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, H3R and H4R 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-9H- 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; Notovich et al., 2010). Alternatively, in native and heterologous H1R expression systems, H1R signaling via Gαi/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 Kottlikoff, 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-κB (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 (Alewijnse 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-Gαs fusion proteins, guanosine 5′-O-[(3′-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 H2R and H3R desensitization after long-lasting or repetitive stimulation. Besides receptor phosphorylation by GRK-2, H2R and H3R 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 H2R and H3R 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 H2R 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 H2R 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-PAB [(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
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 H2R 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 Ganelin, 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...
acting on β2-adrenergic receptors enhance GR activity via a Gβγ/phosphoinositide 3-kinase/protein kinase B pathway (Schmidt et al., 2001). Yet somatostatin and melatonin receptor activation suppresses GR activity through Gαi and Gαq 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, Gαq/PLC signaling inhibits the GR response to dexamethasone. On the other hand, the Gβγ 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 potently inhibit Gαq/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 also been 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 (Hershcovici and Fass, 2011; Sigterman et al.,...
Table 1: Histamine H1R and H2R: signaling pathways, receptor crosstalk, and ligands

<table>
<thead>
<tr>
<th>Signaling Pathway, Ligand, or Receptor</th>
<th>H1R Reference</th>
<th>H2R Reference</th>
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<tr>
<td>Biased ligands</td>
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| Crosstalk with other receptors | ATP receptor, GR | Fitzsimons et al. (2004), Zappia et al. (2015) | \(\text{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.}
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; Moharakeh 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 neuroinflammatory 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 H1R Ligands.** In addition to H2R’s classic regulation of gastric acid secretion, H1R 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 H1R 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 Gα protein by H1R. 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

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### Table 1

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

<table>
<thead>
<tr>
<th>Molecular Mechanism of Action</th>
<th>Therapeutic Use</th>
<th>Pharmacological Effect</th>
<th>Reference</th>
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<tr>
<td><strong>H1R</strong></td>
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<tr>
<td>Current</td>
<td>Antiallergic</td>
<td>Bakker et al. (2001),</td>
<td></td>
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<tr>
<td>Gq/11 activity blockade;</td>
<td>Repositioning</td>
<td>Panula et al. (2015)</td>
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<tr>
<td>NF-κB inhibition</td>
<td>Analgesia;</td>
<td>Krystal et al. (2011),</td>
<td></td>
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<tr>
<td></td>
<td>neurodegenerative disorders; sleep disorders; stress induced hypertension</td>
<td>de Almeida et al. (2015), Shan et al. (2015), Apolloni et al. (2016), Rocha et al. (2016), Stein et al. (2016)</td>
<td></td>
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<tr>
<td><strong>H2R</strong></td>
<td>Gastric acid secretion regulation</td>
<td>Chronic heart failure; diabetes; colorectal cancer</td>
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<tr>
<td>Current</td>
<td>Repositioning</td>
<td>Panula et al. (2015)</td>
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<tr>
<td>Biased agonism; GR crosstalk</td>
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<tr>
<td>Nontraditional</td>
<td>Neuroprotection; anti-inflammatory potentiation</td>
<td>Moniri et al. (2004), Zappia et al. (2015)</td>
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<tr>
<td><strong>H1R</strong></td>
<td>Gastric acid secretion rebound; AML treatment</td>
<td>Reher et al. (2012a,b), Alonso et al. (2014, 2015)</td>
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</table>

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 H1R and H2 R 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; Martin 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; Aureliou 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 imipramide 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 (Noseglo, 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.

**References**


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