstrated for H1R, the histamine binds to transmembrane (TM) domains 3 (aspartate) and TM 5 (threonine and aspartate). The short 3rd intra-cellular loop and the long C-terminal tail make a suitable feature of H2R subtype, and the rat N-terminal extracellular tail has N-linked glycosylation sites [164]. Similar to H1R, H2R is expressed in different cell types (Table **2**). It has been documented that H2R is mostly involved in suppressive activities

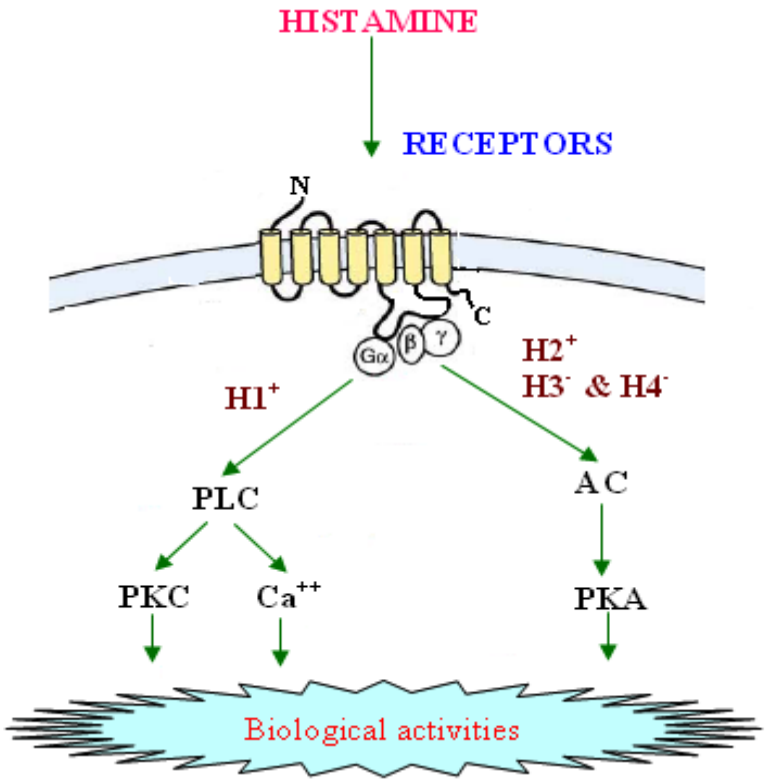


Fig. (4). The classical binding sites of histamine and their main signaling pathways such as AC (adenylate cyclase), PKC (protein kinase C), PKA (protein kinase A), PLC (phospholipase C), $H1^+$ or $H2^+$ (stimulation *via* H1 or H2 receptor), $H3^-$ & $H4^-$ (inhibition *via* H3 and H4 receptors).

of histamine, while positive effects are mediated through H1R. It was quite clear that the activation of H2R regulates various functions of histamine including heart contraction, gastric acid secretion, cell proliferation, differentiation and immune response. It has been demonstrated that H2R antagonists, such as zolantidine, is active in the treatment of stomach and duodenal ulcers and it strongly suggests that the clinical potency relates to the antagonistic effect of these drugs on the secretion of stomach acids [14].

Hill [89] designed a study to map the distribution of H2Rs by using radiolabeled H2R-antagonists, and achieved more affinity with [3H] titotidine (Table **1**) for the H2R in guinea pig brain, lung parenchyma, and CHO-K1 cells transfected with the human H2-receptor cDNA [165-167], but it was not successful in the studies of rat brain [168]. The most successful H2R-radioligand is [125I]iodoaminopotenti-dine, which has high affinity (K_D 50.3 nM) for the H2R in brain membranes (Table **1**) [129, 169-171] and also in CHO-K1 cells expressing the cloned rat H2R [171]. This compound has also been used for autoradiographic mapping of H2Rs in the brain of mammal [131, 170]. [125I]iodoaminopotentidine is also the most successful H2R-radioligand (Table **1**), which was used to map the distribution of H2Rs in human brain with highest densities in the basal ganglia, hippocampus, amygdale, and cerebral cortex, and also lowest densities were identified in cerebellum and hypothalamus [170]. In guinea pig brain, a similar distribution has been observed [129]. Irreversible labeling has also been successfully seen by [125I]iodoazidopotentidine (Table **1**) [129, 169]. H2R-stimulated cyclic AMP accumulation or adenylyl cyclase activity in Fig. (**4**) has been shown in various tissues including gastric cells, cardic tissue and brain [165, 172, 173] and gastric cells [174]. The potent effect of H2Rs have been demonstrated on gastric acid secretion and the inhibition of this secretory process through H2R antagonists had provided regulatory evidence for physiological role of histamine in gastric acid secretion [175, 176]. In cardiac tissues of most animal species, high concentrations of histamine were present which can mediate positive chronotropic and inotropic impacts on atrial or ventricular tissues by H2R stimulation [177, 178]. Also H2R-mediated smooth muscle relaxation has been documented in vascular smooth muscle, uterine muscle and in airways [179-183]. Hill [89] had demonstrated that the effects of H2Rs can inhibit a variety of functions within the immune system. H2Rs have been shown to negatively regulate the release of histamine on basophils and mast cells [184, 185]. The inhibition of antibody synthesis, T-cell proliferation, cell-mediated cytolysis, and cytokine production were the increasing evidence of H2Rs on lymphocytes [186-189]. The chemical structure of specific H2R-antagonist and -agonists are shown in Figs. (**5**, **6**).

2. Structural Biology of Receptor

The structural studies of H2R have been demonstrated using [125I]iodoazidopotentidine and sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and it was suggested that the H2R in guinea pig hippocampus and striatum has a molecular weight of 59 kDa [129]. However, comparison with the calculated molecular weights (40.2 to 40.5 kDa) for the cloned H2Rs indicates that the native H2R in the brain of guinea pig was glycosylated. It was highly significant with the proposal that entire cloned H2R proteins

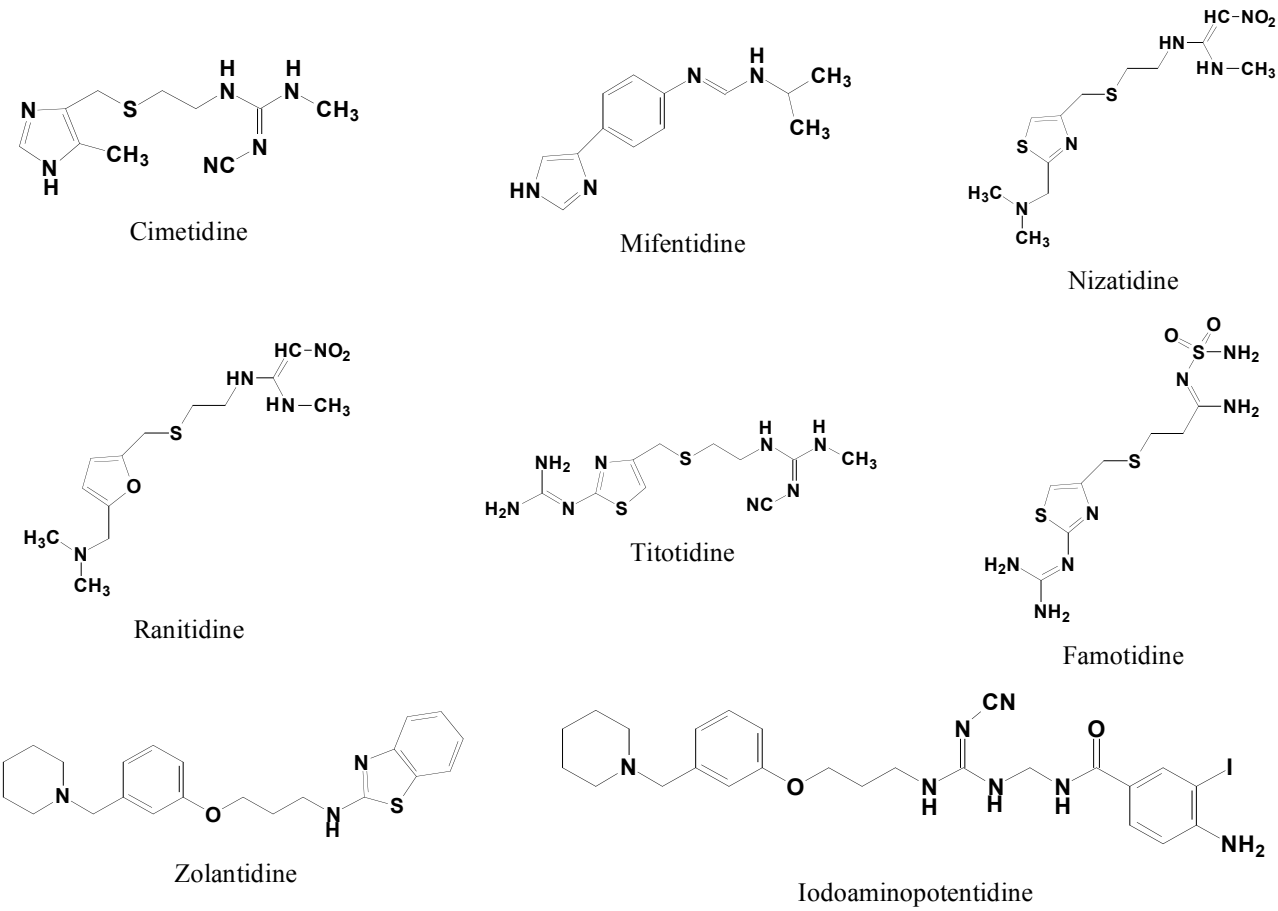


Fig. (5). Chemical structures of some histamine H2-receptor-antagonists.

possess N-glycosylation sites in the N-terminus region [190-192]. Fukushima *et al.* [193] has suggested that removal of these glycosylation sites by site-directed mutagenesis showed that N-glycosylation of the H2R is not essential for cell surface localization, ligand binding, or coupling *via* Gs to adenylyl cyclase. Gantz and colleagues for the first time successfully cloned H2R using the polymerase chain reaction to amplify a partial length H2R sequence from canine gastric parietal cDNA using degenerate oligonucleotide primers and this sequence was then used to identify a full length H2R clone following screening of a canine genomic library [167]. Following this cloning, many researchers have cloned the rat, human, guinea pig, and mouse H2Rs [167, 191, 192, 194]. These intronless gene (DNA) sequences encode 359 amino acids for canine, human, guinea pig or 358 amino acids for rat receptor protein which has the general properties of a G-protein-coupled receptor (GPCR) (Table **2**). The radioligand binding studies using [125I]iodoaminopotentidine were attempted to show the expression of rat and human H2R proteins in CHO cells and revealed the expected pharmacological specificity as shown in Table **1** [150, 171]. Chromosomal mapping studies have demonstrated that the H2R gene was localized to human chromosome 5 [192]. Birdsall [140] has compared H2R sequence with other biogenic amine G-protein coupled receptors (GPCRs), and demonstrated that an aspartate in transmembrane (TM) domain 3 and an aspartate and threonine residue in TM 5 were more responsible for histamine binding. Replacement of aspartate (98) with asparagine residue in the canine H2R provides significant results in a receptor that does not bind the titotidine, an antagonist, and hence does not stimulate cyclic adenosine monophosphate (cAMP) accumulation in histamine response [195]. On changing the aspirate (186) residue of TM 5 to an alanine residue there occurs complete loss of the antagonist titotidine binding without affecting the EC 50 for cAMP formation in response to histamine stimulation. Other change was observed on changing the threonine (190) residue to an alanine residue, resulted in a lower K_D for titotidine antagonist and also a reduction in both the histamine EC 50 value and maximal cAMP response [195]. Mutation of Aspirate (186) and Glycine (187) residue in the canine histamine H2-receptor to Alanine (186) and Serine (187) residue produces a bifunctional receptor, which can be activated through adrenaline, and inhibited *via* both cimetidine and propranolol [196]. Thus, these results indicate that pharmacological specificity of the H2R resides in only limited key amino acid residues.

3. Signaling Mechanisms

H2R is coupled both to adenylate cyclase and to phosphoinositide second messenger systems *via* separate GTP-dependent mechanisms. Receptor binding stimulates activation of c-Fos, c-Jun, protein kinase C (PKC) and p70S6kinase [14, 89, 145, 174] see in Fig. (**4**). Histamine

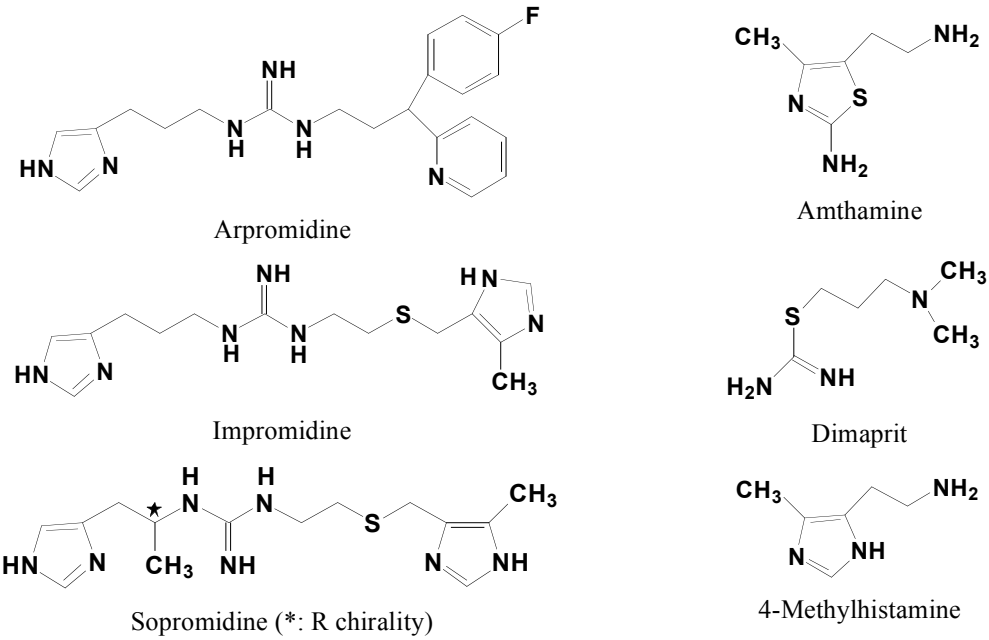


Fig. (6). Chemical structures of some histamine H2-receptor-agonists.

was proved to be a highly potent stimulant of cAMP accumulation in various cells, and H2R-dependent impacts of histamine were predominantly mediated through cAMP [14, 174], particularly those of central nervous system (CNS) origin [23]. Thus, H2R-mediated impacts on cAMP accumulation have been well documented and had been demonstrated in brain slices, gastric mucosa, fat cells, cardiac myocytes, vascular smooth muscle, basophils and neutrophils [23, 172, 197-199]. In addition, H2R-mediated cAMP accumulation had been observed in Chinese hamster ovary (CHO) cells transfected with the rat, canine, or human H2R cDNA [167, 190, 193, 200]. In both brain and cardiac muscle membranes, the direct stimulation of adenylyl cyclase activity in cell free preparations had been detected [201, 202].

However, Hill [89] had suggested that the caution is required regarding the interpretation of receptor characterization studies using histamine-stimulated adenylyl cyclase activity alone. A most striking feature of studies of H2R-stimulated adenylyl cyclase activity in membrane preparations was the potent antagonism demonstrated with certain neuroleptics and antidepressants [204]. In intact cellular systems, most of the neuroleptics and antidepressants were approximately 2 orders of magnitude weaker as antagonists of histamine-stimulated cAMP accumulation [203, 205]. One highly potential explanation of these variations resides within the buffer systems used for the cell-free adenylyl cyclase assays, and some differences in potency of some antidepressants and neuroleptics have been demonstrated when membrane binding of H2Rs has been evaluated using [125I]iodoaminopotentidine (Table **1**). However, the variations observed in the Ki values deduced from studies of ligand binding in different buffers are not as large as the variations in K_B values obtained from functional studies. For example, in the case of amitriptyline, no difference was observed in binding affinity in Krebs and Tris buffers [206]. In addition to Gs-coupling to adenylyl cyclase, H2Rs are coupled to other signaling systems also. For example, H2R stimulation has been demonstrated to enhance the intracellular free concentration of calcium (Ca^{2+}) ions in gastric parietal cells [207, 208]. In some cell systems, $G\alpha_q$ coupling to PLC and intracellular Ca^{2+} had been demonstrated (Table **2**). In HL-60 cells, a similar calcium (Ca^{2+}) response to H2R stimulation had been demonstrated [209], and similar case was observed in hepatoma-derived cells transfected with the canine H2Rs cDNA [210]. Therefore, the influence on $[Ca^{2+}]i$ was accompanied by both an increase in inositol trisphosphate accumulation and a stimulation of cAMP accumulation in these latter cells [210]. It was interesting to note that in these cells the H2R-stimulated calcium and inositol trisphosphate responses were both inhibited by cholera toxin treatment, whereas cholera toxin produced the expected increase in cAMP levels [208, 210]. H2Rs release Ca^{2+} from intracellular calcium stores in single parietal cells [211] and no effect of H2R agonists was observed on intracellular calcium levels or inositol phosphate accumulation in CHO cells transfected with the H2R of human [144]. Thus, the effect of H2R stimulation on intracellular Ca^{2+} signaling may be highly cell-specific.

The stimulation of H2R produces both inhibition of P2u-receptor-mediated arachidonic acid release and an increase in cAMP accumulation in CHO cells transfected with the rat H2R [171]. However, Traiffort *et al.* [171] had demonstrated that the effect on phospholipase A2 activity (i.e., arachidonic acid release) was not mimicked by forskolin, PGE1, or 8-bromo-cAMP, suggesting a mechanism of activation that is independent of cAMP-mediated protein kinase A activity. However, inhibitory effects of H2R stimulation were observed on phospholipase A2 activity in CHO cells transfected with the human H2R [200]. Thus, these cAMP-independent effects might depend on the level of receptor expression or subtle differences between clonal cell lines.

C. Histamine H3-Receptor

1. Cellular Distribution and Functional Characterization

The function of histamine as neurotransmitter has been proved with the discovery of the H3R. It was mainly involved in brain functions, also the peripheral effect of histamine on mast cells *via* H3Rs, which mainly involves the nervous system, and might be connected to a local neuron-mast cell interaction [212]. Its involvement in cognition, sleep-wake status, energy homeostatic regulation and inflammation had attracted many pharmaceutical researches for numerous, so far unmet, therapeutic approaches in different peripheral, but mainly central diseases [213, 214]. A recent study had reported that it is presynaptically located as autoreceptor controlling the synthesis and release of histamine [215]. It was observed that H3-autoreceptor activation stimulates the negative feedback mechanism that reduces central histaminergic activity [216]. H3R's heterogeneity in binding and its functional studies has well been documented, and suggested more than one H3R subtype. This assumption had been confirmed by demonstration of several H3R variants, generated from the complex H3R gene by alternative splicing. The three functional isoforms have been found in the rat, and they all vary in length of the 3rd intracellular loop, their distinct central nervous system (CNS) localization, and differential coupling to adenylate cyclase and MAPK signaling. Similar results in case of humans were obtained [217-219].

Thus, numerous isoforms are found in different species and different tissues leading to the assumption that signaling fine-tuning may be controlled *via* receptor oligomerization or formation of isoforms [220].

H3R is anatomically localized primarily to the CNS with prominent expression in basal ganglia, cortex hippocampus and striatal area. In the periphery, H3R can be found with low density in gastrointestinal, bronchial and cardiovascular system [221]. The high apparent affinity of R-(α)-methylhistamine for the H3R has enabled the use of this compound as a radiolabeled probe (Table **1**) [222]. In rat cerebral cortical membranes, this compound (R-(α)-methylhistamine) has been used to identify a single binding site, and which in phosphate buffer has the important pharmacological characteristics of the H3R [222, 223]. In rat brain membranes, [3H]R-(α)-methylhistamine binds with high affinity (K_D 50.3 nM), although its binding capacity is low (~ 30 fmol/mg protein) [222]. It was significantly notable that the autoradiographic studies with [3H]R-(α)-methylhistamine have described the presence of specific thioperamide-inhibitable binding in several rat brain regions, especially cerebral cortex, striatum, hippocampus, olfactory nucleus, and the bed nuclei of the stria terminalis, which receive ascending histaminergic projections from the magnocellular nuclei of the posterior hypothalamus [222, 224]. In human brain and the brain of nonhuman primates, the H3Rs have also been visualized [225]. H3R binding has also been characterized using [3H]R-(α)-methylhistamine in guinea pig lung [222], guinea pig cerebral cortical membranes [226], guinea pig intestine and guinea pig pancreas [227]. Nα-methylhistamine as a radiolabeled probe had proved successful for the H3R (Table **1**). The relative agonist activity of Nα-methylhistamine (with respect to histamine) was significantly similar for all three histamine receptor (HRs) subtypes, but the binding affinity of histamine and Nα-methylhistamine for the H3R was several orders of magnitude higher than for either H1- or H2-receptors [23, 131]. Nα-methylhistamine can identify high-affinity H3R sites in both rat [228, 230] and guinea pig [227] brain. The binding of H3-receptor-agonists to H3Rs in brain tissues was found to be regulated by guanine nucleotides, implying its relation to heterotrimeric G-proteins [222, 223, 228, 229]. Also the binding of H3R agonists appears to be more sensitive to several cations. For example magnesium (Mg^{2+}) and sodium (Na^{+}) ions inhibit [3H]R-(α)-methylhistamine binding in guinea pig and rat brain [226], and the presence of calcium (Ca^{2+}) ions has been shown to reveal heterogeneity of agonist binding [223]. It is important to note that the inhibitory effect of sodium (Na^{2+}) ions on agonist binding means higher B_{max} values that were usually obtained in sodium-free Tris buffers compared with the Na/K phosphate buffers [228]. The multiple histamine H3R subtypes exist in rat brain (termed H_{3A} and H_{3B}) on the basis of [^{3}H]N$^{\alpha}$-methylhistamine binding in rat cerebral cortical membranes in 50 mM Tris buffer (Table **1**) [230]. Based on these conditions, the selective histamine H3-antagonist thioperamide can discriminate two affinity-binding states [230]. However, Heterogeneity of thioperamide binding was sodium (Na^{2+}) ions concentration dependent or depends on guanine nucleotides within the incubation medium [228]. Thus, in the presence of 100 mM sodium chloride, thioperamide binding conforms to a single binding isotherm [228], and H3R can exist in different conformations for which thioperamide, but not agonists or other H3R-antagonists (clobenpropit) can discriminate. This suggests that the equilibrium between these conformations is altered by guanine nucleotides or sodium (Na^{2+}) ions [228]. If this speculation is correct, it is likely that the different binding sites represented resting, active, or G-protein-coupled conformations of the H3R. Furthermore, if thioperamide preferentially binds to uncoupled receptors, then this compound should exhibit negative efficacy in functional assays. Radiolabeled H3R antagonists [125I]iodophenpropit, has been used to label histamine H3Rs in rat brain membranes (Table **1**) [231]. The inhibition curves for iodophenpropit and thioperamide were consistent with interaction with a single binding site, but H3R agonists were found to be able to discriminate both high- [4 nM for R-(α)-methylhistamine] and low- [0.2 mM for R-(α)-methylhistamine] affinity binding sites [231]. [^{3}H]GR16820 and [^{125}I]iodoproxyfan have been proved useful as high-affinity radiolabeled H3R-antagonists [232, 233]. In rat striatum, in the IUPHAR classification of histamine receptors 267 presence of guanine nucleotides such as guanosine 59*O*- (3-thiotriphosphate) (GTPgS), 40% of the binding sites exhibited a 40-fold lower affinity for H3-agonists, providing further evidence for a potential linkage of H3Rs to G-proteins. In rat brain membranes, [^{3}H]thioperamide and [^{3}H]5-methylthioperamide, both have been used to label H3R [234]. However, [^{3}H]thioperamide was shown to bind additionally to low affinity, high-capacity, non H3R sites [234]. The localization of H3Rs had come out from functional studies, primarily involving inhibition of neurotransmitter release. The H3R was first characterized as an auto receptor regulating histamine synthesis and release from rat cerebral hippocampus, cortex, and striatum [222, 235]. In human

cerebral cortex, the H3R-mediated inhibition of histamine release has also been demonstrated [235]. Differences in the distribution of H3R binding sites and the levels of histidine decarboxylase (an index of histaminergic nerve terminals) suggested at an early stage that H3Rs were not confined to histamine-containing neurons within the mammalian CNS [222, 236]. It has been documented by the observations that H3Rs can regulate neurotransmitter release in mammalian brain as serotonergic, noradrenergic, cholinergic, and dopaminergic [237-240]. H3R activation inhibits the firing of the histamine-neurons in the posterior hypothalamus by a mechanism different from auto-receptor functions found on other aminergic nuclei, and presumably a block of Ca^{2+} current [241]. H3Rs were found to regulate the release of sympathetic neurotransmitters in guinea pig mesenteric artery [242], human saphenous vein [243], guinea pig atria [244, 245], and human heart [246].

An important inhibitory effect of H3R activation on release of neuropeptides (tachykinins or calcitonin gene-related peptide) from sensory C fibers has been investigated from airways [247], meninges [248], skin [249], and heart [250]. The modulation of acetylcholine, capsaicin, and substance P effects by H3Rs in isolated perfused rabbit lungs has also been reported [251]. There was evidence that H3R activation can inhibit the release of neurotransmitters from nonadrenergic- noncholinergic nerves in guinea pig bronchioles [252] and ileum [253]. In guinea pig ileum, the H3R-antagonists betahistine and phenylbutanoylhistamine were much less potent as inhibitors of H3R-mediated effects on nonadrenergic-noncholinergic transmission than they were as antagonists of histamine release in rat cerebral cortex [253].

A similar low potency has been investigated for betahistine and phenylbutanoyl histamine antagonists for antagonism of H3R-mediated [^{3}H]acetylcholine release from rat entorhinal cortex [239], and antagonism of H3R-mediated 5-hydroxytryptamine release from porcine enterochromaffin cells [254]. These investigations provide possible support for the existence of distinct H3R subtypes and it had been shown that phenylbutanoylhistamine can inhibit [^{3}H] acetylcholine release from rat entorhinal cortex slices, and synaptosomes by a nonhistamine receptor mechanism [255]. Therefore, the potency of phenylbutanoylhistamine as H3R-antagonist in those preparations can be highly underestimated because of the additional nonspecific activities of the drug [255]. The inhibitory effect of H3-receptor stimulation on 5-HT release from porcine enterochromaffin cells in strips of small intestine [254] provides evidence for H3-receptors regulating secretory mechanisms in non-neuronal cells. Hence, it can be concluded that H3R may be present in gastric mast cells or enterochromaffin cells and exert an inhibitory effect on histamine release and gastric acid secretion. In conscious dogs, H3R activation had been observed to inhibit gastric acid secretion [256], and in isolated rabbit fundic mucosal cells. An autoregulation of histamine synthesis by H3R had also been investigated [257]. It had been demonstrated that H3R relaxes rabbit middle cerebral artery by an endothelium-dependent pathway involving both nitric oxide and prostanoid release [258, 259]. H3-receptor stimulation can activate adrenocorticotropic hormone release from the pituitary cell line AtT-20 [260]. Therefore, H3R provides constitutive properties, which means part of the receptor population spontaneously undergoes allosteric transition leading to a conformation, to which G protein can bind [261, 262], and also H3R-knock out mice manifest an obese phenotype (characterized through increased body weight, food intake, adiposity, and reduced energy expenditure). Recently, it has been observed that H3R express insulin and leptin resistance as well as a diminution of the energy homeostasis-associated genes UCP1 and UCP3 [263]. The chemical structure of specific H3R-antagonists and –agonists are shown in Figs. (**7**, **8**).

2. Structural Biology of Receptor

The H3-receptor is also G protein-coupled (GPCR) and had been cloned [22]. Its gene consists of 4 exons spanning 5.5 kb on chromosome 20 (20q13.33) in humans (Table **2**). Structural studies of H3R are very limited and there are only few reports on its purification studies. By using [^{3}H]histamine as a radioligand, the solubilization of a H3R protein from bovine whole brain has been reported and then Size-exclusion chromatography has revealed an apparent molecular mass of 220 kDa [229]. However, because the solubilized receptor retained its guanine nucleotide sensitivity and it is likely that the molecular mass of 220 kDa represents a complex of receptor, G-protein, and digitonin [229]. Cherifi *et al*. [264] have reported the solubilization (with Triton X-100) and purification of the H3-receptor protein from the human gastric tumoral cell line HGT-1. After gel filtration and sepharose-thiopheramide affinity chromatography, protein has been purified with a molecular mass of approximately 70 kDa (see Table **2**).

3. Signaling Mechanisms

The signal mechanisms used by the H3R remain largely subject to hypothesis, but there is increasing evidence to suggest that this receptor belongs to the G-protein-coupled receptors (Gi/o) (Table **2**), and its activation leads to inhibition of cAMP formation, accumulation of Ca^{2+} and stimulation of mitogen-activated protein kinase (MAPK) pathway [212], see Fig. (**4**). This evidence had been obtained from ligand-binding studies that involve the modulation by guanine nucleotides of H3R-agonist binding [223, 226, 228-230] and H3R-agonist inhibition of H3R-antagonist binding [231, 233, 265]. The direct evidence for a functional H3R-G-protein linkage came from studies of [^{35}S]GTPgS binding to rat cerebral cortical membranes [266]. In rat cerebral cortical membranes, the presence of H1R- and H2R-antagonists (0.1 mM mepyramine and 10 mM titotidine), and both R-(α)-methylhistamine and N-(α)-methylhistamine generated a concentration dependent stimulation of [35S]GTPgS binding (EC_{50} = 0.4 and 0.2 nM) [266]. Notably, this response was inhibited *via* pretreatment of membranes with pertussis toxin, and implying a direct coupling to a Gi or Go protein [266]. The evidence of pertussis toxin-sensitive G-proteins in the response to H3R stimulation came from studies of H3R signaling in human and guinea pig heart [244, 246]. H3R-activation appeared to lead to an inhibition of N-type Ca^{2+} channels responsible for voltage dependent release of noradrenaline in human and guinea pig heart [244, 246], but several investigations have failed to demonstrate an inhibition of adenylyl cyclase activity in different tissues and cells [264, 267] which might suggest that H3Rs couple to Go proteins.

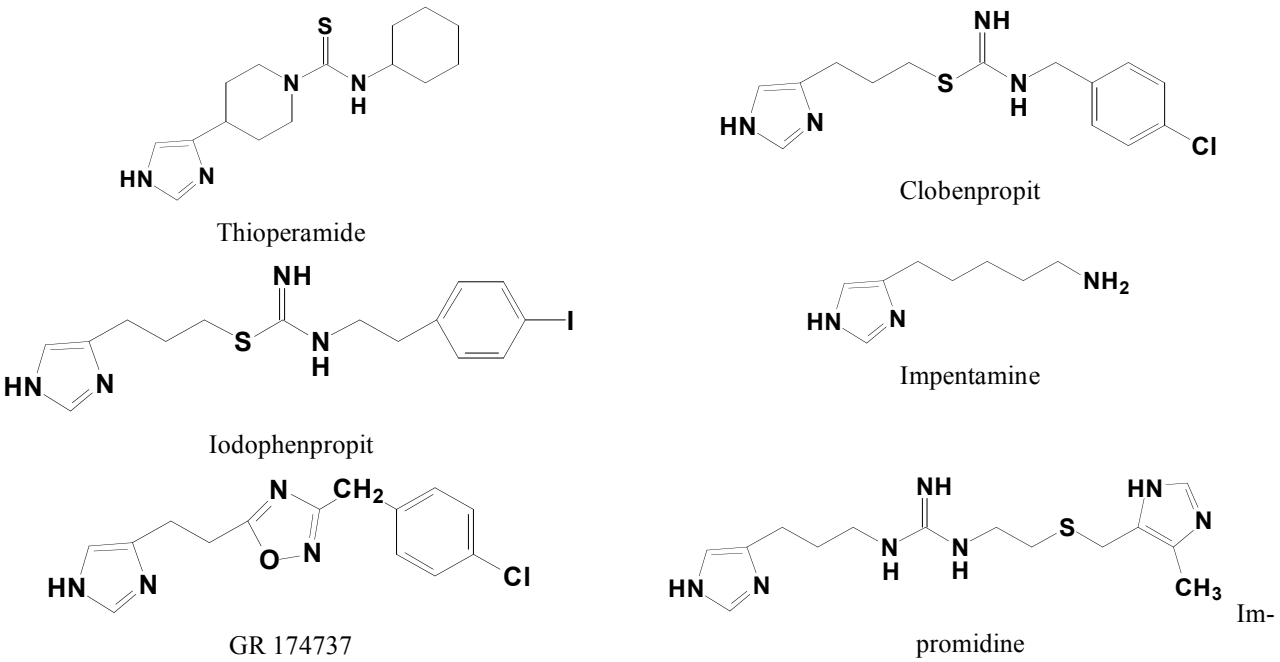


Fig. (7). Chemical structures of some histamine H3-receptor-antagonists.

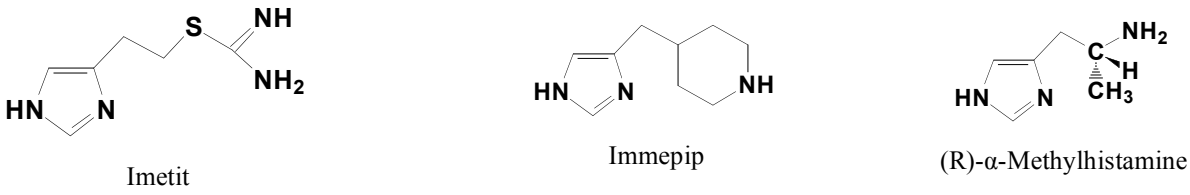


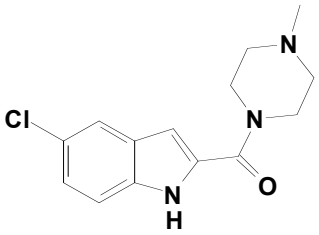
Fig. (8). Chemical structures of some histamine H3-receptor-agonists.

D. Histamine H4-Receptor

1. Cellular Distribution and Functional Characterization

The discovery of the H4-receptor adds a new chapter to the histamine story. The H4R is preferentially expressed in intestinal tissue, spleen, thymus, medullary cells, bone marrow and peripheral hematopoietic cells, including eosinophils, basophils, mast cells, T lymphocytes, leukocytes and dendritic cells. However, moderate positive signals have also been detected in brain, spleen, thymus, small intestine, colon, heart, liver and lung. Although first expression studies demonstrated the absence of H4Rs in the central nervous system (CNS), but in situ hybridization studies suggested evidence for their human brain localization in low density. The relatively restricted expression of the H4R provides an important role in inflammation, hematopoiesis and immunity by the regulation of H4R expression *via* stimuli such as IFN, TNF-α and IL-6, IL-10, and IL-13. Basophils and mast cells express H4R-mRNA. The H4R mediates chemotaxis of mast cells and eosinophils as well as control cytokine release from dendritic cells and T cells. It was demonstrated that the H4R is participated, along with the H2R, in the control of IL-16 release from human lymphocytes. It had also been hypothesized that H4R selective antagonist might be useful in helping to treat anti-inflammatory potency in models of asthma, arthritis, colitis and pruritis. Antagonists, such as JNJ 7777120, have also been shown to be effective in various model of inflammation. Up to now, very little is known about the biological functions of H4R. There are few reports in the literature, providing evidence for chemotactic activity in mast cells and eosinophils or control of IL-16 production by $CD8^+$ lymphocytes. It suggests an important role of H4R in the regulation of immune function and offers novel therapeutic potentials for histamine receptor ligands in allergic and inflammatory diseases [268-280]. A recent study showed the role of H4R in mast cell, eosinophil, and T cell function, as well as the effects of its antagonist, JNJ 7777120, in a mouse peritonitis model pointing to a more general role for H4R in inflammation. Selective H4R antagonists like JNJ 7777120 shows potential role in treatment of inflammation in humans. In many diseases such as allergic rhinitis, asthma, and rheumatoid arthritis, conditions where eosinophils and mast cells are involved, H4R antagonists have therapeutic utility [281]. The discovery of H4R and its emerging role in inflammation had spurred new interest for the functions of histamine in inflammation, allergy and autoimmune diseases. Early results in animal models suggest that H4R antagonists may have utility in treating various conditions in humans, in particular, in diseases in which histamine is known to be present and in which H1R antagonists are not clinically effective [282]. Obviously, a better functional characterization of H4R benefits from the exploitation of new, specific tools, such as the recently developed potent and selective non-imidazol H4R antagonist [281]. It can be expected that the role of H4R will be more important in autoimmune disorders, allergic conditions and nociceptive responses in the

H4-receptor antagonists



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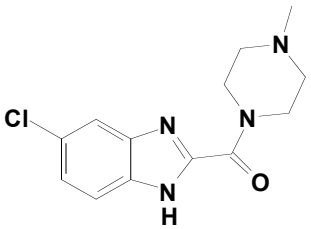

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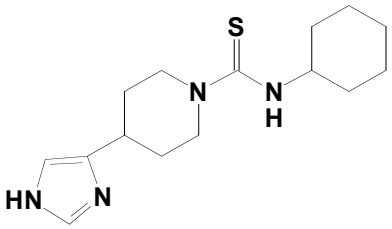
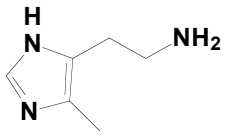
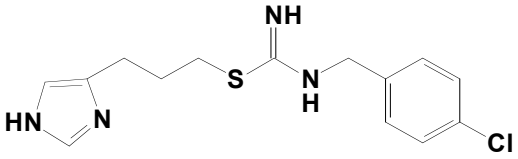


Thioperamide (partial H4R-antagonist)

H4-receptor agonists



4-Methylhistamine



Clobenpropit (partial H4R-agonist)

Fig. (9). Chemical structures of specific H4-receptor-antagonists and -agonists.

near future. The chemical structure of specific H4R-antagonists and –agonists are shown in Fig. (**9**).

2. Structural biology of Receptor

The human H4-receptor gene was mapped to chromosome 18q11.2 which encodes a 390 amino acid and also related to seven transmembrane G-protein coupled receptor. It shares 37-43% homology (58% in transmembrane regions) with the H3-receptor and a similar genomic structure. The H4R gene spans more than 21 kbp and contains three exons, separated by two large introns (>7 kb) (Table **1**) with large interspecies variations from 65-72% homology in sequences. Analysis of the 5′ flanking region did not reveal the canonical TATA or CAAT-boxes. The promoter region contains several putative regulatory elements involved in proinflammatory cytokine signaling pathways. H4Rs are coupled to Gi/o, which initiates various transduction pathways such as inhibition of forskolin-induced cAMP formation, enhanced calcium influx and MAPK activation. In accordance with the homology between the two receptors, several H3R-agonists and antagonists were recognized by the H4R, although with different affinities. It has been observed that H3R-agonist R-α-methyl histamine acts on H4R with several hundred times less potency. Similar effect has been seen with thioperamide, the classical H3R antagonist which also behave like a H4R antagonist (Table **1**), though with a much lower affinity and clobenpropit, also a H3R antagonist, which exerts agonistic activity on H4R [Table **1**; 21, 273, 274, 283-286].

Albeit histamine binding to H4R is very similar to that reported for the other histamine receptors (it shows the importance of the Asp 94 residue in transmembrane region (TM) 3 and the Glu 182 residue in the TM 5) however, some differences exist and these were exploited to design specific tools. Mouse, rat and guinea pig H4Rs have been cloned and characterized and were found to be only 68, 69, and 65% homologous respectively to their human counterpart. These studies have revealed substantial pharmacological variations between species, with higher affinity of histamine for human and guinea pig receptors than for their rat and mouse equivalents [287].

3. Signaling Mechanisms

The signal mechanisms used by the H4R remain highly subject to the G-protein-coupled receptors (Gi/o), and its activation leads to an inhibition of adenylyl cyclase and downstream of cAMP responsive elements (CRE) as well as activation of mitogen-activated protein kinase (MAPK) and phospholipase C with Ca^{2+} mobilization (Table **2**); see Fig. (**4**).

IV. HISTAMINE: NON-CLASSICAL BINDING SITES

A. Cytochrome P450

The human cytochrome P450 (CYP450) superfamily comprises 57 genes encoding heme-containing enzymes, which are found in the liver as well as in extrahepatic tissues (adrenals, and peripheral blood leukocytes), where they can be stimulated by various stimuli [288, 289] (Fig. **10**). They are not only involved in metabolism of large number of foreign substances, but also play an important role in diverse physiological processes [generation, transformation or inac-

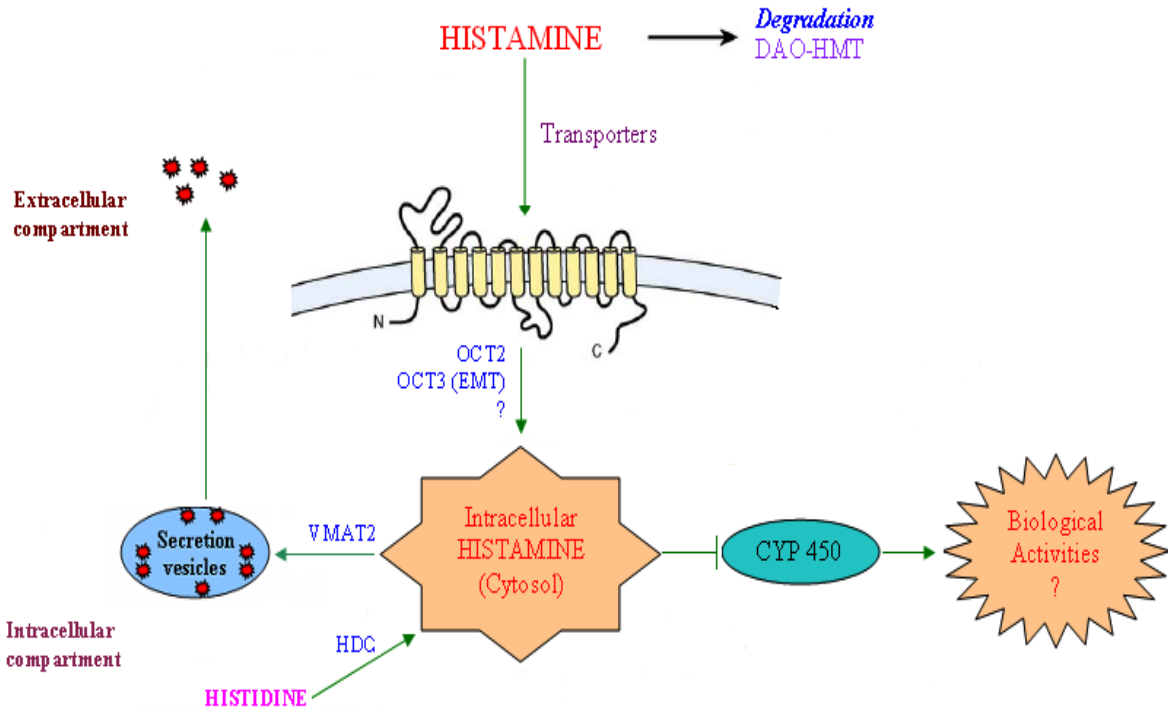


Fig. (10). The non-classical histamine binding sites and their main signaling pathways such as DAO: diamine oxidase; HMT: histamine methyl transferase; OCT: organic cation transporter; HDC: histidine decarboxylase; CYP 450: cytochrome P450; VMAT: vesicular monoamine transporter.

tivation of endogenous ligands (steroids and lipids)], which are involved in cell regulation [290].

Binding of histamine to CYP450 had been shown by Branders, who proposed a second messenger role for intracellular histamine *via* this binding site. This hypothesis was mainly based on a finding that N, N diethyl-2-(4-(phenylmethyl)phenoxy) ethanamine (DPPE), an arylalkylamine analogue of tamoxifen inhibits the binding of histamine to CYP450 [291]. DPPE allosterically modify histamine binding to the heme moiety of CYP450 enzymes and inhibited platelet aggregation, as well as lymphocyte and hematopoietic progenitor proliferation [292, 293]. The effect of DPPE on histamine binding was found to be highly complicated and depends on the nature of the P450 enzymes. Thus, it inhibits the action of histamine on CYP2D6 and CYP1A1, which enhances its effect on CYP3A4 and does not affect CYP2B6 [294]. The heme moiety of CYP450 binds to several histamine antagonists [295, 296], particularly H3R antagonists (thioperamide, clobenproprit and ciproxyfan) [297]. This property explains some effects of these antagonists, when used at high doses. Notably, histamine interacts with CYP450 and it has been demonstrated that CYP2E1 and CYP3A were upregulated in histidine decarboxylase (HDC)-deficient mice [298].

B. Transporters of Histamine

Histamine (2-(1H-imidazol-4-yl) ethanamine) is synthesized in the cytosol and requires a specific transport into secretory vesicules where it is sequestered. Vesicular monoamine transporters (VMATs) are proteins, which accomplish this specific task for several neurotransmitters [299] (Fig. **10**). The two subtypes of monoamine transporters are VMAT1 and VMAT2 (that have been cloned and characterized) but VMAT2 can transport histamine. Vesicular monoamine transporter 2 (VMAT2) had been cloned from rat and human brain, bovine adrenal medulla and a basophilic leukemia cell line. When histamine biosynthesis was enhanced then its expression was found to be up regulated by several stimuli. The increased VMAT2 expression in IL-3-dependent cell lines was enhanced with enhanced histamine synthesis in response to calcium (Ca^{2+})ionophore [300]. VMAT2 is responsible for the transport of histamine into secretory granules of enterochromaffin-like (ECL) cells. The gene expression of VMAT2 was found to be modulated *via* cytokines, either positively (TGFa) or negatively (IL-1 and TNF-α) [301]. VMAT2-deleted granules do not release histamine upon activation, even though granule cell fusion does still occur [302]. The bone marrow-derived mast cells from histidine decarboxylase (HDC)-deleted mice are completely devoid of endogenous histamine but can take up the mediator from histamine-supplemented medium and store it in secretory granules. Hence, two transporters are essential to:

1. insure the passage across the plasma membrane, and
2. cross the vesicular membrane.

First transporter has not been identified yet, but the second transporter seems to be vesicular monoamine transporter 2 (VMAT2). The non-neuronal monoamine transporters that actively remove monoamines from extracellular space have been described as organic cation transporter 1 (OCT1), OCT2, and extraneuronal monoamine transporter (EMT). EMT was also designated as OCT3. The expression of OCT1 was found to be restricted to liver, kidney and intestine, OCT2 in brain and kidney, while EMT showed a broad tissue distribution. It has been established that OCT1 cannot transport histamine, conversely to OCT2 and EMT for which

it is a good substrate [303]. Thus, EMT appeared to be a good candidate as histamine transporter in mast cells and basophils, accounting for their capacity to take up the mediator from the environment.

V. IMMUNE REGULATION BY HISTAMINE IN IMMUNOMODULATION AND ALLERGIC INFLAMMATION

Histamine exerts a very important immunomodulatory effect *via* H1-, H2-, H3-, and H4-receptors [1, 20, 128, 188, 189, 270, 304; Table **3**]. According to the cell differentiation stage and microenvironment influences, the receptors expression changes. Histamine shows proinflammatory or anti-inflammatory effects, depending on the predominance of the type of histamine receptor (H1R, H2R, H3R & H4R) and on the experimental system studied. Histamine had proinflammatory activity through the H1R, and is involved in the development of various aspects of antigen-specific immune response including the maturation of dendritic cells (DCs) and the modulation of the balance of type 1 helper (Th1) T cells and type 2 helper (Th2) T cells. Histamine blocks humoral immune responses by means of a specific mechanism in which it induce an increase in the proliferation of Th1 cells and in the production of interferon γ (IFN- γ). Histamine also stimulates the release of proinflammatory cytokines and lysosomal enzymes from human macrophages and shows the capacity to influence the activity of immune cells including mast cells, basophils, eosinophils, fibroblasts, lymphocytes, neutrophils, epithelial and endothelial cells. The role of histamine in autoimmunity and malignant disease through the H1R is well documented [20, 128]. Histamine also plays a pivotal role in allergic inflammation which is a complex network of cellular events and involves redundant mediators and signals. Histamine is released from the granules of mast cells and basophils ($Fc\varepsilon RI^+$ cells) along with several mediators such as tryptase, leukotrienes, prostaglandins, and other newly generated mediators. Histamine was found in relatively large (μg) quantities per 1 million cells, in contrast to leukotrienes and other mediators (which are present in picograms), after allergen challenge in sensitized persons. Most of the potent effects of histamine in allergic inflammation occur through H1Rs [1, 13, 20; Table **3**], while hypotension, flushing, headache, and tachycardia occur both by the H1- and H2-receptors in the vasculature [305]. Whereas, nasal congestion and cutaneous itch occurs both by the H1- and H3- receptors [306, 307]. Histamine also acts as a contributor to the late allergic response by generating a stimulatory signal for the production of cytokines, the expression of cell adhesion molecules and class II antigens.

VI. EFFECT OF HISTAMINE IN IMMUNE CELLS WITH RESPECT TO ALLERGIC DISEASES

Histamine's classical effects, expressed at the organ level, have been documented and were highly emphasized in allergies and autoimmune diseases. Histamine directly or indirectly influences the activity of various inflammatory/effector/immunologic cell types involved in the pathogenesis of several diseases. Indeed, several studies have suggested that histamine receptors (HRs) are expressed on mast cell and basophils; lymphocytes; neutrophils; monocytes, macrophages and dendritic cells (DCs); eosinophils; epithelial cells; endothelial cells, and therefore modulate the function of these cells in immune system.

A. Mast Cells and Basophils

Recent studies shed light on the potent role of histamine in mast cells and basophils, both types of cells can themselves be modulated by histamine as they express H1-, H2- and H4-receptors [271, 308, 309]. The peritoneal and skin mast cells exhibited aberrant granules with very low electron density, in HDC-deficient mice, which indicated the drastic decrease in the granule contents including granule proteases and sulfated proteoglycans [310]. The critical roles of histamine in cutaneous and systemic anaphylaxis have been suggested by using the HDC-deleted mice [311, 312] and it remained a possibility that diminished granule constituents, such as proteases, make contribution to the relief of anaphylaxis in the mutant mice. How histamine regulates allergic responses by maturation of tissue mast cells requires to comprehend detailed studies on the effect of absence of histamine on mast cell function. Impact of histamine was also demonstrated in the migration of mast cells which was mediated exclusively through the H4R [271]. It has been shown that histamine acting through H4Rs can stimulate chemotaxis of murine mast cells *in vitro* [271] and lead to changes in tissue localization *in vivo* [281]. A hematopoietic organ, bone marrow, contains certain types of cells which can produce histamine in response to IL-3 [30, 313]. The role of IL-3 -sensitized histamine synthesis in bone marrow remains to be clarified [39], however, a study suggested a unique circuit of newly synthesized histamine and its implication in basophil precursors [314]. It has been documented that bidirectional transport of histamine is facilitated largely through organic cation transporter 3 (OCT3) in the plasma membranes of the $Fc\varepsilon RI^+$, c-kit^- bone marrow cells. It had been demonstrated that intracellularly stimulated histamine in the organic cation transporter 3 (OCT3)-deleted cells has suppressive impacts on expression of HDC, IL-4, and IL-6. This suggests not only the feedback inhibition of histamine synthesis but also the suppression of Th2 cytokine production through immature basophils [303, 315]**.** In addition, histamine receptor binding studies with specific receptor antagonists have suggested that basophils express predominantly H2R, and these were involved in the regulation of IgE-stimulated histamine release, as demonstrated through increased histamine release in the presence of anti-IgE and cimetidine (a H2R antagonist) but not in the presence of anti-IgE and thioperamide (a H3R antagonist) [316-318]. H2Rs in mast cells show various effects such as inhibition of histamine release and modulation of cytokine production [319]. It has been suggested that H3R functions on mast cells but many of these properties may be attributed to the H4R as the ligands used were not specifically selective. H3R expression was not detected in some types of mast cells [271].

B. Lymphocytes

The expression of histamine receptors (HRs) on the cell surface of immunocompetent cells, including lymphocytes (B-cells and T-cells) and their effects mediated by receptors (HRs) have been published in several studies and significantly reviewed [320] (Fig. **11**). It has been concluded that both histamine receptors (H1 and H2) are present on the

Table 3. Immunopharmacological Profiles of Histamine Receptor Subtypes

Characteristics	Histamine H1R	Histamine H2R	Histamine H3R	Histamine H4R
[a]General function	Increased pruritus, pain, vasodilation, vascular permeability, hypotension; flushing, headache, tachycardia, bronchoconstriction, stimulation of airways, vagal stimulation of airway vagal receptors; decreased atrioventricular-node conduction time.	Increased gastric acid secretion, vascular permeability, hypotension, flushing, headache, tachycardia, chronotropic and inotropic activity, bronchodilatation, mucus production (airway).	Prevents excessive bronchoconstriction; mediates pruritus (no mast-cell involvement).	Differentiation of myeloblasts and promyelocytes.
[a]Function in immune modulation and allergic inflammation	Increases release of histamine and other mediators; increases cellular adhesion molecule expression and chemotaxis of eosinophils and neutrophils; increases antigen-presenting cell capacity, co-stimulatory activity on B cells; increases cellular immunity (Th1), IFN-γ, autoimmunity. Decreases humoral immunity and IgE production.	Decreased eosinophil and neutrophil chemotaxis; induction of interleukin-10, suppression of interleukin-12 by dendritic cells; development of Th2 or tolerance inducing dendritic cells; induction of humoral immunity; suppression of Th2 cells and cytokines; indirect role in allergy, autoimmunity, malignant disease, and graft rejection.	Probably involved in control of neurogenic inflammation through local neuron-mast cell feedback loops; proinflammatory activity; increased APC (antigen-presenting cell) capacity.	Increased Ca^{2+} flux in human eosinophils; increased eosinophil chemotaxis; increases IL-16 production (H2-receptor also involved).
[b]Physiological relevance	Cycle of sleeping and waking, food intake, thermal regulation, emotions and aggressive behavior, locomotion, memory, and learning, contraction of smooth muscles.	Neuroendocrine, gastric acid secretion.	Presynaptic heteroreceptor; decreased histamine, dopamine, serotonin, noradrenaline and acetylcholine release, sleep, food intake.	Chemotaxis.
[b]Pathophysiological relevance	Allergic reaction.	Gastric ulcer.	Cognitive impairment, seizure, metabolic syndrome?	Inflammation, immune reaction
[a, b]Antagonists	Clinically usable (Mepyramine, chlorpheniramine, astemizole, terfenadine, loratidine, triprolidine, diphenhydramine, cetirizine, desloratidine, fexofenadine)	Clinically usable (Cimetidine, zolantidine, tiotidine, femotidine, nizatidine, and ranitidine)	Clobenpropit, Iodophenpropit, Thioperamide	JNJ 7777120, JNJ 10191584

[399[a], 221[b]].

lymphocytes but there is only few data available on the functional significance of the H1R and the distribution of H2R on lymphocyte subsets in general, signaling through the H1R was associated with enhancement and signaling through the H2R with inhibition of lymphocyte responses. It has been suggested by several studies that histamine and its derivatives can inhibit the immune response by enhancing the activity of T suppressor cells through H2R and natural suppressor cells *via* H1R [321, 322]. The impacts of histamine on T helper lymphocytes are differential and complex; see in Fig. (**11**). T lymphocytes, mainly T helper lymphocytes, play a significant role in the pathogenesis of atopic asthma. Helper T lymphocytes can be divided into two subsets (T helper type 1 cells (Th1) and Th2) based on their cytokine profile and distinct functions and both the subsets play distinctive roles in the development, initiation, and regulation of the immune response. Th1 cells were found to be responsive in delayed type hypersensitivity (DTH) and cytotoxic response, while Th2 cells were involved in allergic disease *via* activating B-lymphocytes and regulating antibody (IgG and IgE) secretion; see in Fig. (**11**). Th1 cells secrete important cytokines as interleukin (IL)-2, IFN-γ, IL-3, and granulocyte monocyte colony stimulating factor (GM-CSF), while Th2 cells secrete cytokines such as IL-3, IL-4, IL-5, IL-10, IL-13, and GM-CSF. Histamine downregulates the proliferation of Th1 cells (which control cytotoxic response and delayed-type hypersensitivity) and upregulates the proliferation of Th2 cells (which regulate allergic disease and asthma) [323].

Histamine also regulates the development of an allergic state by enhancing the secretion of Th2 cytokines such as IL-4, IL-5, IL-10 and IL-13 and by inhibiting the production of Th1 cytokines IL-2 and IFN-γ and monokine IL-12 [324-330]. It had been demonstrated in several studies that histamine dose-dependently upregulate the secretion of Th2 cytokines (IL-5, IL-10, and IL-13) and down regulate the secretion of Th1 cytokines (IL-2 and IFN-γ) in cloned murine T helper cells [327-329]. It has also been demonstrated that Th1 and Th2 cells express distinct surface histamine receptor (HR) patterns (Th1 cells that express predominantly H1R and Th2 cells express H2R). Histamine increases Th1-type responses by triggering H1R and negatively regulates both Th1 and Th2-type responses by H2R as suggested by enhanced release of tumour necrosis factor (TNF)-α and de-

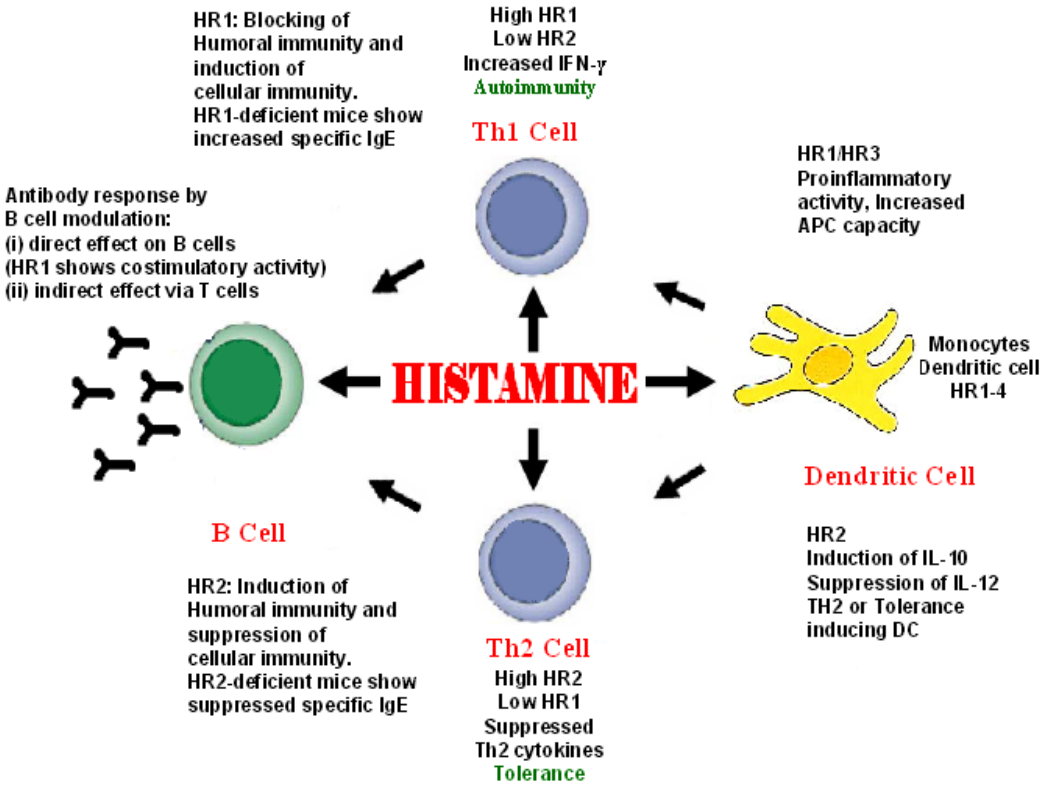


Fig. (11). Histamine regulates monocytes, dendritic cells, T cells and B cells in lymphatic organs and subepithelial tissues in allergic inflammation. Monocytes and dendritic cells express all four known histamine receptors (HR1, HR2, H3R and HR4). HR1 and HR2 induce proinflammatory activity and enhanced antigen presenting cell capacity, whereas HR2 plays an important suppressive role on monocytes and monocyte-derived dendritic cells (MDDC).

creased release of interleukin (IL)-4 and IL-13, respectively [331]. The differential expression of these cells to histamine is a result of the type of intracellular signals generated *via* histamine activation. Notably, H1R signaling involves calcium-dependent phospholipase stimulation and generation of IP3, while H2R signaling involves adenylate cyclase stimulation and cAMP formation.

The receptor binding study of human peripheral blood lymphocytes has suggested that histamine trifluoromethyltoludine (HTMT) derivative lead to a two-phase enhancement in intracellular calcium (Ca^{2+}) and an increase in inositol phosphate (IP3) production. The increase in calcium (Ca^{2+}) was thoroughly antagonized through high concentrations of histamine but not by the classical histamine H1-, H2- or H3- receptor antagonists [332]. These observations demonstrate that HTMT have a specific binding site on lymphocytes, which is different for three classic histamine receptors. Several functional studies demonstrated that histamine primarily modulates T-suppressor activity including delayed type hypersensitivity (DTH), cytotoxic T-lymphocyte-mediated target cell killing, cell-mediated lympholysis, and natural killer activity by H2R signaling [333]. Although, some studies suggest that activation of the H2Rs indirectly increases the allergic cascade. Suppressor T-cells were found to be more responsive to histamine than T helper cells or cytotoxic T cells [334]. Likewise, the response to histamine in T helper cells and cytotoxic T-cells was highly enhanced after mitogenic stimulation [334]. It is more important to note that in humans, histamine suppresses the proliferation of mixed T lymphocytes *via* H2R [335, 336]. Further, it had been confirmed that histamine inhibited lipopolysaccharide (LPS)-stimulated IFN-γ-gene expression from human peripheral blood mononuclear cells (PBMC) [337]. IFN-γ cytokine releases human CD4+T-cell clones, which are classified as either Th0, Th1 or Th2 based on their cytokines (IL-4 and IFN-γ) secretion patterns [338]. Notably, histamine-induced inhibition of IFN-γ secretion was seen in Th1 clones but not Th2 clones and the effect was reversed by H2R and not H1- or H3-receptor antagonists. Histamine has been demonstrated to directly enhance the synthesis of the proinflammatory cytokines (IL-1b and IL-6) through lymphocytes, anti-CD23- and anti-CD28-stimulated release of IL-4 and IL-5 (but not IL-2) or IFN from T lymphocytes can be inhibited by terfenadine treatment [320]. Similarly, several other studies have suggested that histamine leads to synthesis and release of a lymphocyte chemo-attractant factor (LCF) from H2R bearing lymphocytes and also results in release of two different types of lymphocyte migration inhibitory factors (LyMIFs) from only a subset of H2R bearing lymphocytes [339, 340].

C. Neutrophils

Neutrophils have been demonstrated to express H1R and H2R [341, 342], and it had been suggested that the impacts of histamine on neutrophils are inhibitory *via* H2R. *In vitro* studies showed the autologous serum-sensitized chemotaxis of neutrophils both in normal, atopic subjects which is abolished by histamine in a dose-dependent manner, and this inhibition was more effective in atopic individuals [343]. It

is more important to note that incubation of neutrophils from these individuals with cimetidine, but not promethazine, causes reversal of the histamine-sensitized inhibition of neutrophil chemotaxis. *In vivo* study has demonstrated that the histamine administration by either infusion and subcutaneous injection or inhalation diminished neutrophil chemotaxis in healthy volunteers [344]. Several studies have suggested that histamine inhibits the activation of neutrophils as demonstrated by inhibition of fMet-Leu-Phe induced superoxide (O^{2-}) formation, degranulation and membrane potential changes acting by H2R signaling [345, 346].

D. Monocytes, Macrophases and Dendritic Cells

The presence of histamine receptors (H1R and H2R) on human monocytes and macrophages [347, 348] indicates that in allergic disease histamine also modulate the activity of these cells. Differentiation of monocytes into macrophages causes switching over from H2R to H1R [347]. Several other recent studies have suggested (investigations which were performed with exogenously added histamine) that it has a potential role in modulating maturation and function of monocytes, and dendritic cells. Activated monocytes and dendritic cells have a significant potential role in release of histamine, which acts in autocrine and paracrine fashion and modifies dendritic cell markers. Histamine was found to inhibit the production of TNF-α and IL-12, and to augment the production of IL-10 in response to Toll-like receptor ligands by acting on the H2R, in human monocytes [24, 89, 349, 350], while, in human monocyte-derived dendritic cells similar inhibition of IL-12 and enhancement of IL-10 production was investigated. Recently, H4R involvement in suppression of IL-12 was observed [351]. In the *P. acnes*-primed and LPS-stimulated hepatitis model, endogenous histamine production *via* macrophages and Kupffer cells was reported to play a protective role through acting on the H2R [352]. This study was performed with attention to endogenous histamine synthesis in macrophages and Kupffer cells. Furthermore, it has been documented that dendritic cells (DC) are especially antigen-presenting cells, which mature from monocytic and lymphoid precursors and leads to acquisition of dendritic cell (DC) 1 and DC2 phenotypes that drives the development of Th1 and Th2 cells, respectively. Histamine potentially participates in functions and activity of DC precursors as well as their immature and mature forms. It is important to note that immature and mature dendritic cells (DCs) express all four histamine receptors [270, 353, 354] see in Fig. (**11**) for more details. Furthermore, in the differentiation process of DC1 from monocytes, H1R and H3R act as positive stimulants that enhance antigen-presentation capacity and proinflammatory cytokine production and also Th1 priming activity. H2R acts as a suppressive molecule and enhances IL-10 production, and stimulates IL-10 producing T-lymphocytes (Th2 cells) for antigen-presentation [355]. The suppressive impact of histamine by H2R seems through the regulation of ICAM-1 and B7.1 expression facilitating the reduction of innate immune responses activated by LPS [356]. Indeed, histamine stimulates intracellular Ca^{2+} flux, chemotaxis, and actin polymerization in immature dendritic cells due to activation of H1R and H3R subtypes. Notably, in maturation of dendritic cells (DCs) results in loss of these responses. However, histamine dose dependently augments intracellular cAMP levels and stimulates IL-10 secretion in maturing dendritic cells, while inhibiting production of IL-12 through H2R [355]. Human monocyte-derived dendritic cells express both histamine receptors (H1R and H2R) and can stimulate CD86 expression *via* histamine, while human epidermal Langerhans cells express neither H1R nor H2R due to effect of transforming growth factor (TGF)-β [357].

E. Eosinophils

Eosinophils express both histamine H1- and H2-receptors. The effect of histamine on eosinophils is stimulatory at lower concentrations. It had been suggested that preincubation of eosinophils with 10^{-5}M or higher concentrations of histamine suppressed the chemotactic response of eosinophils to endotoxin-activated serum (C5a) while preincubation of eosinophils with a lower concentration of 10^{-6}M histamine had the inverse effect, enhancing the C5a-activated eosinophil chemotaxis. Furthermore, H2R- and H1R-antagonists, respectively, inhibited these impacts. The expression of a novel H3R mediates the direct eosinophil chemotactic response towards histamine [358]. It has also been observed that this receptor seems to have similar antagonist binding activities to those reported for the H3R observed in the CNS, although it does not bind R-α-methylhistamine or N-α-methylhistamine with similar potency as histamine suggesting differences between the activities and function of H3Rs expressed in CNS and on the eosinophil. Histamine acting *via* the H1R also augments eosinophil C3b receptor expression [359], and it was considered as an important mechanism that was found to be involved in the amplification of complement-dependent parasite killing. However, 0.1–50 mM histamine was demonstrated to block eosinophil degranulation, as shown by diminished release of C5a-mediated eosinophil peroxidase [360]. It has been suggested that selective H2R agonists produced an impact similar to that shown by histamine and that cimetidine (H2R-antagonist) reversed this inhibitory impact of histamine. Furthermore, in contrast, treatment with neither mepyramine (H1R-antagonist) nor thioperamide (H3R-antagonist) significantly inhibited the C5a-induced release of eosinophil peroxidase from eosinophils suggesting the significant role of H2R in same respect. An important relation between histamine and eosinophil in allergic disease has been documented *in vivo* in patients with allergic rhinitis undergoing segmental allergen challenge, and followed by airway sampling *via* bronchoalveolar lavage (BAL) after 5 min and 48 h [361]. While, in response to *in vitro* antigen challenge, maximal blood histamine release was determined in each patient before segmental bronchoprovocation. The number of eosinophils in BAL samples collected after 48 h were significantly enhanced and correlated with the maximal basophil histamine release noted for each individual suggesting a direct causal relationship between basophilic mediator release and airway eosinophilia.

F. Epithelial Cells

The implications of histamine have been observed in cultured human bronchial epithelial cells that demonstrate functionally active H1R and H2R as demonstrated by histamine-induced generation of cGMP for H1R and cAMP for H2R and blockage of cGMP release by treatment with pyrilamine and cAMP release by treatment with titotidine [362]. Recently, the expression of H1-receptor on cultured human

ocular and nasal epithelial cells indicates that histamine may potently influence the property of these cells [363, 364]. It has been demonstrated that nasal and bronchial epithelial cells synthesizes and release distinct biologically active mediators including cell adhesion molecules, endothelin, cytokines, arachidonic acid metabolites, major histocompatibility complex class (MHC) II antigens, neuropeptide degrading enzymes and nitric oxide that influence the migration, activation and also function of both structural and inflammatory cells involved in the pathophysiology of allergic rhinitis and asthma [365, 366]. Notably, the implications of histamine on mediator release from human bronchial epithelial cells demonstrated that H1R modulation with 2 mM histamine led to induction of cytoplasmic phospholipase A2 mRNA, activation of the transcription factor NF-kβ, production of leukotriene B4, and expression of IL-8 [367]. It has been shown that histamine-induced enhancement in leukotriene B4 was inhibited by incubation of the cells with specific 5-lipoxygenase activating protein inhibitors and Zileuton and expression of IL-8 was blocked by diphenhydramine, and 5-lipoxygenase activating protein inhibitors and Zileuton indicating an important network of histamine-modulated inflammatory mechanisms within the airways. Similarly, histamine induced the release of IL-6, IL-8 and GM-CSF from human corneal and conjunctival epithelial cells in a dose-dependent manner at physiologically or pathologically relevant concentrations and several H1R-antagonists, but not H2R-antagonist (ranitidine) or H3R-antagonist (thioperamide) blocked this cytokine release [368]. Indeed, the role of epithelial cells as modulators of inflammation, mainly in allergic diseases has been an important subject of much discussion for future prospects.

G. Endothelial Cells

The contribution of endothelial cells to the pathophysiology of allergic disorder has mainly been investigated. The significant effect of histamine on vascular permeability has well been demonstrated and is a consequence of H1R signaling that results in the contraction of F-actin fibres of the endothelial cytoskeleton and formation of gaps in the post capillary venules and extravasation of macromolecules [369]. The functionally potent H1R and/or H2R is expressed on human endothelial cells present in distinct tissues (the airway mucosa, eye, skin, brain and umbilical vein) [370]. Human umbilical vein endothelial cells have been the most investigated in mechanistic studies, because of comparatively easier and greater access to these cells. Currently, in a recent study it has been suggested that histamine itself regulates the expression of histamine receptor (HR) subtypes on endothelial cells and influences the overall significant role in inflammatory response in allergic disease [371]. It has been documented that the levels of mRNA for both the receptors (H1R and H2R) were down regulated by histamine, of which the effect on H2R-mRNA was rapid and long lasting, compared with a less pronounced, transient and shorter lasting impact on the H1R-mRNA. Furthermore, the H2R-mRNA was exclusively down regulated as a result of H1R protein activation. Histamine-induced receptor signaling on the endothelial cells directly modulates inflammatory changes in these cells. Therefore, treatment of human umbilical vein endothelial cell cultures with 10^{-4}M or 10^{-5}M histamine resulted in the release of lipophilic neutrophil chemoattractant activity from endothelial cells, an effect inhibited by cimetidine but not by diphenhydramine [372]. Histamine or H1R- or H2R-agonist stimulated adhesion of neutrophils to endothelial cells, participated in activation of phospholipase C, guanylate cyclase and nitric oxide synthase isozymes, since inhibition of these enzymes with specific inhibitors decreases this adhesion [372]. The impact of histamine was found to be mediated by both H1-receptor and H2-receptor signaling and modulation of P-selectin on endothelial cells in the mesentery. Thus, histamine receptors are involved in significant implications in the field of histamine research in endothelial cells.

VII. IMPLICATION OF HISTAMINE ON CYTOKINES PRODUCTION

It has been documented that histamine stimulates cytokine synthesis in allergic inflammation *via* two main different mechanisms:

(a) Direct effects of histamine on cytokine synthesis and

(b) Modulation of cytokine production stimulated by immunologic stimuli.

Histamine differentially modulates IL-4 and IFN-γ release from T cells [338], inhibits TNF-α [373] and IL-12 synthesis *via* human monocytes [374] while it directly modulates IL-10 [330] and IL-18 production from human monocytes [375]. In addition, it inhibits IFN-γ, TNF-α, and IL-12 and enhances IL-10 synthesis in LPS- or mitogen-activated, peripheral blood mononuclear cells [374, 376], and increases IL-1 stimulated synthesis of IL-6 by monocytes [377]. These complex impacts of histamine were found to be mediated through the activation of H1R [378], H2R [374], and H3R on immune cell cytokine synthesis [330]. Recently, cloned H4R has been characterized as functionally active to modulate cytokines [274, 284, 285]. Several investigators have observed that low concentrations of histamine [i.e., found in the bronchoalveolar lavage (BAL) fluid of patients with bronchial asthma or at other sites of allergic inflammation] [352, 379], modulates human lung macrophages. The rationale for studying human lung macrophage was the high prevalence of macrophages in the human lung parenchyma and in the BAL fluid [380]. An important study has been done on macrophages, which were purified (approximately 98%) from the lung parenchyma of thoracic surgery. Patients were incubated (1 to 18 h) with low doses of histamine (10^{-9} to 10^{-7} mol/L) that was compared to those released *in vivo* in distinct pathophysiology. It has been observed that histamine stimulated the de novo synthesis of IL-6 from macrophages [304], and these impacts were reproduced *via* the H1R agonist (6-[2-(4-imidazolyl)ethylamino]-N-(4-trifluoromethylphenyl) heptane carboxamide) but not by the H2-receptor agonist (dimaprit) suggesting that those were H1R mediated events [304]. Thus, these results are in line with the general investigation that H1R modulation is related with intracellular Ca^{2+} influx and demonstrated that this signal transduction pathway is active in human macrophages [381]. The H1R-mediated activation of macrophages was documented by demonstrating that histamine-induced IL-6 release was blocked in a concentration-dependent fashion by enhancing concentrations of the selective H1R-antagonist (fexofenadine) [304]. While the H2R-antagonist (ranitidine) had no effect on IL-6 release or Ca^{2+} signal produced by histamine. A more valuable research in this field has provided the sig-

nificant evidence that low concentrations of histamine promote exocytosis and IL-6 synthesis by inducing H1Rs and activating intracellular Ca^{2+} signaling in macrophages. This investigation enhances the intriguing possibility that, *via* activating macrophage functions, histamine might be implicated in the long-term control of inflammation.

VIII. SIGNIFICANCE OF HISTAMINE IN AUTOIMMUNITY AND IN ALLERGIC DISEASES

It is highly significant in field of immunomodulation that endogenous levels of histamine influence the repertoire of autoantibodies. Histamine has been observed to influence several aspects of the immune response, including antibody production [12, 13, 189]. It has been characterized that the repertoire of natural autoantibodies in histidine decarboxylase (HDC) diminished mice [33] was unable to produce histamine. HDC-diminished and wild type mice differed in the patterns of reactivity of their immunoglobulin-M (IgM) and immunoglobulin-G (IgG) natural autoantibodies [382]. The natural autoantibodies in HDC diminished sera manifested a larger repertoire of IgM autoantibodies than did the wild type sera [382]. The self-antigens bound by IgM from HDC diminished mice includes structural proteins, enzymes related with cellular metabolism, double-stranded DNA and single stranded DNA, and tissue-specific antigens like insulin [382]. It was noted that relatively fewer differences in the natural autoantibodies repertoire of IgG autoantibodies of the mice, notably, the HDC diminished sera reacted with glutamic acid decarboxylase (GAD) [382], an antigen related with autoimmune diabetes [383]. It has been documented that GAD-specific antibodies in HDC diminished mice reflect an enhanced susceptibility to develop autoimmune diabetes. Therefore, this demonstrates that factors not directly associated to antigenic activation such as endogenous levels of histamine can influence the natural autoantibodies repertoire [382]. Thus, disorders of immune system characterized by altered levels of endogenous histamine, such as allergies, might be reflected as specific alterations in the repertoire of natural autoantibodies.

A. Urticaria and Angioedema

Urticaria is the medical word for itchy wheals or hives (pale red swellings of skin "wheals" that occur in groups on any part of the skin) and angioedema known as deep mucocutaneous swelling often occur together with urticaria. Urticaria is classified, based on its temporal evolution, as acute (less than 6 weeks) or chronic (more that 6 weeks). Acute urticaria is related with sensitivity to foods, latex, and certain drugs and is often immunoglobulin-E (IgE)-mediated. Chronic urticaria includes the physical urticarias and urticarial vasculitis but allergic causes of chronic urticaria were rarely identified. Some cases of chronic urticaria have been associated with circulating IgG autoantibodies against FcεRIα [384] and autoantibodies against IgE [385]. The frequency of autoantibodies to FcεRIα in chronic urticaria has been estimated 30-50%. These autoantibodies to FcεRIα found to be functional i.e. they can cause histamine release from basophils under *in vitro* condition, however, evidences increasingly suggests that such autoantibodies were also functional *in vivo*. Other evidences have suggested that the serum from many patients with chronic urticaria causes an immediate autologous wheal and flare response (i.e. a positive autologous serum skin test) and many of such patients have evidence of circulating functional IgG autoantibodies to the high affinity IgE receptor (FcεRIα). The current mainstream thought is that in such patients the IgG autoantibodies causes the visible urticarial skin lesions. It has been documented that in chronic urticaria the autoantibodies causing histamine release were predominantly IgG1 and IgG3. Thus, the presence of these autoantibodies characterizes the so-called chronic autoimmune urticaria. A cause-and-effect relation between levels of autoantibodies, histamine-releasing factors, and the clinical manifestations of chronic urticaria has still a part of research. However, severe cases often suggest that autoantibodies or circulating histamine-releasing factors do have an important role [386]. Hereditary angioedema is a rare autosomal dominant disorder caused by the absence of the inhibitor of the first component of complement.

B. Allergic Rhinitis

Allergic rhinitis has been characterized by itching, sneezing, rhinorrhea, and nasal obstruction. Perennial allergic rhinitis can be distinguished from non-allergic, non-infectious forms of rhinitis [idiopathic (vasomotor) rhinitis, non-allergic rhinitis with eosinophilia syndrome, hormonal rhinitis, drug-stimulated rhinitis, and food-induced rhinitis]. The treatment of allergic diseases (allergic rhinitis) consists of allergen avoidance, anti allergic medication, and immunotherapy for specific allergens which is known as desensitization or hyposensitization. Recently, the drugs commonly used to treat allergic rhinitis are antihistamines (histamine antagonists) and anticholinergic agents for the relief of symptoms and corticosteroids to suppress allergic inflammation. H1R-antagonists (loratadine, cetirizine, and fexofenadine) are less sedating and more pharmacologically selective than earlier antihistamines. Some H1R-antagonists (cetirizine) block allergen-sensitized infiltration of tissue by eosinophils, an influence that may be independent of their impacts on H1R [387].

C. Atopic Dermatitis

Atopic dermatitis (AD) or atopic eczema is a chronic relapsing pruritic skin disease with a high incidence in the first year of life. AD can persist into childhood, symptoms usually remit by puberty. AD is characterized by two phases: 1st phase with acute lesions predominated by Th2 cytokines (IL-4, IL-5 and IL-13), 2nd phase that is associated with eczematous chronic atopic dermatitis lesions by Th1 cytokine (INF-γ and IL-12). Atopic dermatitis can also be present in adults and affects more than 10% of the total population, with 80-90% of those affected being children under 5 years of age in Western population [388, 389]. Atopic dermatitis is often regarded as a cutaneous form of atopy; as a result, 50-80% of children with AD will develop asthma or allergic rhinitis by 5 years of age later in life and the high serous concentration of IgE [390]. This temporal progression of atopic symptoms from atopic dermatitis to allergic sensitization of the skin, food allergy, hay fever (allergic rhinitis) and later airway hyperresponsivness and airway inflammation or asthma, has been named the "allergic march" [391, 392].

In AD, the skin becomes extremely itchy. Scratching leads to redness, swelling, cracking, "weeping" clear fluid, and finally crusting and scaling. It is frequently perceived as

a minor dermatological disorder. However, the high prevalence of this condition carries financial and social cost not only for the community, regarding medical and hospital cost but also for the patient and the patient's family [393]. In AD, inflammation results from interactions of immune cells [T cells (Th1 and Th2), dendritic cells (langerhans dendritic cells and inflammatory dendritic epidermal cells), mast cells and eosinophils] and kerotinocytes. The complex picture of the AD lesion is aggravated by environmental and genetic factors that increase the difficulty of understanding the mechanisms behind this complex pathology [388].

IX. ROLE OF HISTAMINE IN MALIGNANCIES

Malignant melanoma is a well known life-threatening tumor (with a high rate of metastasis and strong malignant potential). Recently, the immune response against melanoma was compromised through multiple escape mechanisms of the tumor, which have been uncovered partially *via* thorough immunological and molecular analyses. These analyses were documented by gene-expression profiling. It has been suggested that melanoma-derived histamine should be included as a significant factor participated in bi-directional interactions between the tumor tissue and infiltrating immune cells. Notably, the presence and activity of histamine has been demonstrated to be relevant by directly stimulating or suppressing growth of the melanoma (i.e. depending on the local histamine receptor balance) and indirectly shifting the local T-cell polarization towards a predominance of Th2 cells [394].

X. RELATION OF HISTAMINE-CYTOKINE DURING HEMATOPOIESIS

Many researchers have reported that exogenous histamine promote the entry of colony-forming units-spleen (CFU-S) into cell cycle and showed that this mediator stimulated granulocyte precursors, when added during *in vitro* cultures [395, 396]. Recently, it has been demonstrated that a similar positive effect on hematopoietic progenitors was induced by endogenous histamine. Histamine is synthesized in response to hematopoietic growth factors (IL-3, GM-CSF and IL-1) generated during the immune response. It was probably not needed for maintaining bone marrow homeostasis, but involved in inducible hematopoiesis, and satisfies the enhanced requirements of an efficient host defense. There were several reports in support of a positive effect of histamine on granulopoiesis, but side effects of some histamine receptor ligands have also been described. Rare cases of agranulocytosis have been observed in response to H2-receptor antagonist (cimetidine) and H4R antagonist (clozapine). It should be confirmed and re-evaluated by several reports, as regards the significant role of various histamine receptors; those expressions are most abundant in bone marrow [14].

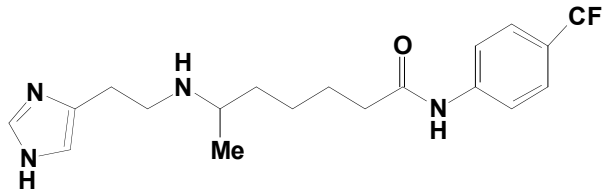
XI. FUTURE PROSPECTS

Histamine receptors have been important drug targets for many years. Their physiological and pathological relevance and distribution in various tissues are being documented, while the exact role of histamine receptors in immunomodulation is still unclear. The previous studies have shown immunomodulatory role of H1- and H2-receptors and their potent role on lymphocytes (T-cells and B-cells), but all these reports have studied the antibody concentrations at a single time period taking single blood samples from experimental animals [105, 188, 189, 397]. Our recent findings in immunoregulatory processes, demonstrated that total antibody, total IgM and total IgG generation profile in pheniramine (H1R-antagonist)-treated group is completely suppressed as compared to ranitidine (H2R-antagonist)- treated and control group, while total antibody and total IgM in ranitidine (H2R antagonist)-treated group is suppressed initially and enhanced in a later phase in comparison to control group, and IgG profile remained suppressed in comparison to control group. Thus, our results demonstrate B-cell proliferation in response to anti-IgM is increased in H2R-antagonist treated rabbits and is diminished in H1R-antagonist treated rabbits, and that H1R-antagonist treated rabbits display diminished antibody production against a T cell-dependent antigen-SRBC as compared with H2R-antagonist treated and control rabbits [398].

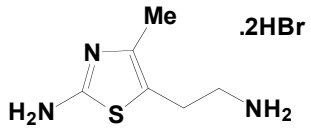
The scope of histamine research has been implicated in immune responses of both the Th1 and Th2 lymphocytes. The newly discovered H4-receptor plays an important role in inflammation and has opened a new way for the functions of histamine in inflammation, allergy and autoimmune diseases. The data on the role of H3- and H4-receptors in immune regulation are limited. Due to lack of immunomodulatory researches on H3- and H4-receptors, we planned ongoing studies to find out immunomodulatory role *via* several specific antagonists and agonists.

The antagonists for H1- and H2-receptors have been introduced into market for a long time and it is assumed that within the next few years the H3- and H4-receptor antagonists will be freely available in market. As we planned our ongoing researches on role of histamine receptors in immunomodulation, Tocris Bioscience, Tocris Cookson Ltd. (United Kingdom) has donated highly potent and specific histaminergic product as quotation code: "Donation 24.08.07" including products HTMT dimaleate [6-[2-(4-imidazolyl)ethylamino]-N-(4-trifluoromethylphenyl)heptanecarboxamide dimaleate], Amthamine dihydrobromide [2-amino-5-(2-aminoethyl)-4-methylthiazole dihydrobromide], (R)-(-)-α-methylhistamine dihydrobromide [(R)-(-)-α-methyl-1H-imidazole-4-ethanamine], Imetit dihydrobromide [5-[2-(imidazol-4-yl)ethyl]isothiourea dihydrobromide], Clobenpropit dihydrobromide [N-(4-Chlorobenzyl)-S-[3-(4(5)-imidazolyl)propyl]isothio urea dihydrobromide], Iodophenpropit dihydrobromide [N-[2-(4-iodophenyl)ethyl]-S-[3-(4(5)-imidazolyl)propyl]isothiourea dihydrobromide] (see chemical structures in Fig. (**12**)). In future, we are planning to conduct researches on immunomodulation by H4-receptor agonist (4-Methylhistamine dihydrochloride) and antagonist (JNJ 10191584 maleate).

Thus, the recent data on the novel functions of histamine receptors (H1-, H2-, H3- and H4) have opened an interesting new chapter in immune regulation and immunomodulation in the history of histamine research and should lead to deeper relevance, and understanding treatments of pathological processes those regulating several essential events in allergies and autoimmune diseases.



H1R-agonist (HTMT dimaleate)



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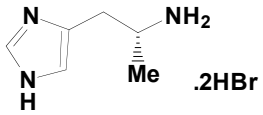
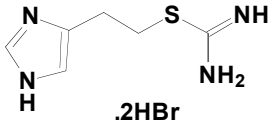
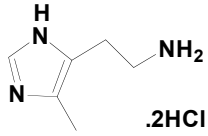


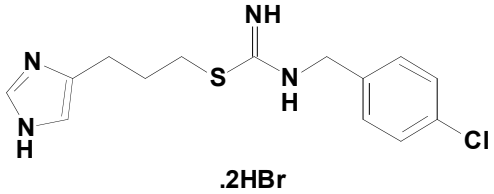
H3R-agonist ((R)-(-)-α-Methylhistamine dihydrobromide)



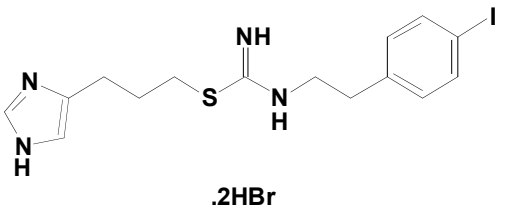
H3R & H4R-agonist (Imetit dihydrobromide)



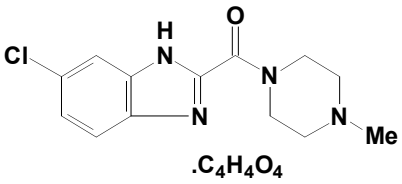
H4R-agonist (4-Methylhistamine dihydrochloride)



H3R-antagonist & H4R-partial agonist (Clobenpropit dihydrobromide)



H3R-antagonist (Iodophenpropit dihydrobromide)



H4R-antagonist (JNJ 10191584)

Fig. (12). Histamine receptors agonists and antagonists kindly donated by Tocris Biosciences, Tocris Cookson Ltd., U.K.

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