

MINIREVIEW—A LATIN AMERICAN PERSPECTIVE ON G PROTEIN-COUPLED RECEPTORS

Current Knowledge and Perspectives on Histamine H₁ and H₂ Receptor Pharmacology: Functional Selectivity, Receptor Crosstalk, and Repositioning of Classic Histaminergic Ligands

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ABSTRACT

H₁ and H₂ histamine receptor antagonists, although developed many decades ago, are still effective for the treatment of allergic and gastric acid-related conditions. This article focuses on novel aspects of the pharmacology and molecular mechanisms of histamine receptors that should be contemplated for optimizing current therapies, repositioning histaminergic ligands for new therapeutic uses, or even including agonists of the histaminergic system in the treatment of different pathologies such as leukemia or neurodegenerative disorders. In recent years, new signaling phenomena related to H₁ and H₂ receptors have been described that make them suitable for novel therapeutic approaches. Crosstalk between histamine receptors and other membrane or

nuclear receptors can be envisaged as a way to modulate other signaling pathways and to potentiate the efficacy of drugs acting on different receptors. Likewise, biased signaling at histamine receptors seems to be a pharmacological feature that can be exploited to investigate nontraditional therapeutic uses for H₁ and H₂ biased agonists in malignancies such as acute myeloid leukemia and to avoid undesired side effects when used in standard treatments. It is hoped that the molecular mechanisms discussed in this review contribute to a better understanding of the different aspects involved in histamine receptor pharmacology, which in turn will contribute to increased drug efficacy, avoidance of adverse effects, or repositioning of histaminergic ligands.

Introduction

Histamine is a biogenic amine that exerts its physiologic action by binding to receptors belonging to the superfamily of seven transmembrane G protein-coupled receptors (GPCRs). To date, four different types of histamine receptors have been described: H₁R, H₂R, H₃R, and H₄R (Panula et al., 2015).

Most of the studies carried out in the last twenty years were mainly focused on the newly described H₃R and H₄R, whereas H₁R and H₂R were originally characterized many years ago. To date, H₁R and H₂R are the only histamine receptors for which drugs have been approved for use in humans. H₁R and H₂R are still effective targets for the treatment of allergies and some forms of gastric acid-related conditions, and H₁R and H₂R antagonists belong to the top 18 drug classes used

between 1999 and 2012 (Simons and Simons 2011; Kantor et al., 2015; Iwakiri et al., 2016).

The pharmacology of histamine receptors was comprehensively reviewed in numerous excellent articles published recently (Panula et al., 2015; Haas and Panula, 2016). However, based on the enormous costs for developing new drugs, this review aims to discuss the different aspects of histamine receptor function that have been characterized more recently and can be considered for repositioning histaminergic ligands for new therapeutic uses or for optimizing the usage of these existing ligands (Nosengo, 2016). Here, we provide an exhaustive review of novel or potential applications of old histaminergic drugs as well as the potential therapeutic implications of functional ligand selectivity and crosstalk.

H₁R and H₂R Signaling

H₁R canonical signaling involves activation of the Gq/11 protein and its effector phospholipase C (PLC), with a consequent increase in inositol phosphates (IPs) and intracellular

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ABBREVIATIONS: AC, adenylyl cyclase; AML, acute myeloid leukemia; ERK, extracellular signal-regulated kinase; GPCR, G protein-coupled receptor; GR, glucocorticoid receptor, GRK, G protein-coupled receptor kinase; HDC, histidine decarboxylase; IP, inositol phosphate; PAB, (6)-*cis*-5-phenyl-7-dimethylamino-5,6,7,8-tetrahydro-9*H*-benzocycloheptane; PAT, (2)-*trans*-1-phenyl-3-dimethylamino-1,2,3,4-tetrahydronaphthalene; PLC, phospholipase C; ROS, reactive oxygen species.

calcium levels in most systems, as well as the activation of small G proteins Rac and RhoA (Gutowski et al., 1991; Notcovich et al., 2010). Alternatively, in native and heterologous H₁R expression systems, H₁R signaling via Gi/o, phospholipase A2 activation, and cGMP and nitric oxide production has been described (Richelson, 1978; Snider et al., 1984; Leurs et al., 1994; Seifert et al., 1994; Wang and Kotlikoff, 2000; Prast and Philippu, 2001). In the mammalian brain, adrenal glands, and Chinese hamster ovary cells, activation of H₁R may also stimulate adenylyl cyclase (AC) with consequent intracellular cAMP production (Keogh and Marley, 1991; Marley et al., 1991). Aside from the signaling events triggered by ligand binding, H₁R was shown to display high levels of spontaneous receptor activity in the absence of agonists. H₁R was also shown to constitutively activate both IP production and modulation of gene expression under the control of nuclear factor- κ B (Bakker et al., 2001; Fitzsimons et al., 2004). On the basis of these observations, all clinically relevant H₁R ligands were reclassified as H₁R inverse agonists (Bakker et al., 2000). However, since all marketed antihistamines are actually inverse agonists, it cannot be determined whether this pharmacological property is therapeutically more relevant than neutral antagonism or histamine receptor blockade.

In most tissues where H₂R is expressed, H₂R couples to Gs protein and its activation stimulates AC-mediated cAMP production (Alewijns et al., 1998; Monczor et al., 2003; Panula et al., 2015). The coupling of H₂R to Gs proteins was demonstrated by agonist-induced photoaffinity-labeling studies with GPCR-Gas fusion proteins, guanosine 5'-O-(3-[³⁵S]thio)triphosphate binding, as well as steady-state GTP hydrolysis (Leopoldt et al., 1997; Kelley et al., 2001; Wenzel-Seifert et al., 2001). H₂R displayed lower affinity for histamine than the H₃ and H₄ subtypes and had high constitutive activity toward cAMP production (Panula et al., 2015).

In some H₂R native or heterologously expressing cells, H₂R can also couple to Gq/11 proteins in addition to the classic signaling through Gs protein, leading to IP synthesis and a consequent increase in intracellular Ca²⁺ concentration (Panula et al., 2015). H₂R stimulation by histamine was shown to potently inhibit phospholipase A2 activity, triggering arachidonic acid synthesis (Traiffort et al., 1992). Interestingly, some actions mediated by H₂R, such as modulation of cell proliferation and gene expression, are shown to involve the modulation of signaling cascades that are usually associated with tyrosine kinase receptors, such as the extracellular signal-regulated kinase (ERK1/2) or phosphoinositide 3-kinase pathway (Leopoldt et al., 1997; Mettler et al., 2007; Bonini et al., 2011; Luo et al., 2013; Alonso et al., 2016). In addition, histamine or H₂R agonists inhibit the activity of NADPH oxidase, the enzyme responsible for the generation of reactive oxygen species (ROS), in myeloid cells (Aurelius et al., 2012).

All H₂R antagonists that are used clinically, including cimetidine, famotidine, and ranitidine, behave as inverse agonists (Smit et al., 1996; Monczor et al., 1998). However, as with H₁R ligands, whether inverse agonism is relevant for their therapeutic action remains to be elucidated.

Studies have shown that G protein-coupled receptor kinase (GRK)-2 is the principal kinase that participates in both H₁R and H₂R desensitization after long-lasting or repetitive stimulation. Besides receptor phosphorylation by GRK-2, H₁R and H₂R desensitization also involves the inactivating action of the regulator of G protein signaling domain of GRK-2 over the

G proteins (Shayo et al., 2001; Fernández et al., 2002; Iwata et al., 2005; Fernandez et al., 2011). After GRK-mediated phosphorylation, receptors are internalized in clathrin-coated pits by a mechanism dependent of arrestin and/or dynamin action and they are recycled back to the cell surface or degraded in lysosomes (Fernandez et al., 2008; Hishinuma et al., 2010).

Although H₁R and H₂R were the first to be characterized, they continue to demonstrate unique signaling complexities that may account for their effects on biologic systems and may provide the basis for yet-unexplored therapeutic strategies. In the following sections, we discuss more recently described features of the signaling molecular mechanisms of H₁R and H₂R and their potential therapeutic implications.

Biased Signaling at H₁ and H₂ Histamine Receptors

Growing evidence shows that the multiplicity of signaling events associated with a unique GPCR leads to the identification of ligands that bind the receptor and then favor some specific signaling events among the texture of receptor possibilities. A critical assumption is that the heterogeneity of active receptor conformations spontaneously exists and the ligand stabilizes a particular conformational subset that fails to evoke some of the responses but may stimulate other signaling events of the receptor to which it binds (Kenakin, 2004; Rajagopal et al., 2010). This process of "stimulus trafficking" has also been referred to as biased agonism or functional selectivity, and it explains why a ligand causes differential activation of only some of the signaling pathways associated with a specific receptor (Pupo et al., 2016).

This pluridimensional aspect of efficacy was extensively studied for the adrenergic receptors (Galandrin and Bouvier, 2006) and the angiotensin II receptor (Wei et al., 2003). Prior studies demonstrate that biased agonism is a phenomenon that also occurs for several GPCRs including H₁R and H₂R in native and recombinant systems (Moniri et al., 2004; Reher et al., 2012a; Alonso et al., 2014, 2015).

Biased Signaling for H₁R Ligands. The discovery of agonists acting at H₁R has been disregarded for a long time and efforts were focused on the development of ligands that block the H₁R-mediated histamine allergic action. Although histamine possesses several physiologic and pathophysiologic effects acting at H₁R, a therapeutic use for H₁R agonists has not yet been found. However, one of the seminal studies providing experimental evidence to underpin the concept of biased agonism was performed at H₁R. Two H₁R ligands of the same class that mainly differed with regard to stereochemistry, *cis*-PAB [(6)-*cis*-5-phenyl-7-dimethylamino-5,6,7,8-tetrahydro-9H-benzocycloheptane] and *trans*-PAT [(2)-*trans*-1-phenyl-3-dimethylamino-1,2,3,4-tetrahydronaphthalene], displayed functional heterogeneity at modulating the PLC/IP versus AC/cAMP signaling pathways of H₁R. Whereas PAB presented partial agonism at activating the PLC/IP cascade and no efficacy at the AC/cAMP pathway, PAT behaved oppositely by stimulating cAMP production and blocking IP formation (Moniri and Booth, 2004; Moniri et al., 2004). cAMP production after endogenous histamine stimulation of H₁R leads to the activation of tyrosine hydroxylase (the enzyme responsible for L-dopa synthesis), the precursor of dopamine, noradrenaline, and adrenaline. Moniri

and Booth (2006) reported that this differential activation of AC/cAMP and consequently tyrosine hydroxylase by H₁R ligands in mammalian brain and adrenal tissues could have implications in the treatment of several neurodegenerative disorders, as further discussed below.

Biased Signaling for H₂R Ligands. As mentioned previously, H₂R blockers used in the clinic for treatment of gastric acid-related disorders (e.g., cimetidine, famotidine, and ranitidine) are well known inverse agonists regarding cAMP production (Smit et al., 1996; Monczor et al., 1998). Interestingly, although they diminish cAMP production, all of these ligands (as well as tiotidine, the classic reference ligand used in research) behave as full agonists with regard to H₂R desensitization and internalization. Although the extent and rate of H₂R internalization induced by inverse agonists was similar to that of agonist-promoted endocytosis, it was independent of GRK-2-mediated phosphorylation. Moreover, the protein partner profile and receptor fate of H₂R once it is endocytosed are strikingly different when desensitization/internalization processes are triggered by agonists or inverse agonists (Alonso et al., 2014). However, cimetidine, famotidine, ranitidine, and tiotidine also present a biased profile toward activation of the ERK1/2 signaling pathway over cAMP production. Again, although inverse agonists and histamine or H₂R agonists have positive efficacy in increasing ERK1/2 phosphorylation, the underlying mechanisms are different. H₂R agonist-stimulated ERK1/2 phosphorylation is mediated by dynamin, whereas cimetidine, ranitidine, and tiotidine lead to an increase in phospho-ERK levels by a mechanism that is independent of dynamin or even H₂R internalization but is mediated by Gβγ (Xu et al., 2008; Alonso et al., 2014, 2016). Notably, ERK1/2 modulation is involved in the regulation of histidine decarboxylase (HDC) expression, the enzyme responsible for histamine synthesis (Colucci et al., 2001).

Biased agonism has also been described for H₂R in neutrophils and eosinophils. These cells are chemoattracted and migrate to the focus of infection, releasing a variety of cytotoxic enzymes, cytokines, and ROS playing a pivotal role in host defense against microbes and viruses (Pincus et al., 1982; Burde et al., 1989; Adamko et al., 2002; Rothenberg and Hogan, 2006; Soehnlein et al., 2009; Sadik et al., 2011; Reher et al., 2012b). H₂R activation results in inhibition of granulocyte superoxide release (Gespach and Abita, 1982; Burde et al., 1989; Ezeamuzie and Philips, 2000). Although cAMP increments are related to inhibition of ROS release, substantial evidence has shown that H₂R agonists dimaprit and impromidine are biased ligands toward ROS inhibition over cAMP production in neutrophils and eosinophils (Reher et al., 2012a). Given the use of histamine-mediated inhibition of ROS release for the treatment of acute myeloid leukemia (AML) (Aurelius et al., 2012), this ligand bias could be of great value in the clinic, as further discussed below.

Histaminergic Regulation of the Signaling of Other Receptors

Considerable progress in biochemistry and molecular biology in recent years has led to significant changes in how cellular signaling is studied and how the experimental results are interpreted. Traditionally, studies focused on outlining direct upstream and downstream interactions as linear paths

that transmit information from the cell environment to intracellular effectors, through receptors (Weng et al., 1999). Holistic analyses of signaling pathways in cell systems revealed that signals do not necessarily disseminate in a linear manner. Alternatively, cellular signaling networks are composed of modules that cannot be considered as isolated entities and that regulate multiple functions integrating the information the cell receives from the environment, producing a unified response dependent of the context (Jordan et al., 2000; Bockaert et al., 2003; Di Roberto et al., 2016).

H₁R and H₂R Interfere in the Activity of Other GPCRs. Several ways in which GPCRs functionally interact with other pathways have been described. In particular, some inverse agonists of histamine receptors are shown to interfere with the response of other GPCRs that share the same signaling pathway. For example, tiotidine, after binding to H₂R, impairs the signaling of other Gs-coupled GPCRs such as the β-adrenergic, calcitonin, and prostaglandin E₂ receptors (Monczor et al., 2003; Tubio et al., 2010). Furthermore, the mere overexpression of H₂R interferes with the signaling of these GPCRs and H₂R knockdown potentiates their response (Tubio et al., 2010). In the same way, mepyramine binding to H₁R interferes with the signaling of the Gq-coupled ATP receptor. These ligands are thought to stabilize a conformation of the receptor that (although inactive) may couple and recruit G protein, making it less available for other unrelated receptors that signal through the same pathway (Fig. 1, top). This interpretation also explains why the phenomenon of interference is no longer observed after G-protein overexpression (Fitzsimons et al., 2004; Tubio et al., 2010).

H₁R and H₂R Crossregulation. H₁R and H₂R are coexpressed in most cell types, such as neurons, granulocytes, lymphocytes, monocytes/macrophages, dendritic cells, endothelial and epithelial cells, and airway and vascular smooth muscle cells (Parsons and Ganellin, 2006; Jutel et al., 2009). In these systems, the action of endogenous histamine may result from the balance and coordination of the signaling events activated by the H₁R and H₂R histamine receptor subtypes (or even others).

H₁R and H₂R crossregulation has been described. In recombinant and native systems, both receptors were desensitized when cells were exposed to a sustained stimulus with any H₁R or H₂R agonist (Alonso et al., 2013). This cross-desensitization occurs by a mechanism that is not dependent of second messengers and their kinases. Fluorescence resonance energy transfer assays revealed that after activation of H₁R and H₂R, the receptors colocalize in endosomes forming heteromers. Hence, negative histamine receptor crossregulation results, having physiologic consequences, conditioning the extent of cell proliferation or cell death after receptor stimulation (Alonso et al., 2013). This observation indicates that the biologic output after H₁R or H₂R stimulation is conditioned or even dampened by this mechanism (Fig. 1, middle).

H₁R and H₂R Modulation of Nuclear Receptor Activity. Crosstalk between signals triggered by membrane receptors has been widely studied and described. On the contrary, modulation of nuclear receptor activity by GPCRs is much less documented. However, some studies have explored the possibility of regulating the transcriptional activity of glucocorticoid receptors (GRs) through the modulation of GPCR-mediated signaling. Adrenaline and noradrenaline

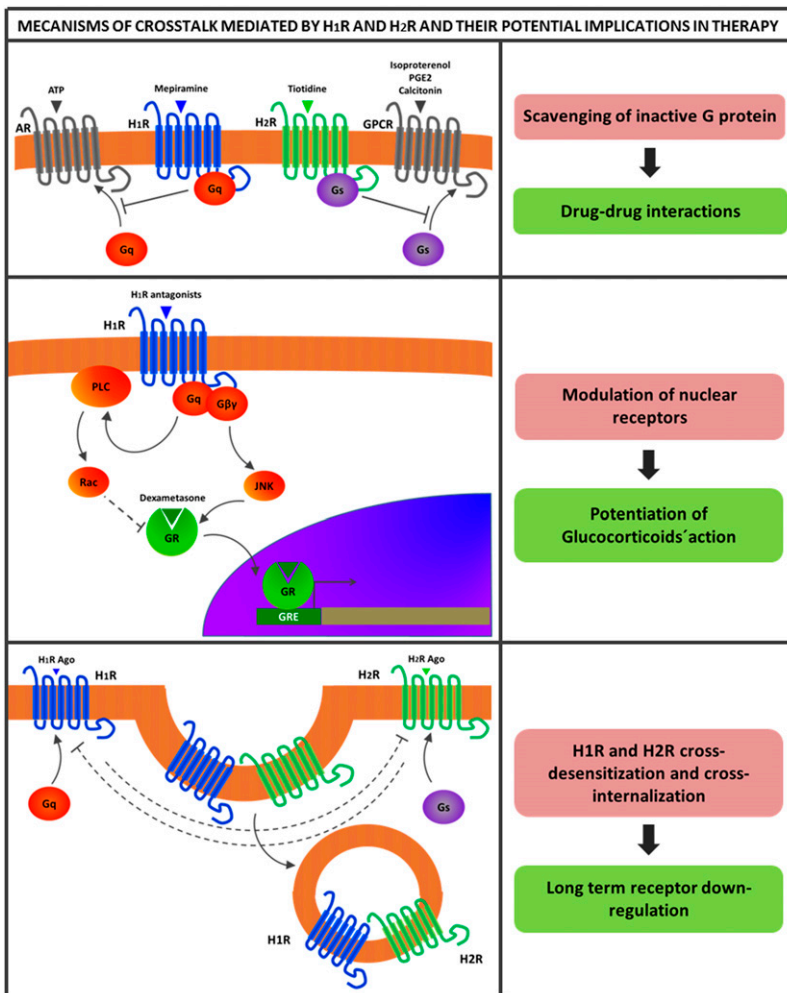


Fig. 1. Mechanisms of crosstalk mediated by H₁R and H₂R and their potential implications in therapy. (Top) Inverse agonists acting at H₁R or H₂R promote receptor binding to G protein in an inactive form, making it less available to other GPCRs that signal through the same pathway. (Middle) Antihistamines acting at H₁R potentiate dexamethasone-induced GR transcriptional activity. (Bottom) H₁R and H₂R crossdesensitize when stimulated with either H₁ or H₂ agonists. The molecular mechanisms underlying the described effects are detailed in the main text.

acting on β 2-adrenergic receptors enhance GR activity via a $G\beta\gamma$ /phosphoinositide 3-kinase/protein kinase B pathway (Schmidt et al., 2001). Yet somatostatin and melatonin receptor activation suppresses GR activity through $G\beta\gamma$ and $G_{\alpha i}$ proteins, respectively (Kiefer et al., 2005; Kino et al., 2005).

Despite the common therapeutic association between GR agonists and antihistaminergic ligands, few studies have been conducted to characterize the effects of H₁R signaling on GR activity. Investigators recently observed that histamine, as well as antihistamines, are able to potentiate GR activity (Zappia et al., 2015). When H₁R is stimulated by histamine, a complex dual process triggers. On the one hand, $G_{\alpha q}$ /PLC signaling inhibits the GR response to dexamethasone. On the other hand, the $G\beta\gamma$ dimer enhances the GR response to dexamethasone through Jun kinase-mediated phosphorylation of the receptor. The balance of both regulatory pathways results in the activation of GR activity. However, since H₁R inverse agonists potentially inhibit $G_{\alpha q}$ /PLC signaling, they also lead to potentiation of the GR response to dexamethasone (Fig. 1, bottom) (Zappia et al., 2015). This potentiating effect of histamine and antihistamines on GR activity is shown to alter the expression of endogenous genes transactivated and transrepressed by dexamethasone and related to inflammatory processes (Zappia et al., 2015). This somehow paradoxical effect, in which antihistamines actually behave as partial agonists concerning GR activity, has profound clinical

consequences as we further discuss below. Table 1 summarizes the above information regarding histamine receptor signaling.

Pharmacology of H₁ and H₂ Histamine Receptors: From Classic Uses to Repurposing and Novel Indications

Classic Clinical Uses of Histaminergic Ligands. Antihistamines have a well established place in the treatment of diverse allergic situations, including anaphylactic shock, and are promptly available as prescription and over-the-counter drugs. Therapeutically relevant H₁R drugs are inverse agonists: loratadine, azelastine, fexofenadine, desloratadine, levocetirizine, cetirizine, and olopatadine. These ligands are widely used in the treatment of hay fever, allergic rhinitis and conjunctivitis, and hives (Simons and Simons, 2011). Antihistamines have been also formulated for local application to the mucosa or skin, diminishing the symptoms caused by localized or systemic histamine (Ostrom, 2014; Solelhac and Charpin, 2014).

H₂R antagonists cimetidine, ranitidine, nizatidine, and famotidine are classic treatments for patients presenting gastric or duodenal ulcers, dyspepsia, or gastroesophageal reflux disease (Hershovici and Fass, 2011; Sigterman et al.,

TABLE 1
Histamine H₁R and H₂R: signaling pathways, receptor crosstalk, and ligands

Signaling	H ₁ R		H ₂ R	
	Pathway, Ligand, or Receptor	Reference	Pathway, Ligand, or Receptor	Reference
Main signaling pathway involved	Gq/11/PLC/Ca ²⁺ /PKC; Rac, RhoA	Gutowski et al. (1991), Notcovich et al. (2010)	Gs/AC/PKA	Panula et al. (2015)
Other signaling pathways regulated	Gi/0; PLA2; AC/cAMP; NF-κB	Snider et al. (1984), Leurs et al. (1994), Seifert et al. (1994), Bakker et al. (2001), Prast and Philippu (2001)	Gq/11; PLA2; ERK1/2; PI3K	Leopoldt et al. (1997), Mettler et al. (2007), Bonini et al. (2011), Luo et al. (2013), Alonso et al. (2016)
Classic reference ligand	Mepyramine	Sadek and Stark (2016)	Iodoaminopotentidine	Hirschfeld et al. (1992)
Biased ligands	(-) <i>trans</i> -PAT; (±) <i>cis</i> -PAB	Moniri et al. (2004)	Famotidine; cimetidine; tiotidine; ranitidine	Alonso et al. (2014, 2015)
Crosstalk with other receptors	ATP receptor; GR	Fitzsimons et al. (2004), Zappia et al. (2015)	β-adrenergic receptor; calcitonin receptor; PGE2 receptor	Monczor et al. (2003), Tubio et al. (2010)

NF-κB, nuclear factor-κB; PGE2, prostaglandin E2; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PLA, phospholipase A.

2013). Antibiotic therapies for *Helicobacter* infections and the discovery of proton pump inhibitors have overtaken the anti-secretory H₂R antagonists for gastroesophageal symptomatic treatment (Marshall and Warren, 1984; Marshall et al., 1988; Olbe et al., 2003). However, there has been a renaissance in the use of H₂R antagonists to prevent gastrointestinal ulcers among patients taking nonsteroidal anti-inflammatory drugs (Koch et al., 1996; Rostom et al., 2002). For example, a combination of ibuprofen and the H₂R antagonist famotidine (DUEXIS; Horizon Pharma, Lake Forest, IL) is available for the treatment of arthritis (Laine et al., 2012).

On the basis of these findings and taking into account the more recently described functional selectivity and crosstalk of H₂R, it is necessary to consider these phenomena in the context of the clinical use of H₂R blockers. The inhibition of gastric acid secretion is achieved by blocking the canonical AC/cAMP signaling pathway of H₂R. However, some H₂R inverse agonists are shown to increase phospho-ERK levels mimicking the effects of histamine (Alonso et al., 2015). As mentioned previously, ERK activation induces the expression of HDC, the enzyme that synthesizes histamine, potentially increasing the synthesis of the ligand that it is supposed to antagonize (Alonso et al., 2016). Moreover, long-term H₂R blockade increases the parietal cell response to histamine and leads to tolerance to treatment with H₂ antagonists. This is explained by an increase in receptor membrane expression due to structural stabilization of H₂R by the inverse agonists (Smit et al., 1996). However, the induction of HDC expression by famotidine can be an additional explanation regarding the undesired rebound effects of H₂R blockers, and it may also explain why these ligands produce increased hypersecretion of gastric acid after withdrawal (Smith et al., 1999). If this is the case, an H₂R neutral antagonist or inverse agonist that fails to induce HDC expression would avoid such undesired effects.

Although G protein scavenging by H₁ or H₂ inverse agonists was mentioned above, we could not find examples in the literature in which this phenomenon would be responsible for adverse effects or drug–drug interactions. However, these effects cannot be discarded a priori, since G protein scavenging has actual consequences on the response of other GPCRs that are coupled to the same signaling pathway.

Potential Repurposing of Classic H₁R Ligands. Despite the extensive study and clinical applications of histamine H₁R and H₂R pharmacology, there are novel and proposed

uses for repositioning histaminergic ligands. Since 2011, the National Institutes of Health has augmented activities to facilitate repurposing of existing drugs (Huang et al., 2011). In this context, histaminergic ligands are low-cost drugs with very good, established safety profiles and no patent protection, which allows fast tracking for human trials.

Based on the recently described crosstalk between H₁R signaling and GR activity, antihistaminic and antiallergic ligands could potentially be repositioned as adjuvants for corticoid therapies to diminish the adverse effects of corticoids. As mentioned above, H₁R inverse agonists are able to modulate GR transcriptional activity by potentiating trans-activation and transrepression of key genes in the inflammatory response (Zappia et al., 2015). The existence of relevant cell types coexpressing both receptors, such as endothelial cells, dendritic cells, monocytes, neutrophils, T and B cells, and microglia, suggests that this interaction may have implications for the regulation of inflammation in several systems (Lu et al., 2006; Panula et al., 2015). In the search for strategies to improve the beneficial/undesired effect ratio in the clinical administration of glucocorticoids, add-on therapies have had very good results. These therapies consist of the combination of corticoids with other drugs that potentiate corticoid effects by a different mechanism of action, thereby decreasing the dose of corticoid administered as well as diminishing its adverse effects. By this approximation, corticoids have been used in combination with β2-adrenoreceptor agonists (e.g., theophylline) or with leukotriene receptor antagonists (e.g., montelukast) to treat asthma (Louis et al., 2012). In this regard, combination therapy with glucocorticoids and antihistamines may not only be beneficial for patients with concomitant allergic and inflammatory processes, but the antihistamine-potentiating effects of such therapy may also allow a reduction in corticoid doses.

In support of this hypothesis, the antihistamine olopatadine was shown in vivo to enhance prednisolone inhibition of scratching and skin symptoms in an atopic dermatitis murine model (Kagawa et al., 2010). Likewise, H₁R blocker azelastine reduced the frequency of administration of inhaled corticosteroids without loss of pulmonary function in a clinical trial with patients with chronic asthma (Busse et al., 1996).

Repositioning of antihistaminergic ligands is also proposed by taking advantage of the generalized actions that are mediated by histamine throughout the body and the ubiquitous expression of

H₁R. Novel clinical applications for these ligands are being investigated, with different degrees of success.

The action of H₁R in the central nervous system was originally seen as an undesired action of antihistamines due to sedative effects of first-generation antiallergic drugs. However, new approaches rely on histamine H₁R central expression. Histamine has been implicated in pain modulation, augmenting the transmission of nociceptive impulses; considerable evidence indicates that several H₁ blockers are indeed analgesic agents (McHugh and McHugh, 2000; Mobarakeh et al., 2000; Sakurada et al., 2004). Recent data indicate that cetirizine potentiates the analgesic and antiedematogenic effects of morphine (Stein et al., 2016), suggesting an unexplored use for classic antihistamines in pain relief.

H₁R antagonists are also proposed to be beneficial in the treatment of neurodegenerative disorders that have a neuro-inflammatory component, such as Parkinson disease and amyotrophic lateral sclerosis (Dong et al., 2014; Rocha et al., 2014). Chronic treatment with clemastine enhances neuronal survival and modulates the expression of inflammatory genes in microglia (Apolloni et al., 2016). Furthermore, it has been suggested that the blockade of histamine-induced dopaminergic neuronal toxicity would improve neuronal protection, with potential clinical applications for Parkinson disease (Rocha et al., 2016).

Histaminergic neurons are active during wakefulness and are inhibited during rapid eye movement sleep by GABAergic neurons located in the hypothalamus (Shan et al., 2015). On that basis, antihistamines with central action (e.g., diphenhydramine and doxylamine) are widely used for insomnia therapy, although their use is not recommended for long periods due to rapidly developed tolerance (Krystal, 2015). The U.S. Food and Drug Administration approved the antihistamine doxepin for the “treatment of insomnia characterized by difficulties with sleep maintenance” (Neubauer, 2014), which is consistent with published data indicating that antihistamines have greater effects on sleep maintenance than on sleep onset (Morin et al., 2005; Glass et al., 2008). Although concerns have been raised regarding the degree to which these properties reflect specific H₁R antagonism or nonspecific action over muscarinic M₁ receptors, this possibility

has been ruled out by the observation that low doses of doxepin (that act solely on H₁R) show a significant improvement in total sleep time and efficiency with no evidence of morning residual impairment or sedation (Scharf et al., 2008; Krystal et al., 2011; Krystal, 2015)

Potential Repurposing of Classic H₂R Ligands. In addition to H₂R’s classic regulation of gastric acid secretion, H₂R signaling has also been implicated in the development of cardiovascular disease. High concentrations of histamine are found in cardiac tissues and the positive inotropic effects mediated by H₂R stimulation may be important in the pathophysiology of cardiovascular disease (Eckel et al., 1982; Kirch et al., 1992; Hattori, 1999; Shi et al., 2015). In fact, the blocking of histamine release or H₂R antagonism prevented heart failure in rabbits with doxorubicin-induced cardiomyopathy and dogs with sustained atrial tachycardia (Takahama et al., 2010). In addition, H₂R^{-/-} knockout mice had resistance to heart failure and had lower levels of cardiac fibrosis when subjected to transverse aortic constriction (Zeng et al., 2014). Although there is no current evidence supporting this, it would be interesting to determine whether the cardioprotective action of H₂R blockers relies, at least partially, on decreased responsiveness of the β-adrenoreceptor due to scavenging of Gαs protein by H₂R. In a prospective study conducted in a cohort from the Multi-Ethnic Study of Atherosclerosis with more than 6000 cases, Leary et al. (2016) concluded that the use of H₂R antagonists prevented the onset of chronic heart failure. On the basis of this evidence, H₂R ligands are being repurposed as reliable drugs to provide benefits to patients with chronic heart failure.

In addition to these attempts to reposition classic histaminergic ligands, they are also being considered for improving diabetic conditions and treating infections and cancer (for review, see Deva and Jameson, 2012; Pantziarka et al., 2014; Pini et al., 2016).

Biased Signaling and Novel Drugs of the Classic Histaminergic System. Several drugs marketed worldwide act on receptors that demonstrate biased agonism (Kenakin and Miller, 2010). Although there is a clear theoretical advantage in this pharmacological complexity, there are currently no

TABLE 2

Clinical uses of histaminergic ligands according to their molecular mechanisms of action: current, proposed, and nontraditional

H ₁ R				H ₂ R			
Molecular Mechanism of Action	Therapeutic Use	Pharmacological Effect	Reference	Molecular Mechanism of Action	Therapeutic Use	Pharmacological Effect	Reference
	Current	Antiallergic	Bakker et al. (2001), Panula et al. (2015)	Gs/AC/cAMP inhibition	Current	Gastric acid secretion regulation	Panula et al. (2015)
Gq/11 activity blockade; NF-κB inhibition	Repositioning	Analgesia; neurodegenerative disorders; sleep disorders; stress induced hypertension	Krystal et al. (2011), de Almeida et al. (2015), Shan et al. (2015), Apolloni et al. (2016), Rocha et al. (2016), Stein et al. (2016)		Repositioning	Chronic heart failure; diabetes; colorectal cancer	Pantziarka et al. (2014), Leary et al. (2016), Pini et al. (2016)
Biased agonism; GR crosstalk	Nontraditional	Neuroprotection; anti-inflammatory potentiation	Moniri et al. (2004), Zappia et al. (2015)	Biased agonism	Nontraditional	Gastric acid secretion rebound; AML treatment	Reher et al. (2012a,b), Alonso et al. (2014, 2015)

NF-κB, nuclear factor-κB.

drugs approved for their use based on their biased therapeutic profiles (Kingwell, 2015). In general, biased ligands could surmount on-target undesirable events circumventing certain pathways, or they could enhance their therapeutic efficacy by avoiding or stimulating specific negative or positive feedback loops in their signaling pathways. The recent development of some new drugs has taken advantage of this signaling multiplicity of ligands with promising results (Violin et al., 2014).

This functional heterogeneity has been described for H₁ and H₂ histamine receptors as mentioned above. In the brain, histamine not only signals through the canonical Gq/calcium pathway by acting through the presynaptic H₁R, but it also stimulates AC/cAMP signaling. Neuronal activation of the cAMP pathway leads to tyrosine hydroxylase activity and dopamine synthesis. Interestingly, this behavior, dependent of the AC/cAMP pathway, is conserved in *trans*-PAT biased agonism without stimulating the canonical calcium signaling that may account for histamine-mediated allergic responses and hyperalgesia (Galeotti et al., 2004; Moniri et al., 2004). This biased behavior may be of possible value in treating neurodegenerative or neuropsychiatric disorders involving dopamine synthesis.

H₂R agonists have been also proposed as promising drugs for the inhibition of neutrophil and eosinophil function since they inhibit superoxide anion formation by these cell types (Reher et al., 2012a).

Histamine dihydrochloride (Ceplene; Immune Pharmaceuticals, New York, NY) has been approved for the treatment of patients suffering from AML, and H₂R agonists are being extensively studied as promising drug candidates for the treatment of AML and inflammatory diseases (Burde et al., 1989, 1990; Jutel et al., 2009; Martner et al., 2010). By inhibiting ROS production, H₂R ligands allow agents that stimulate the immune system (e.g., interleukin-2) to effectively activate cytotoxic cells, improving tumor cell death (Hellstrand, 2002). As a result, combined histamine and interleukin-2 postremission therapy was shown to significantly prevent AML relapse (Buyse et al., 2011; Aurelius et al., 2012).

As mentioned above, H₂R agonists are reported to inhibit ROS generation in myeloid cells by a mechanism that is not mediated by cAMP accumulation. Indeed, dimaprit and impromidine were described as H₂R biased agonists toward ROS inhibition in neutrophils and eosinophils (Reher et al., 2012a). These results suggest that H₂R biased signaling toward the inhibition of ROS production may present a beneficial effect by allowing cytotoxic cells to kill leukemic cancer cells (Monczor et al., 2016). Table 2 summarizes the above-presented data concerning the current and potential clinical applications of histaminergic ligands.

Final Considerations

Getting a drug to market takes 13–15 years and costs between 2 and 3 billion dollars on average; repositioning a drug takes less than one-half of that time and costs almost one-tenth of this amount (Nosengo, 2016). Molecular pharmacology studies rely on the ultimate understanding of the effects of a given ligand on a biologic system that may account for its therapeutic utility. Although histaminergic ligands for H₁R and H₂R were described several decades ago, recently discovered signaling phenomena can be very useful to conceive

novel therapeutic strategies or to optimize treatments already in use. In the same way, improved understanding of the complete picture of histamine actions may help to repurpose classic histaminergic low-cost ligands with novel therapeutic uses. In the attempt to understand the pharmacology of a ligand, there is always a risk regarding the election of the “experimental eyes” that are used to estimate its action and efficacy. The latter advances in physics, biology, and chemistry have been beneficial for the measurement of the ability of histaminergic ligands to produce a biologic response or to interfere in the response of other receptors, further enhancing knowledge even about the classic pharmacology of H₁R and H₂R. Although the basis of histaminergic clinical pharmacology goes back to the prototypical effects described long ago by Sir James Black (Black et al., 1972), it is hoped that the mechanistic aspects discussed in this review will improve understanding of the histaminergic system as well, helping to repurpose classic ligands of the histaminergic system, increase drug efficacy, and avoid adverse effects.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Monczor, Fernandez.

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