Histamine and Its Receptors

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Introduction

Histamine has been recognised for almost a century to be a mediator of acute allergic responses. β-Imidazolylethylamine was first synthesised in 1907 by Windaus and Vogt [1] and was later named *histamine* (from the Greek *histos* = tissue) because of its ubiquitous presence in animal tissues, particularly in mast cells. In classic pharmacological studies, Sir Henry Dale demonstrated the potent bronchoconstrictor and vasodilator activity of histamine when injected intravenously into animals [2]. In the same laboratory 13 years later, it was noted that many of the symptoms of antigen injection into sensitised animals could be reproduced by histamine and it was, therefore, considered to be a humoral mediator of the acute allergic response [3]. With the description of the wheal-and-flare response in human skin, Thomas Lewis further expanded on the vascular actions of histamine [4]. However, it was not until 1953 that histamine present in human skin was localised to mast cells of the dermis [5].

Histamine is synthesised in the Golgi apparatus of mast cells and basophils by decarboxylation of its precursor amino acid, histidine, under the influence of histidine decarboxylase. It is stored in ionic association with the acidic residues of the glycosaminoglycan (GAG) side chains of heparin or related proteoglycan [6]. Once in the extracellular environment, histamine is metabolised rapidly (t½ ~1 min) by either of two enzymatic pathways, by ring methylation by histamine-*N*-methyltransferase (HMT) or by oxidative deamination by diamine oxidase (DAO), the dominant route of metabolism depending on the tissue. HMT is a ubiquitous enzyme, which is regarded as the key enzyme for histamine metabolism in the bronchial epithelium and nasal mucosa [7, 8]. Because HMT is an intracellular enzyme and histamine is a charged molecule, which enters the intracellular space with difficulty, a facilitated uptake mechanism, known historically as ‘uptake 2’ is

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R. Pawankar et al. (eds.), *Allergy Frontiers: Classification and Pathomechanisms*,
DOI: 10.1007/978-4-431-88315-9_21, © Springer 2009

necessary. This is performed by a group of organic cationic transporters (OCTs), predominantly OCT-2 and extraneuronal monoamine transporter (EMT), sometimes known erroneously as OCT-3 [9]. The reaction product of HMT-catalysed histamine metabolism, *N*-methylhistamine, is excreted by the kidney and may be measured in the urine as an index of endogenous histamine release [10]. A proportion of the methylated product is oxidised further by monoamine oxidase and excreted as methylimidazole acetic acid. In mammals, diamine oxidase expression is restricted to specific tissues, the highest activities being in the intestine, placenta and kidney, where it is thought to be responsible for blocking the transport of extracellular histamine from these organs into the circulation [11]. Although diamine oxidase is usually found associated with the plasma membrane, it is a soluble protein and is thought to be released into the extracellular environment upon cell stimulation [12] allowing it to act as either a cell-associated or cell-free enzyme. Diamine oxidase oxidises histamine to imidazole acetic acid. This intermediate undergoes condensation with phosphoribosyl diphosphate followed by dephosphorylation forming the terminal metabolite, riboside-*N*-3-imidazole acetic acid.

Mast cells isolated from human lung, skin, lymphoid tissue and small intestine contain 3–8 pg of histamine per cell [13–15]. Histamine is secreted spontaneously at low levels by mast cells, the resting level in the skin being approximately 5 nM [16], somewhat higher than those of 0.5–2 nM found in the plasma. In normal individuals, urinary histamine clearance is around 10 μg/24 h, while in mastocytosis it may exceed 150 μg/24 h [17].

G Protein-Coupled Receptors

In humans, there are four subtypes of histamine receptors, H_1, H_2, H_3 and H_4, all encoded on different genes [18]. All histamine receptors identified so far are members of the superfamily of G protein-coupled receptors (GPCR). This superfamily represents at least 500 individual membrane proteins that share a common structural motif of seven-transmembrane (TM) α-helical domains, numbered TM I–VII, arranged in a circular fashion [19–21] (Fig. 1). All GPCRs have specific receptor site, usually within the central core of the cylinder formed by the transmembrane α-helical domains. These sites confer ligand specificity, ligands ranging from photons, Ca^{2+} ions and small organic molecules to complex polypeptide hormones [22]. The common functional characteristic of all GPCRs is their intracellular signal mediation, activation of a Gαβγ heterotrimer of the cytosolic G protein complex (Fig. 1) [19].

The intracellular mechanisms of signal transduction by GPCRs is the subject of an excellent review by McCudden and colleagues in 2005 [23]. In this review, guanine nucleotide-binding proteins or ‘G proteins’ are referred to as cellular ‘switches’, which alternate between a GDP-bound off state and a GTP-bound on state (Fig. 2). In the inactive state, the Gα subunit binds GDP and is closely associated with the Gβγ heterodimer, the resultant trimeric complex being closely associated with the cytosolic domain of the GPCR. In this state, Gβ facilitates the coupling of Gα to the receptor and also acts as a guanine nucleotide dissociation inhibitor (GDI) for

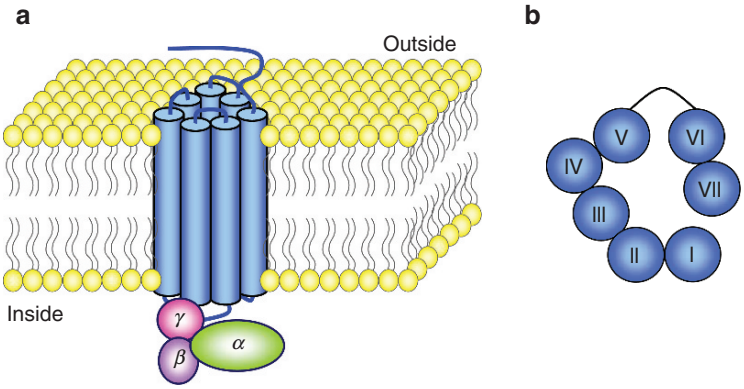

Fig. 1 Diagram of a GPRC within a membrane. (**a**) The Gγβα complex can be seen associated with the intracellular part of the receptor complex. (**b**) Numbering of the transmembrane (TM) domains of a GPCR. The inside and outside of the cell are labelled in this figure. This orientation is consistent in all figures

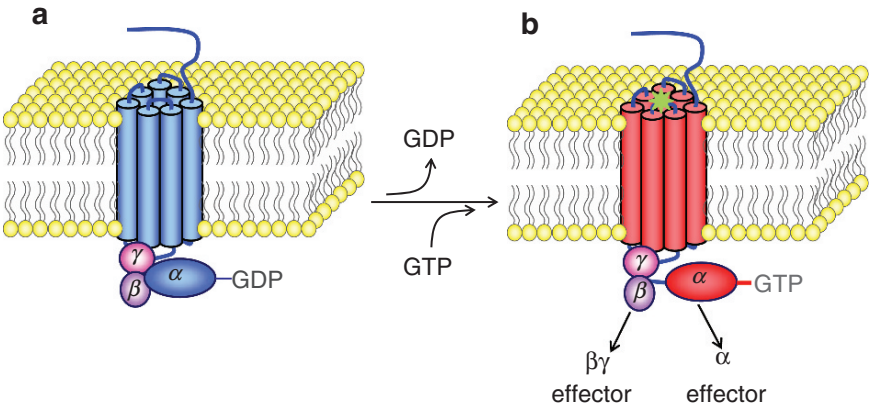

Fig. 2 Standard model of the activation of a GPCR. In the absence of ligand, the Gα subunit is GDP-bound and closely associated with α γβ the Gγβ heterodimer. The Gα-GDP/Gγβ heterotrimer interacts with the cytosolic loops of a seven-transmembrane-domain G protein-coupled receptor (GPCR). Gγβ facilitates the coupling of Gα to receptor and also acts as a guanine nucleotide dissociation inhibitor (GDI) for Gα-GDP, slowing the spontaneous exchange of GDP for GTP. Ligand binding (green star) stimulates guanine nucleotide exchange factors to induce a conformational change in the Gα subunit, allowing it to exchange GTP for GDP. Gγβ dissociates from Gα-GTP, and both Gα-GTP and Gγβ may then signal to their respective effectors. The cycle returns to the basal state when Gα hydrolyses the gamma-phosphate moiety of GTP, a reaction that is augmented by GTPase-accelerating proteins (gaps) such as the regulator of G protein signalling (RGS) proteins

Gα-GDP, slowing the spontaneous exchange of GDP for GTP. Activation of the receptor occurs by binding to a site on the GPCR specific for each ligand. In the case of the histamine H_1-receptor, histamine cross-links a site on transmembrane domain III containing an aspartate residue with one on transmembrane domain V containing

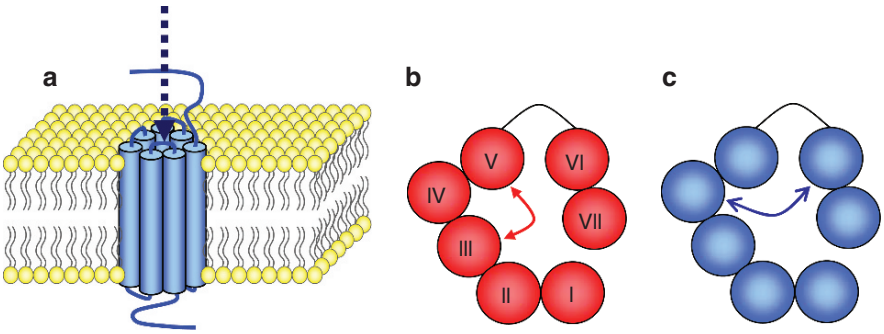

Fig. 3 The binding of histamine and cetirizine to the H_1-receptor. (**a**) The ligand-binding site for GPCR is within the transmembrane (TM) domains. (**b**) Histamine links TMS III and V to stabilise the receptor in the active state. (**c**) Cetirizine, an H_1-antihistamine, links TMS IV and VI to stabilise the receptor in the inactive state

lysine and asparagine residues (Fig. 3) [24]. This induces a conformational change in the GPCR, which causes the rapid dissociation of the Gαβγ trimer from the receptor [25], an event which stimulates the Gα subunit to exchange GDP for GTP and separate from the Gβγ subunit, allowing both subunits to signal to their respective effectors. The cycle returns rapidly to the basal state by the hydrolysis of the Gα GTP to GDP, a reaction that is augmented by GTPase-accelerating proteins (GAPs) such as the regulator of G protein-signalling (RGS) proteins.

In the human genome, there are 16 Gα genes, which encode for 23 known Gα proteins giving wide diversity to GPCRs. While these are normally classified by their structure, these proteins may also be divided into four major classes according to their cellular targets: Gαs, which stimulates adenylyl cyclase to generate cyclic AMP; Gαi, which inhibits adenylyl cyclase and thus opposes the action of Gαs; Gαq, which activate phosphoinositide-specific phospholipase C (PI-PLC) isoenzymes; and Gα12/13, which can regulate the small G-associated protein, RhoA.

In addition to a large number of Gα proteins, there are five known human Gβ and 12 human Gγ subunit genes resulting in at least 60 potential combinations of Gβγ dimers. The Gβγ dimer was once thought only to facilitate coupling of Gαβγ heterotrimers to GPCRs and act as a Gα inhibitor. However, it is now known that Gβγ subunits are free to activate a large number of their own effectors, including the regulation of K^+ channels, Ca^{2+} channels, adenylyl cyclase and a variety of kinases.

The Concept of Inverse Agonism

The classical concept of interactions of competitive agonists and antagonists with receptors was formulated by Ariëns in 1964 in his book *Molecular Pharmacology* [26] (Fig. 4). This theory stated that an *agonist* must have both *affinity* to combine with the receptor and *efficacy* to stimulate the receptor. A ‘full agonist’ was defined

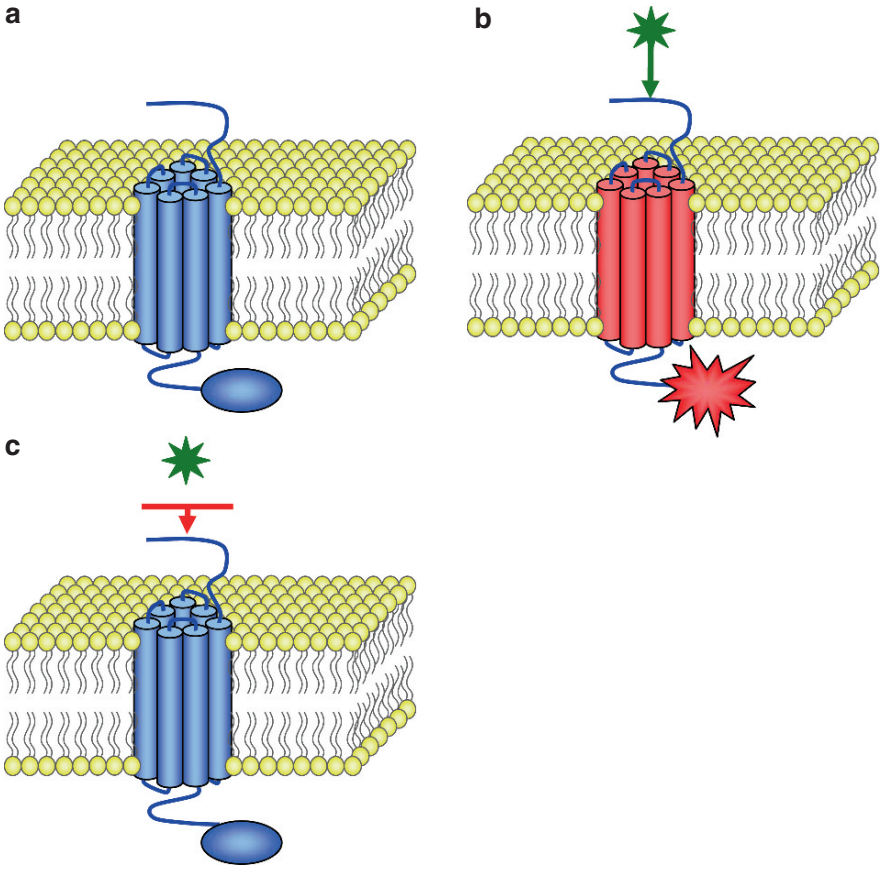

Fig. 4 The classical concept of interactions of competitive agonists and antagonists with receptors. (**a**) An unstimulated receptor where the Gαβγ complex is in the inactive state (blue oval). (**b**) An activated receptor where an agonist (green star) interacts with the ligand-binding site leading to the activation of the Gαβγ complex (red star). (**c**) A 'blocked' receptor where an antagonist (red line) has interacted with the ligand-binding site and prevented the agonist from binding. The Gαβγ complex is in the inactive state (blue oval)

as a compound that had maximal efficacy at its receptor and was given an intrinsic activity = 1. To explain the observation that not every agonist induced the same maximum effect at its receptor, the term 'partial agonist' was introduced for weaker agonists with an intrinsic activity of less than 1. In this scheme, an 'antagonist' was described as a compound with *affinity* for the receptor and but *no efficacy* to stimulate it. By definition antagonists possess an intrinsic activity of 0.

Thus, using this concept, an antagonist prevented receptor stimulation by binding to a receptor thereby preventing the subsequent binding of an agonist (Fig. 4). In retrospect, it is remarkable that the concepts of receptor stimulation and its blockade were developed over a period of around 75 years using only the measurement of responses of isolated tissues to pharmacological agents. It is only recently

with the advent of techniques for routine cell culture and molecular biology that we have begun to realise the inadequacies of these concepts.

With the introduction of the molecular biology of GPCRs in 1986 [27], it became clear that the single-state model described above was not correct. Instead, we should visualise the receptor as a *two-state model* [28] (Fig. 5a). In this model,

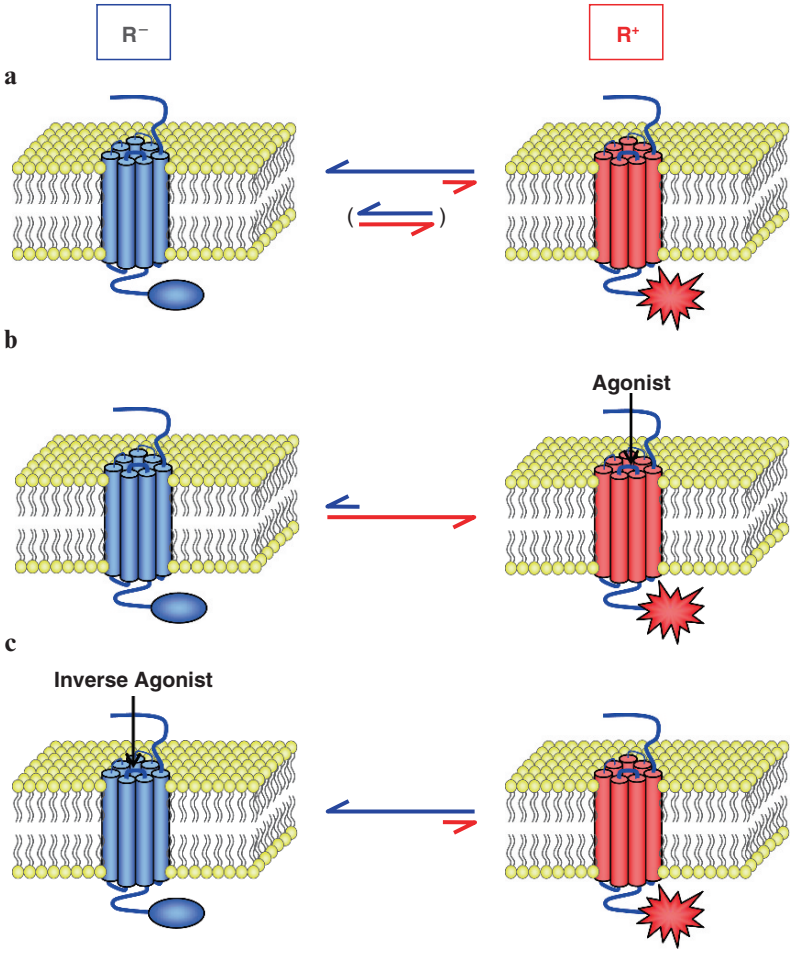

Fig. 5 Simplified two-state model of GPCR activation. In this model the two isomeric forms of the receptor, the inactive state $\mathbf{R}^-$ and the active state ($\mathbf{R}^*$) are in equilibrium (blue and red arrows, respectively). (**a**) In the resting state the equilibrium is usually in favour of the inactive $\mathbf{R}^-$ configuration. However, if the receptor shows constitutive expression, the equilibrium will shift partially to the active $\mathbf{R}^+$ configuration (*arrows* on parentheses). (**b**) Binding of an agonist stabilises the receptor in the active $\mathbf{R}^*$ configuration and swings the equilibrium in that direction to increase receptor signalling. (**c**) Binding of an inverse agonist stabilises the receptor in the inactive $\mathbf{R}^-$ configuration and swings the equilibrium in that direction to decrease receptor signalling. In this model, neutral antagonists have equal affinity for both $\mathbf{R}^-$ and $\mathbf{R}^+$ isoforms of the receptor and, therefore, do not affect the equilibrium between the two states

an equilibrium exists between the receptor isoforms, the inactive $\mathbf{R}^-$ state and the active $\mathbf{R}^+$ state [29, 30]. When viewed from the intracellular space, the transmembrane (TM) domains I–VII of the GPCR are arranged in a clockwise fashion. The conformational switch from $\mathbf{R}^-$ to $\mathbf{R}^+$, which is highly conserved among GPCRs from different families, involves rotation of TM III relative to TM VI [31]. *Full agonists* induce optimal stabilisation of the $\mathbf{R}^+$ state of the GPCR causing the equilibrium to shift maximally towards $\mathbf{R}^+$ (Fig. 5b). The conformational change involved in the isomerisation of $\mathbf{R}^-$ to $\mathbf{R}^+$ enables the GPCR to promote the dissociation of GDP from G proteins, the initial and rate-limiting step in the G protein cycle [32]. Full agonists are very efficient at increasing the basal GDP/GTP exchange rate of the $G\alpha$ subunit of the receptor complex and, thereby, stimulating the downstream events of receptor stimulation. *Partial agonists* are less efficient than full agonists at stabilizing the $\mathbf{R}^+$ state and, therefore, increase GDP/GTP exchange less efficiently. In contrast to, *full inverse agonists* induce optimal stabilisation of the $\mathbf{R}^-$ state of the GPCR, causing the equilibrium to shift maximally towards $\mathbf{R}^-$ and reducing basal GDP/GTP exchange (Fig. 5c). *Partial inverse agonists* have similar effects, but are less efficient than full inverse agonists. *Neutral antagonists* do not alter the equilibrium between $\mathbf{R}^-$ and $\mathbf{R}^+$ and do not change basal G protein activity, but they block both the inhibitory effects of inverse agonists and the stimulatory effects of agonists.

Before explaining the concept of constitutive activity, it is pertinent to highlight the differences between agonist and inverse agonist binding to the receptors. Histamine H_1-inverse agonists bind to different sites on the receptor compared with histamine. For example, in contrast to histamine binds which cross-links TM III and V to activate the receptor, the inverse agonists, cetirizine and acrivastine, cross-link amino acids on TM IV and VI to stabilise the receptor in the inactive form (Fig. 3). Also, the binding times are quite different. For example, the dissociation half-time for levocetirizine, the eutomer of cetirizine, is 142 min [33] compared to a few microseconds for histamine. Thus, if a receptor is constitutively active, the long duration of binding facilitates its reversal by inverse agonists.

The Concept of Constitutive Activity

While it is well established that GPCRs respond to stimulation by extracellular ligands, the concept that they may remain in the 'switched on' state in the absence of ligand stimulation, i.e. in a constitutive or spontaneous manner, is relatively new and potentially important for the understanding of some disease processes [34–36].

The first evidence for constitutive activity of GPCRs was obtained for the δ-opioid receptor [37] and the β_2-adrenoceptor [38]. Since that time, more than 60 wild-type GPCRs and several disease-causing GPCR mutants have been found to exhibit constitutive activity [34].

Smit and colleagues [36] have recently reviewed the known disease-causing GPCR mutants and concluded that single-point mutations of GPCR genes may

cause structural changes in the transcribed receptors that may increase or decrease their constitutive activity. For example, normal parathyroid hormone-related peptide (PHRP) does not express constitutive activity. However, two-point mutations have been reported to be associated with a high level of constitutive activity of the mutant receptor resulting in Jansen-type metaphyseal chondrodysplasia, a rare disorder that is typically characterised by severe growth plate abnormalities that lead to short-limbed dwarfism [39]. Conversely, growth hormone secretagogue receptor-1a (GHSR-1a) naturally possesses a high level of constitutive activity. However, two mis-sense mutations have been reported that selectively reduce the constitutive activity of the GHSR while preserving its ligand responsiveness. These mutations are associated with short stature due to growth failure [40].

In addition to the human GPCR variants described above, a relatively novel and intriguing class of GPCRs, encoded by herpes viruses, exhibit marked constitutive activity. The herpes- and poxviruses encode more than 40 GPCRs, most of them displaying homology to chemokine receptors known to be implicated in the regulation of the immune response. Although the roles of these viral-encoded receptors have not been fully defined, they are believed to subvert the immune system and to contribute to virus-induced pathogenesis (reviewed in [36]).

Wild-type GPCRs, i.e. those found in the most common phenotypes in the natural population, are the subject of a review by Seifert and Wenzel-Seifert [34]. Included in the tabulated list of all the known wild-type GPCRs, which have been shown to exhibit constitutive activity are three reports of constitutive activity in H_1-receptors, three in H_2-receptors, seven in H_3-receptors and two in H_4-receptors. Perhaps the best explored of these is the H_1-receptor-dependent constitutive expression of the transcription factor NF-κB [41]. Interestingly, their data suggest that both Gαq/11 and Gβγ subunits play a role in the agonist-induced H_1-receptor-mediated activation of NF-κB, but that constitutive NF-κB activation by the H_1-receptor is primarily mediated through Gβγ-subunits.

Oligomerisation, Domain Swapping and Receptor Cooperativity

In almost all diagrams of GPCRs they are depicted as single units. This has led to the common belief that they function as discrete monomeric units. However, this is not usually the case. GPCRs are gregarious by nature and readily form dimers and often higher-order oligomers. When forming dimers, GPCRs may form either homodimers or heterodimers, the latter leading potentially to cooperativity. As this new and complex field is largely the domain of molecular biologists and computer simulation scientists, interested readers are directed to a series of recent reviews for further information [42–45]. However, two examples involving histamine receptors are given below (Fig. 6).

The first example involves the co-expression of the Gi/o-coupled human 5-hydroxytryptamine receptor-1B ($5\text{-}HT_{1B}R$) and the Gq/11-coupled human

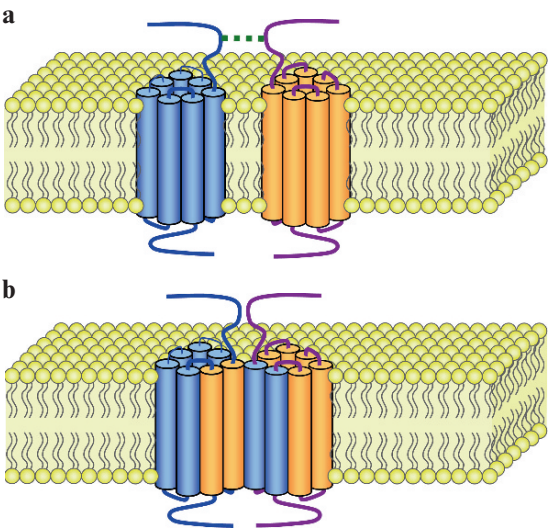

Fig. 6 Dimerisation and domain swapping in GPCRs. (**a**) A simple heterodimer where the two GPCRs are held together by electrostatic bonding (green dotted line) between the extracellular domain of TM I. (**b**) A domain swapped heterodimer where the GPCRs have 'swapped' domains VI and VII

H_1-histamine receptor (H_1R) [46] (Fig. 6a). Co-expression resulted in an overall increase in agonist-independent signalling, which was augmented by 5-$HT_{1B}R$ agonists and inhibited by a selective inverse 5-$HT_{1B}R$ agonist. Furthermore, inverse H_1R agonists inhibited constitutively H_1R-mediated as well as 5-$HT_{1B}R$ agonist-induced signalling in cells co-expressing both receptors. This phenomenon is not solely a characteristic of 5-$HT_{1B}R$ and H_1R receptors, but it is also evident with many other GPCRs ranging from neurotransmitters to cytokines [46]. Such cross-talk is not surprising as, in vivo, cells are co-stimulated simultaneously by a wide variety of agonists and must be able to respond to them all in a coordinated manner.

The second example involves domain swapping in the human histamine H_1-receptor. Bakker and colleagues [47] investigated the potential dimerisation of the wild-type human H_1R in the presence and absence of two mutated H_1R (Fig. 6b). The results demonstrated the presence of both monomeric and homodimeric H_1R together dimers in which there was reciprocal exchange of transmembrane domains 6 and 7 between the receptors present in the dimer. These data suggest that domain swapping between heteromeric GPCRs may occur but its clinical relevance is, as yet, unclear.

Are Inverse Agonism, Constitutive Expression and Receptor Dimerisation Clinically Relevant?

Whenever a new concept is introduced, there is a period of enthusiasm followed by a period of doubt and finally a levelling out of its significance at a realistic level. With inverse agonism, constitutive expression and receptor dimerisation we are

clearly in the first phase, enthusiasm. If constitutive activity of GPCRs is clinically important, particularly in disease settings, then there is a desperate need for the pharmaceutical industry to develop potent and specific ligands and inverse agonists. This is well recognised and research in this area is blossoming [48–51]. We have yet to go through the period of doubt before we really know the clinical relevance of these novel concepts.

Histamine Receptors

The Histamine H_1-Receptor

Most of the clinical symptoms of allergic disease result from H_1-histamine receptor stimulation. In the nose, H_1-antihistamines reduce the symptoms of rhinorrhoea, itching, sneezing and oedema, the last being one component of nasal blockage [52]. The major component of nasal blockage, dilatation of venous capacitance vessels resulting from nasal inflammation, is less amenable to H_1-antihistamine therapy [52]. In the eye, stimulation of H_1-histamine receptors is responsible for the majority of the primary symptoms of seasonal allergic conjunctivitis, namely, lacrimation, reddening, itching and chemosis [53]. In the airways, stimulation of H_1-histamine receptors contributes to the contraction of bronchial smooth muscle and stimulation of mucus production. However, the more dominant role of the leukotrienes in producing these symptoms means that H_1-antihistamines are minimally effective in reducing the symptoms of asthma [54]. In the skin, histamine H_1-receptor-mediated effects include contraction of post-capillary vein endothelial cells to cause a wheal, and sensory nerve stimulation to cause pruritus and a widespread neurogenic flare in which neuropeptides, particularly calcitonin gene-related peptide (CGRP), are the final mediators of the vasodilatation [55].

The Histamine H_1-Receptor and Inflammation

H_1-receptor stimulation may also activate the transcription factor NF-κB [41, 56, 57] (Fig. 7). NK-κB is a key pro-inflammatory cytokine, which is elevated in asthma [58] where it is involved in the production of cytokines, including TNFα, and IL-8, and adhesion molecules such as E-selectin, ICAM-1 and VCAM-1 [59]. As both the H_1-receptor and up-regulation of cytokines and adhesion proteins by NF-κB are known to be involved in allergic conditions [60], it is attractive to speculate that in such disorders the coupling of the H_1-receptor to the NF-κB pathway is of physiological importance [61]. Indeed, the reduction of NF-κB activation by H_1-antihistamines [61–63] may well explain their long-term effects against allergic inflammation and nasal blockage [64–66].

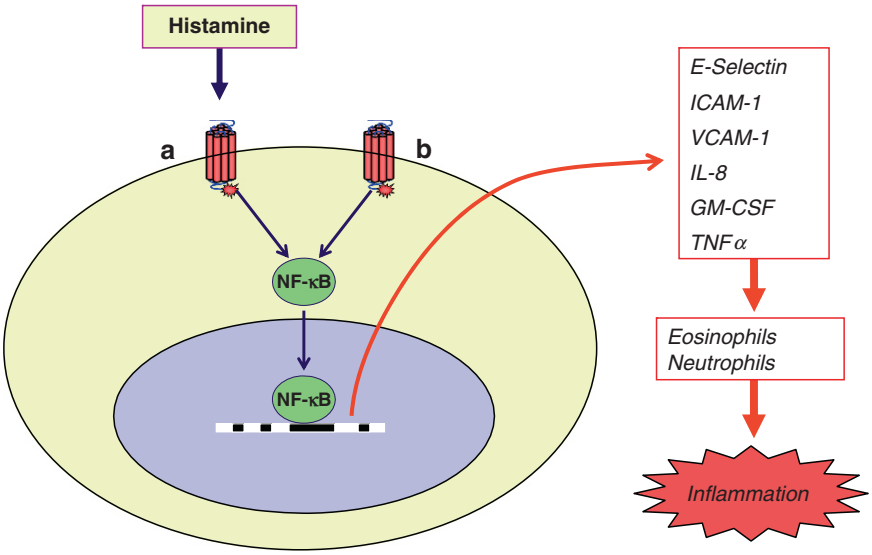

Fig. 7 H_1-receptor activation of the transcription factor NF-κB. Two histamine H_1-receptors are shown activating NF-κB, the left-hand one (**a**) being stimulated by histamine and the right-hand one (**b**) having constitutive expression in the absence of histamine. Activated NF-κB is transported to the cell nucleus where it stimulates the transcription of pro-inflammatory adhesion molecules and cytokines

The Paradox of H_1-Antihistamines and Bradykinin

Bradykinin, a nonapeptide formed by the enzymatic actions of kallikrein on extracellular kininogen, plays a central role in the production of inflammation and pain. It is of particular interest in dermatology because of its ability to cause local oedema and increased blood flow in the skin and because activation of kinin pathways are believed to be involved in angioedema, which occurs in some patients with urticaria, particularly those with hereditary angioedema and C1 esterase deficiency.

When injected intradermally, bradykinin produces a wheal-and-flare response which is, in appearance, very similar to that produced by histamine and histamine-releasing agents. However, assessment of extravascular histamine concentrations by dermal microdialysis showed that bradykinin released negligible quantities of histamine, certainly not sufficient to cause the observed wheal-and-flare response [16, 67]. These results are consistent with in vitro studies, which report that human skin mast cells do not release histamine in response to bradykinin [15, 68] and with the observation that the cutaneous sensation following the intradermal injection of bradykinin, a relatively long-lasting 'burning' sensation, is quite different from that of histamine, suggesting a different mechanism of action [16, 67].

Even though bradykinin releases negligible quantities of histamine, H_1-antihistamines such as mepyramine [69], chlorpheniramine [70], terfenadine [71] and cetirizine [72, 73] are all potent inhibitors of the response. The ability of H_1-antihistamines

to inhibit wheal-and-flare responses to inflammatory mediators, which induce small or negligible amounts of histamine is not unique to bradykinin, having been reported also for methacholine [74, 75] and platelet-activating factor (PAF) [76, 77]. Interestingly, H_1-antihistamines do not block bradykinin-induced responses in the nose [78] and only weakly reverse them in the lung [79].

The mechanism(s) by which H_1-antihistamines abrogate bradykinin-induced responses in the skin is not clear. It is tempting to speculate, therefore, that heterodimerization of histamine H_1-receptors for bradykinin B_2-receptors, M_3-receptors for methacholine and PAF-R for platelet-activating factor may be responsible for the ability of H_1-antihistamines to inhibit the effects of all four stimuli. Indeed, it has already been reported that the bradykinin B_2-receptor has the capability of forming both homodimers and heterodimers, which lead to changes in its responsiveness upon stimulation [80]. However, no direct experimental evidence is currently available to support this hypothesis.

Central Nervous Effects Mediated by the Histamine H_1-Receptor

Histamine is sometimes referred to as a 'waking amine' in that it is significantly increased during awake or light periods during which time it plays a neuroregulatory role. In laboratory animals, specific H_1-receptor agonists increase wakefulness while specific H_1-antihistamines produce opposite effects [81]. Clearly, the ability of H_1-antihistamines to cause sedation is of great clinical importance and is dealt with in the chapter on antihistamines.

Molecular Aspects and Intracellular Signal Transduction

Histamine H_1-receptors cloned from different species show a wide diversity of structure [82–84]. For example, the third intracellular domain of the guinea pig H_1-receptor, the predicted binding site for the GTP-binding protein, showed only 50% identity with those of the rat [84], explaining the diversity of histamine action between these species. However, within each species, there appears to be only a single receptor protein, the human histamine H_1-receptor gene on chromosome 3p25 [85, 86] encoding for a 487 amino acid protein with a molecular mass of 55.8 kDa [85, 87]. Furthermore, the absence of introns in the H_1-receptor gene indicates that a single mRNA will be transcribed with no splice variants [87].

The histamine H_1-receptor belongs to the Gq/11 subtype of GPCR and is a so-called Ca^{2+} mobilizing receptor [46] (Fig. 8). Mobilisation of the Gqα subunit following activation of the H_1-receptor stimulates membrane-associated phospholipase Cβ (PLCβ) to catalyse the hydrolysis of the membrane-associated inositide phospholipid, phosphatidyl 4,5-biphosphate, to form inositol 1,4,5-triphosphate (IP_3) and 1,2-diacylglycerol (DAG). The IP_3 binds to ligand-gated Ca^{2+} channels on

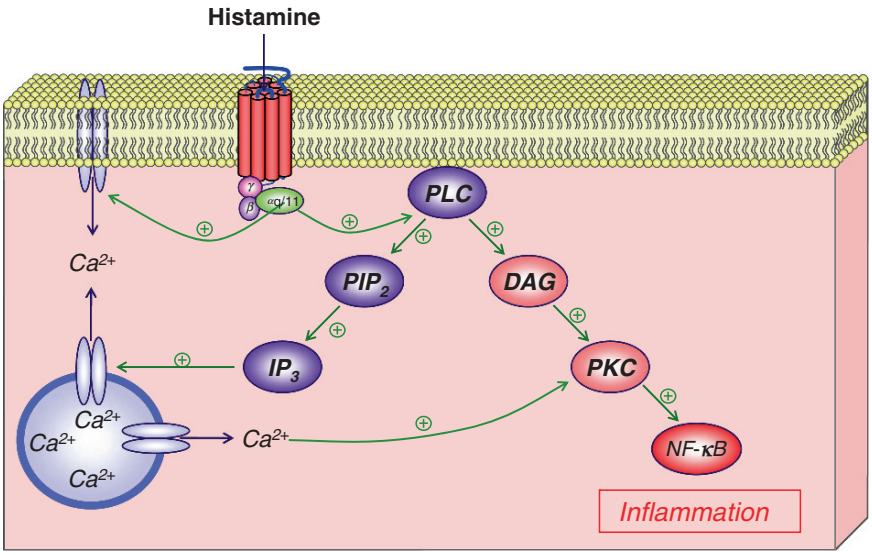

Fig. 8 Activation–secretion coupling of the histamine H_1-receptor. Mobilisation of the Gαq subunit stimulates membrane-associated phospholipase C (PLC) to catalyse the hydrolysis of the membrane-associated inositide phospholipid, phosphatidyl 4,5-biphosphate, (PIP_2) to form inositol 1,4,5-triphosphate (IP_3) and 1,2-diacylglycerol (DAG). The IP_3 binds to ligand-gated Ca^{2+} channels on internal membranes, leading to an influx of calcium ions and production of the physiological response. Activation of protein kinase C (PKC) by DAG in the presence of calcium leads to NF-κB activation

internal membranes, leading to an influx of calcium ions into the cytoplasm where they bind to the calcium modulatory protein, calmodulin. The subsequent activation of calmodulin-dependent kinase leads to production of the physiological response [18, 88, 89].

In addition to stimulating the classical effects, histamine H_1-receptor-mediated effects, histamine acting through the H_1-receptor may also induce the transcription of NK-κB as mentioned above (Fig. 8). Biochemically, this involves the activation of PKC by calcium and diacylglycerol and the stimulation of NF-κB transcription. Recently, Bakker et al. [41] explored the H_1-receptor-mediated activation NF-κB in COS-7 cells transfected with the human H_1-receptor. They showed that both Gαq/11 and Gβγ subunits play a role in agonist-mediated NF-κB activation, but that constitutive NF-κB activation by the H_1-receptor is mediated primarily through Gβγ subunits.

The Histamine H_2-Receptor

The histamine H_2-receptor is a Gs-coupled GPCR, which modulates cell function by elevating cyclic AMP. It was initially defined pharmacologically by Sir James

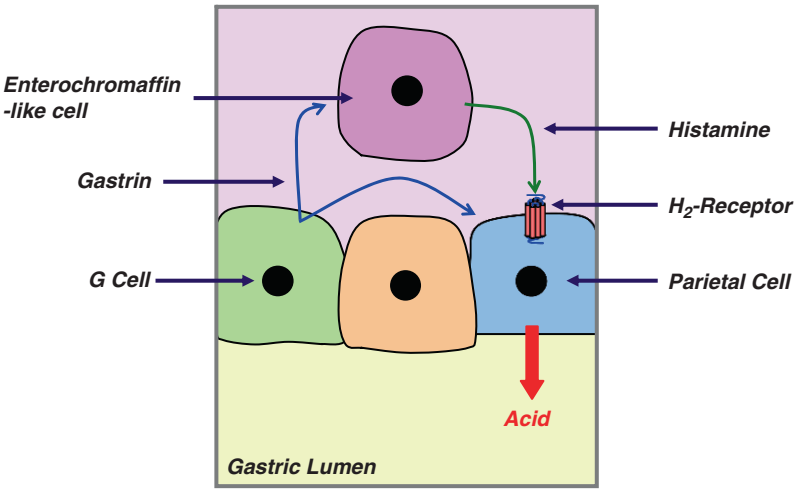

Fig. 9 Stimulation of gastric acid release from the gastric parietal cell stimulated by histamine acting at the histamine H_2-receptor

Black and colleagues [90] following the synthesis of the 'antagonists' burimamide and cimetidine. Subsequently, H_2-receptor antagonists became blockbuster drugs for the control of gastric acid secretion in the treatment of gastric and duodenal ulcers and Zollinger–Ellison syndrome (Fig. 9). More recently, they have been largely superseded by proton pump inhibitors.

The use of highly selective H_2-receptor agonists, such as 4-(*S*)-methylhistamine, dimaprit, amthamine and impromidine, and antagonists such as ranitidine, tiotidine and famotidine, has suggested a wider spectrum of biological actions regulated by this receptor. Possible physiological actions included in a review by Del Valle and Gantz [91] are relaxation of airway and vascular smooth muscle; regulation of chronotropic and inotropic effects in right atrial and ventricular muscle respectively; inhibition of basophil chemotactic responsiveness; inhibition of mitogen-mediated immunocyte proliferation via induction of suppressor T cells; and differentiation of promyelocytic leukemic cells to mature granulocytes.

For allergists, probably the most interesting H_2-receptor-mediated effects are those on the immune system. It has been demonstrated [92] that histamine enhances Th1-type responses by acting on the H_1-receptor, which is predominantly expressed in the Th1 cells, whereas histamine suppresses both Th responses by acting on the H_2-receptor. By these and other mechanisms, histamine interferes with the peripheral tolerance induced during specific immunotherapy. By actions on the H_2-receptor, histamine induces the production of IL-10 by dendritic cells, induces IL-10 production but suppresses IL-4 and IL-13 production by Th2 cells, and enhances the suppressive activity of transforming growth factor β on T cells [93]. These observations suggest that the H_2-receptor might participate in peripheral tolerance or active suppression of inflammatory-immune responses [93]. This is supported by the finding that premedication with the H_1-antihistamine, terfenadine,

during rush immunotherapy with honeybee venom, enhanced long-term immune protection [94].

The immunoregulatory effects of histamine on antigen-presenting cells, such as dendritic cells and monocytes, have been reviewed recently [95]. In monocytes stimulated with Toll-like receptor-triggering bacterial products, histamine, acting through histamine H_2-receptor stimulation inhibits the production of pro-inflammatory IL-1-like activity, TNFα, IL-12 and IL-18, but enhances IL-10 secretion. Histamine H_2-receptor stimulation also down-regulates CD14 expression on human monocytes through the regulation of ICAM-1 and B7.1 expression, leading to the reduction of innate immune responses stimulated by lipopolysaccharide. In maturing dendritic cells, histamine enhances intracellular cyclic AMP levels and stimulates IL-10 secretion, while inhibiting the production of IL-12. Finally, it has been demonstrated recently that histamine H_2-receptor stimulation reduces monocytes apoptosis, thus prolonging their life span and their ability to infiltrate to the site of inflammation. This process has been suggested to contribute to the establishment of chronic allergic disorders, such as atopic dermatitis [96].

Molecular Aspects and Intracellular Signal Transduction

Although it was initially defined pharmacologically in 1972, it was not until nearly 20 years later that the gene for the H_2-receptor, encoded on chromosome 5q, was cloned [97]. Although long and short splice variants of the resultant protein have been isolated, they appear to have similar binding with ligands and similar constitutive activity [98].

The H_2-receptor was initially defined pharmacologically as a Gs-coupled GPCR which modulates cell function by stimulating adenylyl cyclase. However, subsequent studies with the cloned H_2-receptor have shown that it can also couple to phosphoinositide second messenger systems via a Gq subunit [99] (Fig. 10). Further studies demonstrated that there is differential coupling between the Gs and Gq subunits and the second and third intra-cytoplasmic loops of the GPCR [100]. Dual coupling of H_2-receptors to Gs and Gq in cardiac myocytes is suggested to represent a novel mechanism to augment positive inotropic effects by simultaneous activation of two different signalling pathways via one receptor, the activation of the Gs-stimulated cyclic AMP–PKA pathway to promote Ca^{2+} influx through phosphorylation of L-type Ca^{2+} channels together with the Gq-stimulated increase in phosphoinositide turnover and Ca^{2+} release from intracellular stores [101].

The Histamine H_3-Receptor

The histamine H_3-receptor is a Gi/o-coupled GPCR, which serves primarily as a presynaptic receptor for histamine on nerves and is expressed almost exclusively

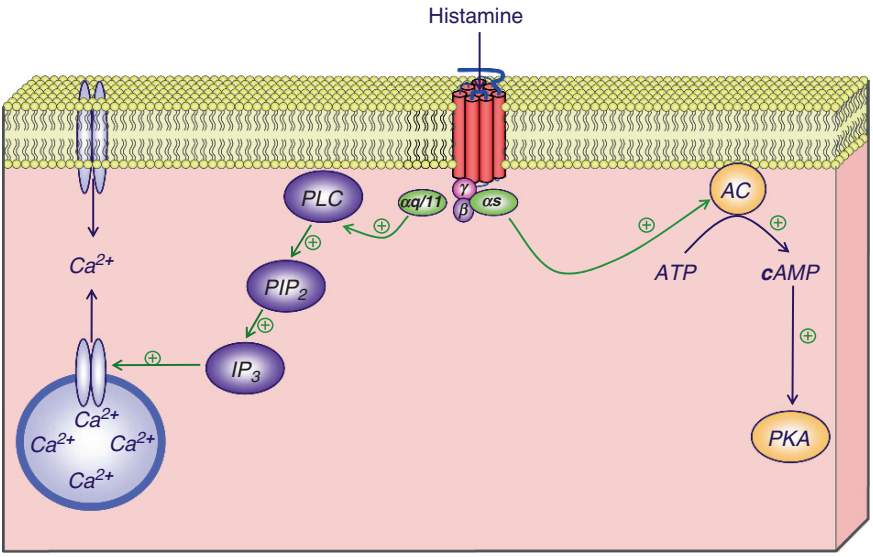

Fig. 10 Activation–secretion coupling of the histamine H_2-receptor Mobilisation of the Gαs subunit stimulates the synthesis of cyclic AMP by membrane-associated adenylyl cyclase (AC) leading to increased activation of protein kinase A (PKA) and production of the physiological response. Also, mobilisation of the Gαq/11 subunit stimulates PLC to form PIP_2 and IP_3 and mobilise calcium as seen in the H_1-receptor

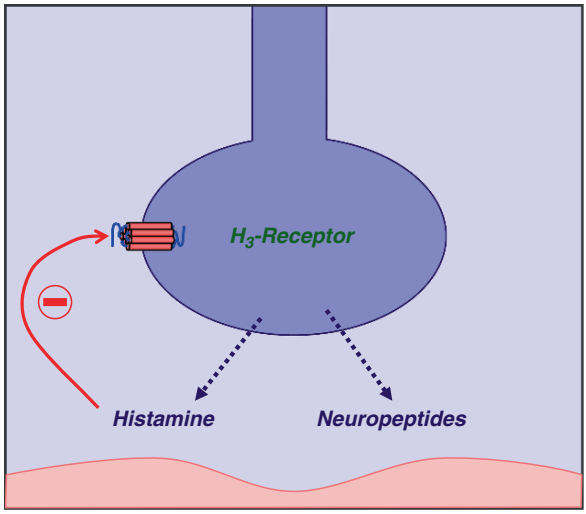

Fig. 11 The histamine H_3-receptor acting as an inhibitory presynaptic receptor for histamine on a nerve

in the brain (Fig. 11). The presence of H_3 receptors in the brain was suggested in 1983 by Jean-Charles Schwartz and his co-workers [102] while investigating the ability of histamine to inhibit its own neuronal synthesis and release from depolarised slices of rat cortex via presynaptic feedback mechanisms. The existence of

the H_3-receptor was confirmed pharmacologically in 1987 following the synthesis of the agonist *R*-α-methylhistamine and the antagonist, thioperamide [103] and cloned in 1999 [104]. Autoradiographic showed that the H3R is primarily in the brain, predominantly in basal ganglia, hippocampus and cortical areas – the parts of the brain that are associated with cognition [105].

Histamine H_3-receptor ligands and antagonists have been the subject of intense research within the pharmaceutical industry over the last decade. Several reviews [106–108] have examined the properties of H_3-receptor antagonists and inverse agonists and suggest that the most promising areas of research are in narcolepsy, cognitive disorders, Alzheimer's disease, obesity, attention impairment and neuropathic pain.

Molecular Aspects and Intracellular Signal Transduction

The human histamine H_3-receptor is a Gi/o-coupled GPCR encoded on chromosome 20 q. The H_3-receptor gene has been reported to contain three exons and two introns [109, 110]. The presence of introns within a gene allows alternative splicing of its products. Indeed, at least 20 isoforms of the human H_3-receptor have been identified to date [111], all of which have the potential of different organ disposition and signal transduction capabilities. Preliminary information on organ disposition indicates that the full length receptor (hH3R-445) is found almost exclusively in the brain, particularly in the thalamus, caudate nucleus, putamen and cerebellum with a lower signal in the amygdala and a faint signal in the substantia nigra, hippocampus and cerebral cortex. No signal was observed in the corpus callosum, spinal cord or in peripheral tissues [109]. In contrast, splice variants hH3R-329 and hH3R-326 showed a high level of expression in the amygdala, substantia nigra, cerebral cortex and hypothalamus, while hH3R-373/365 isoforms are expressed at a high level in the stomach and the hypothalamus [109, 112].

The activation–secretion coupling of the H_3-receptor (Fig. 12) has been the subject of a recent review by Bongers and colleagues [111].

- The primary function of this Gαi/o-coupled GPCR is the inhibition of adenylyl cyclase, which causes a decrease in intracellular cyclic AMP and a subsequent reduction of protein kinase A (PKA) activity. This pathway shows considerably constitutive activity, which may be inhibited by H_3-receptor inverse agonists.
- The H_3-receptor-mediated activation of phospholipase A_2 is also dependent on Gαi/o-proteins. This pathway, which has high constitutive activity, leads to the release of arachidonic acid, which has been suggested to be important in the H_3-receptor-mediated relaxation of the guinea pig epithelium [113].
- Besides H_3-receptor-mediated signalling through Gαi/o-proteins, Gβγ subunits are known to activate signal transduction pathways such as the MAP kinase pathway. MAP kinases are known to have pronounced effects on cellular growth, differentiation and survival, as well as to be important in neuronal plasticity and memory processes [114].

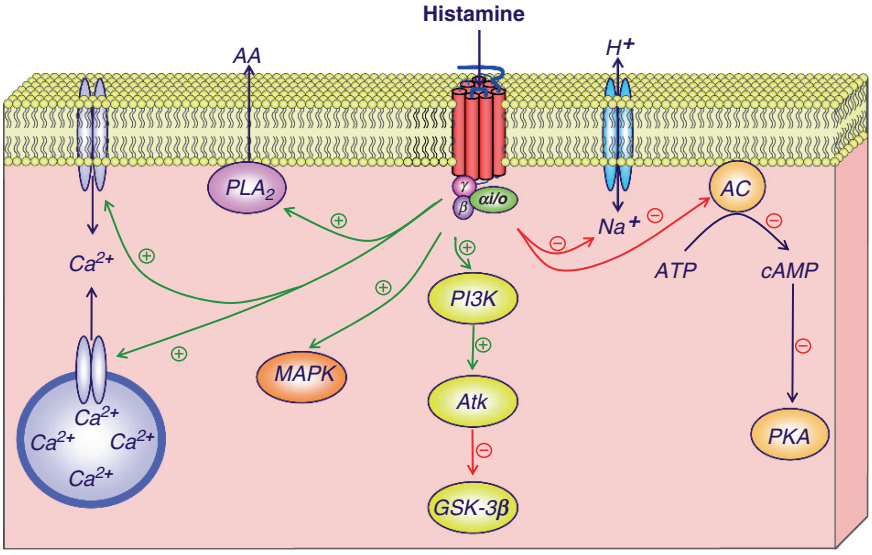

Fig. 12 Activation–secretion coupling of the histamine H_3-receptor The primary function of this Gαi/o subunit is the inhibition of adenylyl cyclase (AC) to cause a decrease in intracellular cyclic AMP and a subsequent reduction of protein kinase A (PKA) activity. The H_3-receptor-mediated activation of phospholipase A_2 (PLA_2) leading to the release of arachidonic acid (AA) is also dependent on Gαi/o-proteins. H_3-receptor-mediated signalling through Gβγ-subunits activates the MAP kinase (MAPK) pathway, Akt/GSK-3β kinases and calcium mobilisation

- Akt/GSK-3β kinases have also been shown to be activated by the H_3-receptor, again an activation pathway, which shows high constitutive activity. In the central nervous system (CNS), the Akt/GSK-3b axis plays a prominent role in brain function and has been implicated in neuronal migration, protection against neuronal apoptosis and is believed to be altered in Alzheimer's disease, neurological disorders and schizophrenia.
- H_3-receptor activation reduces the K^+-induced mobilization of intracellular calcium. This signal transduction mechanism has been linked to inhibitory effect of the H_3-receptor on norepinephrine exocytosis in cardiac synaptosomes [115].
- Activation of the H_3-receptor has been shown to diminish neuronal Na^+ H^+ exchanger activity. Inhibition of this exchanger is essential for the restoration of intracellular physiological pH and preventing acidification during ischemia. It is by this mechanism that H_3-receptor ligands inhibit the excessive release of norepinephrine and the precipitation of cardiac arrhythmias during protracted myocardial ischemia [116].

While the studies of the above pathways have contributed greatly to our knowledge of activation–secretion coupling of the H_3-receptor what is not yet clear is whether they are stimulated preferentially by different isoforms and what is the extent of their clinical relevance.

The Histamine H_4-Receptor

Unlike other histamine receptors, the gene for the H_4-receptor was discovered using knowledge of the human genome and sequence information of the H_3-receptor [117, 118]. Conclusive demonstration of which cell types express the H_4-receptor has been difficult because of its low level of expression and the fact that its expression appears to be controlled by inflammatory stimuli [119]. However, H_4-receptor expression has been shown in the bone marrow and spleen, and on eosinophils and mast cells [120–122].

Ligand-binding studies have shown similarities between the H_3- and H_4-receptors in the binding of the agonist, R-(alpha)-methylhistamine [117] and other H_3-agonists and antagonists, albeit with a different rank order of affinity/potency than at the H_3-receptor [120]. One study suggests that H_4-receptors do not bind conventional H_1- and H_2-antihistamines such as diphenhydramine, loratadine, ranitidine and cimetidine [120]. However, competition-binding studies have shown that some H_1, H_2 and H_3 ligands also show binding at H_4-receptors [123]. The highest affinities were for the tricyclic antidepressants, amitriptyline and chlorpromazine, which also have a high affinity for the H_1-receptor. The other H_1 ligands, which displayed high affinity for H_4-receptors are promethazine, doxepin, indicated for depressive illness, particularly where sedation is required and pruritus in eczema, and cinnarizine, which is indicated for motion sickness and vestibular disorders, such as vertigo, tinnitus, nausea and vomiting in Ménière's disease. The other compounds, which displayed binding were imetit (H_3-selective agonist), imaprit (H_2-selective agonist), mianserin (H_1- and H_2-antagonist), cyproheptadine (nonselective histamine/serotonin antagonist) and clozapine (an atypical antipsychotic drug with high affinity for a large number of receptors) [123].

Functional studies of the H_4-receptor are in their infancy. However, this receptor has been suggested it to be involved in eosinophil chemotaxis and shape change [124–126], in mast cell chemotaxis [121] and in neutrophil chemotaxis by stimulating LTB_4 production [127]. In vivo studies with H_4-receptor-deficient mice and mice treated with H_4-receptor antagonists showed decreased allergic lung inflammation, with decreases in infiltrating lung eosinophils and lymphocytes and decreases in Th2 responses [128]. Ex vivo restimulation of T cells from those animals showed reductions in IL-4, IL-5, IL-13, IL-6 and IL-17 levels. The authors postulate that H_4-receptor blockade on dendritic cells leads to decreases in cytokine and chemokine production and limits their ability to induce Th2 responses.

The expression of histamine H_4-receptors in human synovial cells obtained from patients suffering from rheumatoid arthritis [129, 130], in inflammatory bowel disease [131], in nasal polyposis [132] and in the human placenta in diabetes-complicated pregnancy [133] suggest a widespread role for this receptor in inflammation. Furthermore, its expression on mast cells and eosinophils suggests that the histamine H_4-receptor may represent a therapeutic target for the regulation of immune function, particularly with respect to allergy and asthma.

Molecular Aspects and Intracellular Signal Transduction

The histamine H_4-receptor gene is encoded on chromosome 18q11.2 [117, 123, 134] and has a similar structure to that of the H_3-receptor gene, having three exons and two introns [119]. At the protein level, the human H_4-receptor has a sequence identity of 54% in the transmembrane domains and an overall sequence identity of 31% compared with the H_3-receptor [135]. Only recently have splice variants been reported and that is only in the patent literature [136].

The H_4-receptor is coupled mainly to Gi/o proteins stimulation of which leads to a pertussis-toxin-sensitive decrease in the production of cyclic AMP and the inhibition of downstream events such as cyclic AMP responsive element-binding protein (CREB)-dependent gene transcription [135] (Fig. 13). As with most Gi/o-coupled GPCRs, H_4-receptor activation increases [^{35}S]GTPγS binding [137]. The observation of high basal levels of [^{35}S]GTPγS in cells transfected with H_4-receptors indicates that the H_4-receptor is constitutively active [135]. This is confirmed by the ability of the inverse agonist, thioperamide, to decrease the basal binding of [^{35}S] GTPγS to H_4-receptors in the absence of ligand [137].

Histamine-mediated activation of endogenous H_4-receptors in mast cells results in a clear Ca^{2+} response, which is sensitive to both pertussis toxin and the phospholipase C inhibitor U73122 [121]. These observations indicate that phospholipase C is

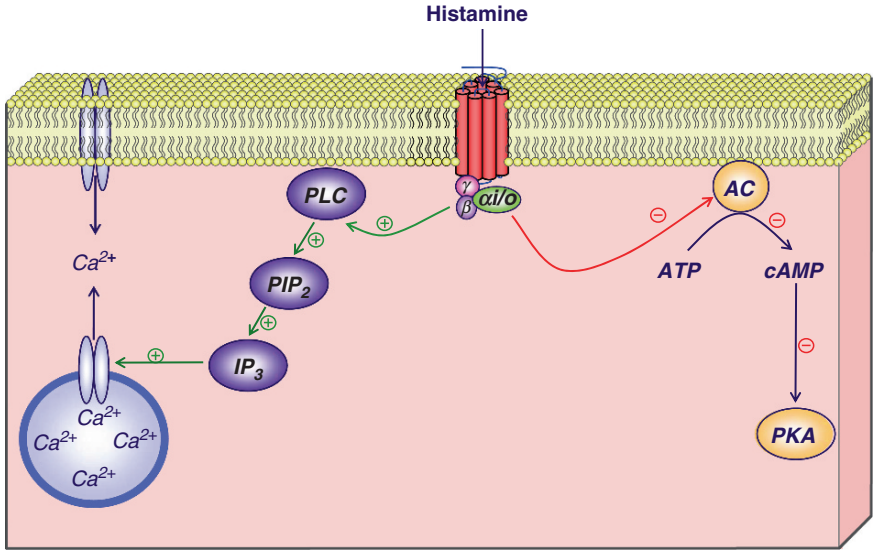

Fig. 13 Activation–secretion coupling of the histamine H4$_3$-receptor Like the H_3-receptor the H_4-receptor is coupled mainly to Gi/o proteins, stimulation of which leads to a decrease in the production of cyclic AMP. Also, the Gβγ subunits that dissociate from Gi/o proteins following H_4-receptor stimulation in mast cells stimulate the PLC/PIP_2/IP_3 pathway to raise intracellular calcium

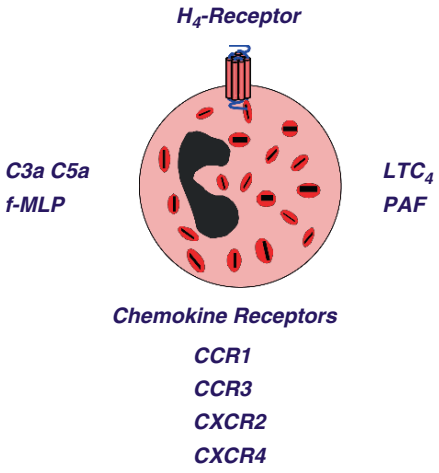

Fig. 14 Receptors linked to eosinophil activation

activated via Gβγ subunits that dissociate from Gi/o proteins following H_4-receptor stimulation in mast cells [135]. This Ca^{2+} response, which is likely to be linked to chemotaxis, has also been demonstrated in eosinophils [125].

While the functional histamine H_4-receptors have been demonstrated on mast cells and eosinophils, their effects on cell activation and their clinical importance compared with cytokines and chemokines are as yet unknown (Fig. 14).

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