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

Current Knowledge and Perspectives on Histamine H_1 and H_2 Receptor Pharmacology: Functional Selectivity, Receptor Crosstalk, and Repositioning of Classic Histaminergic Ligands

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ABSTRACT

H_1 and H_2 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 H_1 and H_2 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 H_1 and H_2 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: H_1R, H_2R, H_3R, and H_4R (Panula et al., 2015).

Most of the studies carried out in the last twenty years were mainly focused on the newly described H_3R and H_4R, whereas H_1R and H_2R were originally characterized many years ago. To date, H_1R and H_2R are the only histamine receptors for which drugs have been approved for use in humans. H_1R and H_2R are still effective targets for the treatment of allergies and some forms of gastric acid–related conditions, and H_1R and H_2R 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.

H_1R and H_2R Signaling

H_1R 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 H_1R expression systems, H_1R 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 H_1R 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, H_1R was shown to display high levels of spontaneous receptor activity in the absence of agonists. H_1R was also shown to constitutively activate both IP production and modulation of gene expression under the control of nuclear factor-κB (Bakker et al., 2001; Fitzsimons et al., 2004). On the basis of these observations, all clinically relevant H_1R ligands were reclassified as H_1R 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 H_2R is expressed, H_2R 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 H_2R to Gs proteins was demonstrated by agonist-induced photoaffinity-labeling studies with GPCR-Gαs fusion proteins, guanosine 5′-*O*-(3-[^{35}S]thio)triphosphate binding, as well as steady-state GTP hydrolysis (Leopoldt et al., 1997; Kelley et al., 2001; Wenzel-Seifert et al., 2001). H_2R displayed lower affinity for histamine than the H_3 and H_4 subtypes and had high constitutive activity toward cAMP production (Panula et al., 2015).

In some H_2R native or heterologously expressing cells, H_2R 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 Ca^{2+} concentration (Panula et al., 2015). H_2R stimulation by histamine was shown to potently inhibit phospholipase A2 activity, triggering arachidonic acid synthesis (Traiffort et al., 1992). Interestingly, some actions mediated by H_2R, 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 H_2R 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 H_2R 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 H_1R 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 H_1R and H_2R desensitization after long-lasting or repetitive stimulation. Besides receptor phosphorylation by GRK-2, H_1R and H_2R 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 H_1R and H_2R 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 H_1R and H_2R and their potential therapeutic implications.

Biased Signaling at H_1 and H_2 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 H_1R and H_2R in native and recombinant systems (Moniri et al., 2004; Reher et al., 2012a; Alonso et al., 2014, 2015).

Biased Signaling for H_1R Ligands. The discovery of agonists acting at H_1R has been disregarded for a long time and efforts were focused on the development of ligands that block the H_1R-mediated histamine allergic action. Although histamine possesses several physiologic and pathophysiologic effects acting at H_1R, a therapeutic use for H_1R 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 H_1R. Two H_1R 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 H_1R. 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 H_1R 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 H_1R ligands in mammalian brain and adrenal tissues could have implications in the treatment of several neurodegenerative disorders, as further discussed below.

Biased Signaling for H_2R Ligands. As mentioned previously, H_2R 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 H_2R desensitization and internalization. Although the extent and rate of H_2R 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 H_2R 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 H_2R agonists have positive efficacy in increasing ERK1/2 phosphorylation, the underlying mechanisms are different. H_2R 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 H_2R internalization but is mediated by $G\beta\gamma$ (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 H_2R 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). H_2R 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 H_2R 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).

H_1R and H_2R 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 H_2R, 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 H_2R interferes with the signaling of these GPCRs and H_2R knockdown potentiates their response (Tubio et al., 2010). In the same way, mepyramine binding to H_1R 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).

H_1R and H_2R Crossregulation. H_1R and H_2R 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 H_1R and H_2R histamine receptor subtypes (or even others).

H_1R and H_2R crossregulation has been described. In recombinant and native systems, both receptors were desensitized when cells were exposed to a sustained stimulus with any H_1R or H_2R 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 H_1R and H_2R, 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 H_1R or H_2R stimulation is conditioned or even dampened by this mechanism (Fig. 1, middle).

H_1R and H_2R 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

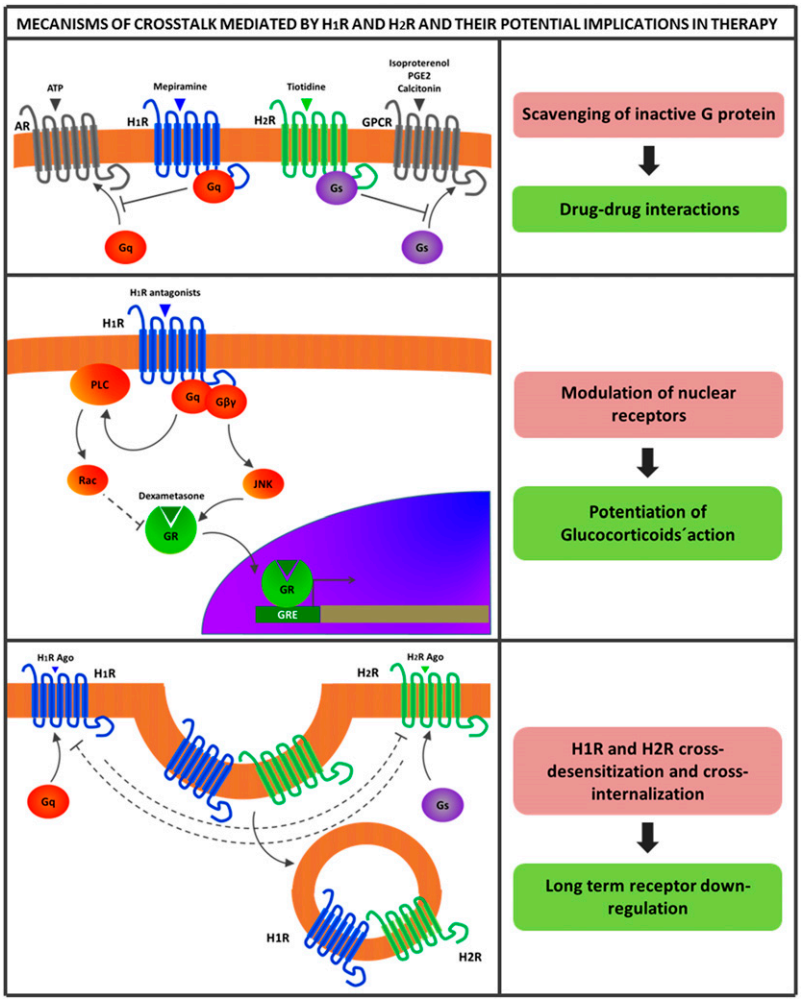

Fig. 1. Mechanisms of crosstalk mediated by H_1R and H_2R and their potential implications in therapy. (Top) Inverse agonists acting at H_1R or H_2R promote receptor binding to G protein in an inactive form, making it less available to other GPCRs that signal through the same pathway. (Middle) Antihistamines acting at H_1R potentiate dexamethasone-induced GR transcriptional activity. (Bottom) H_1R and H_2R crossdesensitize when stimulated with either H_1 or H_2 agonists. The molecular mechanisms underlying the described effects are detailed in the main text.

acting on β2-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 Gαi 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 H_1R signaling on GR activity. Investigators recently observed that histamine, as well as antihistamines, are able to potentiate GR activity (Zappia et al., 2015). When H_1R 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 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 H_1R 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 H_1 and H_2 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 H_1R 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).

H_2R 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 H_1R and H_2R: signaling pathways, receptor crosstalk, and ligands

Signaling	H_1R		H_2R	
	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	(−) *trans*-PAT; (±) *cis*-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 antisecretory H_2R 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 H_2R 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 H_2R 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 H_2R, it is necessary to consider these phenomena in the context of the clinical use of H_2R blockers. The inhibition of gastric acid secretion is achieved by blocking the canonical AC/cAMP signaling pathway of H_2R. However, some H_2R 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 H_2R blockade increases the parietal cell response to histamine and leads to tolerance to treatment with H_2 antagonists. This is explained by an increase in receptor membrane expression due to structural stabilization of H_2R 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 H_2R 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 H_2R neutral antagonist or inverse agonist that fails to induce HDC expression would avoid such undesired effects.

Although G protein scavenging by H_1 or H_2 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 H_1R Ligands. Despite the extensive study and clinical applications of histamine H_1R and H_2R 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 H_1R 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, H_1R inverse agonists are able to modulate GR transcriptional activity by potentiating transactivation 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, H_1R 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

H_1R. Novel clinical applications for these ligands are being investigated, with different degrees of success.

The action of H_1R 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 H_1R central expression. Histamine has been implicated in pain modulation, augmenting the transmission of nociceptive impulses; considerable evidence indicates that several H_1 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.

H_1R 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 H_1R antagonism or nonspecific action over muscarinic M_1 receptors, this possibility has been ruled out by the observation that low doses of doxepin (that act solely on H_1R) 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 H_2R Ligands. In addition to H_2R's classic regulation of gastric acid secretion, H_2R 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 H_2R 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 H_2R antagonism prevented heart failure in rabbits with doxorubicin-induced cardiomyopathy and dogs with sustained atrial tachycardia (Takahama et al., 2010). In addition, $H_2R^{-/-}$ 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 H_2R blockers relies, at least partially, on decreased responsiveness of the β-adrenoreceptor due to scavenging of $G\alpha s$ protein by H_2R. 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 H_2R antagonists prevented the onset of chronic heart failure. On the basis of this evidence, H_2R 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_1R				H_2R			
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 H_1 and H_2 histamine receptors as mentioned above. In the brain, histamine not only signals through the canonical Gq/calcium pathway by acting through the presynaptic H_1R, 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.

H_2R 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 H_2R 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, H_2R 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, H_2R 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 H_2R biased agonists toward ROS inhibition in neutrophils and eosinophils (Reher et al., 2012a). These results suggest that H_2R 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 H_1R and H_2R 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 H_1R and H_2R. 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

Adamko D, Lacy P, and Moqbel R (2002) Mechanisms of eosinophil recruitment and activation. *Curr Allergy Asthma Rep* **2**:107–116.

Alewijnse AE, Smit MJ, Hoffmann M, Verzijl D, Timmerman H, and Leurs R (1998) Constitutive activity and structural instability of the wild-type human H2 receptor. *J Neurochem* **71**:799–807.

Alonso N, Diaz Nebreda A, Monczor F, Gutkind JS, Davio C, Fernandez N, and Shayo C (2016) PI3K pathway is involved in ERK signaling cascade activation by histamine H2R agonist in HEK293T cells. *Biochim Biophys Acta* **1860**:1998–2007.

Alonso N, Fernandez N, Notcovich C, Monczor F, Simaan M, Baldi A, Gutkind JS, Davio C, and Shayo C (2013) Cross-desensitization and cointernalization of H1 and H2 histamine receptors reveal new insights into histamine signal integration. *Mol Pharmacol* **83**:1087–1098.

Alonso N, Monczor F, Echeverría E, Davio C, Shayo C, and Fernández N (2014) Signal transduction mechanism of biased ligands at histamine H2 receptors. *Biochem J* **459**:117–126.

Alonso N, Zappia CD, Cabrera M, Davio CA, Shayo C, Monczor F, and Fernández NC (2015) Physiological implications of biased signaling at histamine H2 receptors. *Front Pharmacol* **6**:45.

Apolloni S, Fabbrizio P, Parisi C, Amadio S, and Volonté C (2016) Clemastine confers neuroprotection and induces an anti-inflammatory phenotype in SOD1(G93A) mouse model of amyotrophic lateral sclerosis. *Mol Neurobiol* **53**:518–531.

Aurelius J, Martner A, Brune M, Palmqvist L, Hansson M, Hellstrand K, and Thoren FB (2012) Remission maintenance in acute myeloid leukemia: impact of functional histamine H2 receptors expressed by leukemic cells. *Haematologica* **97**:1904–1908.

Bakker RA, Schoonus SB, Smit MJ, Timmerman H, and Leurs R (2001) Histamine H (1)-receptor activation of nuclear factor-kappa B: roles for G beta gamma- and G alpha(q/11)-subunits in constitutive and agonist-mediated signaling. *Mol Pharmacol* **60**:1133–1142.

Bakker RA, Wieland K, Timmerman H, and Leurs R (2000) Constitutive activity of the histamine H(1) receptor reveals inverse agonism of histamine H(1) receptor antagonists. *Eur J Pharmacol* **387**:R5–R7.

Black JW, Duncan WA, Durant CJ, Ganellin CR, and Parsons EM (1972) Definition and antagonism of histamine H 2 -receptors. *Nature* **236**:385–390.

Bockaert J, Marin P, Dumuis A, and Fagni L (2003) The 'magic tail' of G protein-coupled receptors: an anchorage for functional protein networks. *FEBS Lett* **546**: 65–72.

Bonini JS, Da Silva WC, Da Silveira CKB, Köhler CA, Izquierdo I, and Cammarota M (2011) Histamine facilitates consolidation of fear extinction. *Int J Neuropsychopharmacol* **14**:1209–1217.

Burde R, Buschauer A, and Seifert R (1990) Characterization of histamine H2-receptors in human neutrophils with a series of guanidine analogues of impromidine. Are cell type-specific H2-receptors involved in the regulation of NADPH oxidase? *Naunyn Schmiedebergs Arch Pharmacol* **341**:455–461.

Burde R, Seifert R, Buschauer A, and Schultz G (1989) Histamine inhibits activation of human neutrophils and HL-60 leukemic cells via H2-receptors. *Naunyn Schmiedebergs Arch Pharmacol* **340**:671–678.

Busse WW, Middleton E, Storms W, Dockhorn RJ, Chu TJ, Grossman J, Weiler JM, Bronsky EA, Mansfield LE, Bell TD, et al. (1996) Corticosteroid-sparing effect of azelastine in the management of bronchial asthma. *Am J Respir Crit Care Med* **153**:122–127.

Buyse M, Michiels S, Squifflet P, Lucchesi KJ, Hellstrand K, Brune ML, Castaigne S, and Rowe JM (2011) Leukemia-free survival as a surrogate end point for overall survival in the evaluation of maintenance therapy for patients with acute myeloid leukemia in complete remission. *Haematologica* **96**:1106–1112.

Colucci R, Fleming JV, Xavier R, and Wang TC (2001) L-histidine decarboxylase decreases its own transcription through downregulation of ERK activity. *Am J Physiol Gastrointest Liver Physiol* **281**:G1081–G1091.
de Almeida DO, Ferreira HS, Pereira LB, and Fregoneze JB (2015) Hypertensive response to stress: the role of histaminergic H1 and H2 receptors in the medial amygdala. *Physiol Behav* **144**:95–102.
Deva S and Jameson M (2012) Histamine type 2 receptor antagonists as adjuvant treatment for resected colorectal cancer. *Cochrane Database Syst Rev* **8**:CD007814.
Di Roberto RB, Chang B, Trusina A, and Peisajovich SG (2016) Evolution of a G protein-coupled receptor response by mutations in regulatory network interactions. *Nat Commun* **7**:12344.
Dong H, Zhang W, Zeng X, Hu G, Zhang H, He S, and Zhang S (2014) Histamine induces upregulated expression of histamine receptors and increases release of inflammatory mediators from microglia. *Mol Neurobiol* **49**:1487–1500.
Eckel L, Gristwood RW, Nawrath H, Owen DA, and Satter P (1982) Inotropic and electrophysiological effects of histamine on human ventricular heart muscle. *J Physiol* **330**:111–123.
Ezeamuzie CI and Philips E (2000) Histamine H(2) receptors mediate the inhibitory effect of histamine on human eosinophil degranulation. *Br J Pharmacol* **131**: 482–488.
Fernandez N, Gottardo FL, Alonso MN, Monczor F, Shayo C, and Davio C (2011) Roles of phosphorylation-dependent and -independent mechanisms in the regulation of histamine H2 receptor by G protein-coupled receptor kinase 2. *J Biol Chem* **286**:28697–28706.
Fernandez N, Monczor F, Baldi A, Davio C, and Shayo C (2008) Histamine H2 receptor trafficking: role of arrestin, dynamin, and clathrin in histamine H2 receptor internalization. *Mol Pharmacol* **74**:1109–1118.
Fernández N, Monczor F, Lemos B, Notcovich C, Baldi A, Davio C, and Shayo C (2002) Reduction of G protein-coupled receptor kinase 2 expression in U-937 cells attenuates H2 histamine receptor desensitization and induces cell maturation. *Mol Pharmacol* **62**:1506–1514.
Fitzsimons CP, Monczor F, Fernández N, Shayo C, and Davio C (2004) Mepyramine, a histamine H1 receptor inverse agonist, binds preferentially to a G protein-coupled form of the receptor and sequesters G protein. *J Biol Chem* **279**: 34431–34439.
Galandrin S and Bouvier M (2006) Distinct signaling profiles of beta1 and beta2 adrenergic receptor ligands toward adenylyl cyclase and mitogen-activated protein kinase reveals the pluridimensionality of efficacy. *Mol Pharmacol* **70**:1575–1584.
Galeotti N, Malmberg-Aiello P, Bartolini A, Schunack W, and Ghelardini C (2004) H1-receptor stimulation induces hyperalgesia through activation of the phospholipase C-PKC pathway. *Neuropharmacology* **47**:295–303.
Gespach C and Abita JP (1982) Human polymorphonuclear neutrophils. Pharmacological characterization of histamine receptors mediating the elevation of cyclic AMP. *Mol Pharmacol* **21**:78–85.
Glass JR, Sproule BA, Herrmann N, and Busto UE (2008) Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: a randomized, placebo-controlled trial. *J Clin Psychopharmacol* **28**:182–188.
Gutowski S, Smrcka A, Nowak L, Wu DG, Simon M, and Sternweis PC (1991) Antibodies to the alpha q subfamily of guanine nucleotide-binding regulatory protein alpha subunits attenuate activation of phosphatidylinositol 4,5-bisphosphate hydrolysis by hormones. *J Biol Chem* **266**:20519–20524.
Haas HL and Panula P (2016) Histamine receptors. *Neuropharmacology* **106**:1–2.
Hattori Y (1999) Cardiac histamine receptors: their pharmacological consequences and signal transduction pathways. *Methods Find Exp Clin Pharmacol* **21**:123–131.
Hellstrand K (2002) Histamine in cancer immunotherapy: a preclinical background. *Semin Oncol* **29** (Suppl 7):35–40.
Hershcovici T and Fass R (2011) Gastro-oesophageal reflux disease: beyond proton pump inhibitor therapy. *Drugs* **71**:2381–2389.
Hirschfeld J, Buschauer A, Elz S, Schunack W, Ruat M, Traiffort E, and Scwartz JC (1992) Iodoaminopotentidine and related compounds: a new class of ligands with high affinity and selectivity for the histamine H2 receptor. *J Med Chem* **35**: 2231–2238.
Hishinuma S, Komazaki H, Fukui H, and Shoji M (2010) Ubiquitin/proteasome-dependent down-regulation following clathrin-mediated internalization of histamine H1-receptors in Chinese hamster ovary cells. *J Neurochem* **113**:990–1001.
Huang R, Southall N, Wang Y, Yasgar A, Shinn P, Jadhav A, Nguyen DT, and Austin CP (2011) The NCGC pharmaceutical collection: a comprehensive resource of clinically approved drugs enabling repurposing and chemical genomics. *Sci Transl Med* **3**:80ps16.
Iwakiri K, Kinoshita Y, Habu Y, Oshima T, Manabe N, Fujiwara Y, Nagahara A, Kawamura O, Iwakiri R, Ozawa S, et al. (2016) Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2015. *J Gastroenterol* **51**:751–767.
Iwata K, Luo J, Penn RB, and Benovic JL (2005) Bimodal regulation of the human H1 histamine receptor by G protein-coupled receptor kinase 2. *J Biol Chem* **280**: 2197–2204.
Jordan JD, Landau EM, and Iyengar R (2000) Signaling networks: the origins of cellular multitasking. *Cell* **103**:193–200.
Jutel M, Akdis M, and Akdis CA (2009) Histamine, histamine receptors and their role in immune pathology. *Clin Exp Allergy* **39**:1786–1800.
Kagawa Y, Izawa K, Yano H, and Kamei C (2010) Synergetic effects of prednisolone and olopatadine on atopic dermatitis model of hairless mice. *Pharmacology* **85**: 286–294.
Kantor ED, Rehm CD, Haas JS, Chan AT, and Giovannucci EL (2015) Trends in prescription drug use among adults in the United States from 1999-2012. *JAMA* **314**:1818–1831.
Kelley MT, Bürckstümmer T, Wenzel-Seifert K, Dove S, Buschauer A, and Seifert R (2001) Distinct interaction of human and guinea pig histamine H2-receptor with guanidine-type agonists. *Mol Pharmacol* **60**:1210–1225.
Kenakin T (2004) Principles: receptor theory in pharmacology. *Trends Pharmacol Sci* **25**:186–192.
Kenakin T and Miller LJ (2010) Seven transmembrane receptors as shapeshifting proteins: the impact of allosteric modulation and functional selectivity on new drug discovery. *Pharmacol Rev* **62**:265–304.
Keogh R and Marley PD (1991) Regulation of cyclic AMP levels by calcium in bovine adrenal medullary cells. *J Neurochem* **57**:1721–1728.
Kiefer TL, Lai L, Yuan L, Dong C, Burow ME, and Hill SM (2005) Differential regulation of estrogen receptor alpha, glucocorticoid receptor and retinoic acid receptor alpha transcriptional activity by melatonin is mediated via different G proteins. *J Pineal Res* **38**:231–239.
Kingwell K (2015) Pioneering biased ligand offers efficacy with reduced on-target toxicity. *Nat Rev Drug Discov* **14**:809–810.
Kino T, Tiulpakov A, Ichijo T, Chheng L, Kozasa T, and Chrousos GP (2005) G protein beta interacts with the glucocorticoid receptor and suppresses its transcriptional activity in the nucleus. *J Cell Biol* **169**:885–896.
Kirch W, Halabi A, and Hinrichsen H (1992) Hemodynamic effects of quinidine and famotidine in patients with congestive heart failure. *Clin Pharmacol Ther* **51**: 325–333.
Koch M, Dezi A, Ferrario F, and Capurso I (1996) Prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal mucosal injury. A meta-analysis of randomized controlled clinical trials. *Arch Intern Med* **156**:2321–2332.
Krystal AD, Lankford A, Durrence HH, Ludington E, Jochelson P, Rogowski R, and Roth T (2011) Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. *Sleep* **34**:1433–1442.
Krystal AD (2015) Current, emerging, and newly available insomnia medications. *J Clin Psychiatry* **76**:e1045.
Laine L, Kivitz AJ, Bello AE, Grahn AY, Schiff MH, and Taha AS (2012) Double-blind randomized trials of single-tablet ibuprofen/high-dose famotidine vs. ibuprofen alone for reduction of gastric and duodenal ulcers. *Am J Gastroenterol* **107**: 379–386.
Leary PJ, Tedford RJ, Bluemke DA, Bristow MR, Heckbert SR, Kawut SM, Krieger EV, Lima JA, Masri CS, Ralph DD, et al. (2016) Histamine H2 receptor antagonists, left ventricular morphology, and heart failure risk: the MESA study. *J Am Coll Cardiol* **67**:1544–1552.
Leopoldt D, Harteneck C, and Nürnberg B (1997) G proteins endogenously expressed in Sf 9 cells: interactions with mammalian histamine receptors. *Naunyn Schmiedebergs Arch Pharmacol* **356**:216–224.
Leurs R, Traiffort E, Arrang JM, Tardivel-Lacombe J, Ruat M, and Schwartz JC (1994) Guinea pig histamine H1 receptor. II. Stable expression in Chinese hamster ovary cells reveals the interaction with three major signal transduction pathways. *J Neurochem* **62**:519–527.
Louis R, Schleich F, and Barnes PJ (2012) Corticosteroids: still at the frontline in asthma treatment? *Clin Chest Med* **33**:531–541.
Lu NZ, Wardell SE, Burnstein KL, Defranco D, Fuller PJ, Giguere V, Hochberg RB, McKay L, Renoir JM, Weigel NL, et al. (2006) International Union of Pharmacology. LXV. The pharmacology and classification of the nuclear receptor superfamily: glucocorticoid, mineralocorticoid, progesterone, and androgen receptors. *Pharmacol Rev* **58**:782–797.
Luo T, Chen B, Zhao Z, He N, Zeng Z, Wu B, Fukushima Y, Dai M, Huang Q, Xu D, et al. (2013) Histamine H2 receptor activation exacerbates myocardial ischemia/reperfusion injury by disturbing mitochondrial and endothelial function. *Basic Res Cardiol* **108**:342.
Marley PD, Thomson KA, Jachno K, and Johnston MJ (1991) Histamine-induced increases in cyclic AMP levels in bovine adrenal medullary cells. *Br J Pharmacol* **104**:839–846.
Marshall BJ, Goodwin CS, Warren JR, Murray R, Blincow ED, Blackbourn SJ, Phillips M, Waters TE, and Sanderson CR (1988) Prospective double-blind trial of duodenal ulcer relapse after eradication of Campylobacter pylori. *Lancet* **2**: 1437–1442.
Marshall BJ and Warren JR (1984) Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* **1**:1311–1315.
Martner A, Thorén FB, Aurelius J, Söderholm J, Brune M, and Hellstrand K (2010) Immunotherapy with histamine dihydrochloride for the prevention of relapse in acute myeloid leukemia. *Expert Rev Hematol* **3**:381–391.
McHugh JM and McHugh WB (2000) Pain: neuroanatomy, chemical mediators, and clinical implications. *AACN Clin Issues* **11**:168–178.
Mettler SE, Ghayouri S, Christensen GP, and Forte JG (2007) Modulatory role of phosphoinositide 3-kinase in gastric acid secretion. *Am J Physiol Gastrointest Liver Physiol* **293**:G532–G543.
Mobarakeh JI, Sakurada S, Katsuyama S, Kutsuwa M, Kuramasu A, Lin ZY, Watanabe T, Hashimoto Y, Watanabe T, and Yanai K (2000) Role of histamine H(1) receptor in pain perception: a study of the receptor gene knockout mice. *Eur J Pharmacol* **391**:81–89.
Monczor F, Copsel S, Fernandez N, Davio C, and Shayo C (2016) Histamine H2 receptor in blood cells: a suitable target for the treatment of acute myeloid leukemia. *Handb Exp Pharmacol* DOI: 10.1007/164_2016_8 [published ahead of print].
Monczor F, Fernandez N, Legnazzi BL, Riveiro ME, Baldi A, Shayo C, and Davio C (2003) Tiotidine, a histamine H2 receptor inverse agonist that binds with high affinity to an inactive G-protein-coupled form of the receptor. Experimental support for the cubic ternary complex model. *Mol Pharmacol* **64**:512–520.
Monczor F, Legnazzi BL, Rivera E, and Davio C (1998) Tiotidine, a classical H2-antagonist, presents characteristics of an inverse agonist in U937 cell line. *Inflamm Res* **47** (Suppl 1):S42–S43.
Moniri NH and Booth RG (2004) Functional heterogeneity of histamine H(1) receptors. *Inflamm Res* **53** (Suppl 1):S71–S72.
Moniri NH and Booth RG (2006) Role of PKA and PKC in histamine H1 receptor-mediated activation of catecholamine neurotransmitter synthesis. *Neurosci Lett* **407**:249–253.
Moniri NH, Covington-Strachan D, and Booth RG (2004) Ligand-directed functional heterogeneity of histamine H1 receptors: novel dual-function ligands selectively

activate and block H1-mediated phospholipase C and adenylyl cyclase signaling. *J Pharmacol Exp Ther* **311**:274–281.
Morin CM, Koetter U, Bastien C, Ware JC, and Wooten V (2005) Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. *Sleep* **28**:1465–1471.
Neubauer DN (2014) New and emerging pharmacotherapeutic approaches for insomnia. *Int Rev Psychiatry* **26**:214–224.
Nosengo N (2016) Can you teach old drugs new tricks? *Nature* **534**:314–316.
Notcovich C, Diez F, Tubio MR, Baldi A, Kazanietz MG, Davio C, and Shayo C (2010) Histamine acting on H1 receptor promotes inhibition of proliferation via PLC, RAC, and JNK-dependent pathways. *Exp Cell Res* **316**:401–411.
Olbe L, Carlsson E, and Lindberg P (2003) A proton-pump inhibitor expedition: the case histories of omeprazole and esomeprazole. *Nat Rev Drug Discov* **2**:132–139.
Ostrom NK (2014) The history and progression of treatments for allergic rhinitis. *Allergy Asthma Proc* **35** (Suppl 1):S3–S10.
Pantziarka P, Bouche G, Meheus L, Sukhatme V, and Sukhatme VP (2014) Repurposing drugs in oncology (ReDO)-cimetidine as an anti-cancer agent. *Ecancermedicalscience* **8**:485.
Panula P, Chazot PL, Cowart M, Gutzmer R, Leurs R, Liu WLS, Stark H, Thurmond RL, and Haas HL (2015) International Union of Basic and Clinical Pharmacology. XCVIII. Histamine receptors. *Pharmacol Rev* **67**:601–655.
Parsons ME and Ganellin CR (2006) Histamine and its receptors. *Br J Pharmacol* **147** (Suppl 1):S127–S135.
Pincus SH, DiNapoli AM, and Schooley WR (1982) Superoxide production by eosinophils: activation by histamine. *J Invest Dermatol* **79**:53–57.
Pini A, Obara I, Battell E, Chazot PL, and Rosa AC (2016) Histamine in diabetes: is it time to reconsider? *Pharmacol Res* **111**:316–324.
Prast H and Philippu A (2001) Nitric oxide as modulator of neuronal function. *Prog Neurobiol* **64**:51–68.
Pupo AS, Duarte DA, Lima V, Teixeira LB, Parreiras-E-Silva LT, and Costa-Neto CM (2016) Recent updates on GPCR biased agonism. *Pharmacol Res* DOI: 10.1016/j.phrs.2016.01.031 [published ahead of print].
Rajagopal S, Rajagopal K, and Lefkowitz RJ (2010) Teaching old receptors new tricks: biasing seven-transmembrane receptors. *Nat Rev Drug Discov* **9**:373–386.
Reher TM, Brunskole I, Neumann D, and Seifert R (2012a) Evidence for ligand-specific conformations of the histamine H(2)-receptor in human eosinophils and neutrophils. *Biochem Pharmacol* **84**:1174–1185.
Reher TM, Neumann D, Buschauer A, and Seifert R (2012b) Incomplete activation of human eosinophils via the histamine H4-receptor: evidence for ligand-specific receptor conformations. *Biochem Pharmacol* **84**:192–203.
Richelson E (1978) Histamine H1 receptor-mediated guanosine 3′,5′-monophosphate formation by cultured mouse neuroblastoma cells. *Science* **201**:69–71.
Rocha SM, Pires J, Esteves M, Graça B, and Bernardino L (2014) Histamine: a new immunomodulatory player in the neuron-glia crosstalk. *Front Cell Neurosci* **8**:120.
Rocha SM, Saraiva T, Cristóvão AC, Ferreira R, Santos T, Esteves M, Saraiva C, Je G, Cortes L, Valero J, et al. (2016) Histamine induces microglia activation and dopaminergic neuronal toxicity via H1 receptor activation. *J Neuroinflammation* **13**:137.
Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E, and McGowan J (2002) Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database Syst Rev* (4):CD002296.
Rothenberg ME and Hogan SP (2006) The eosinophil. *Annu Rev Immunol* **24**:147–174.
Sadek B and Stark H (2016) Cherry-picked ligands at histamine receptor subtypes. *Neuropharmacology* **106**:56–73.
Sadik CD, Kim ND, and Luster AD (2011) Neutrophils cascading their way to inflammation. *Trends Immunol* **32**:452–460.
Sakurada S, Watanabe H, Mizoguchi H, Yonezawa A, Orito T, Katsuyama S, Kuramasu A, Sakurada C, Yanai K, and Sakurada T (2004) Involvement of the histaminergic system in the nociceptin-induced pain-related behaviors in the mouse spinal cord. *Pain* **112**:171–182.
Scharf M, Rogowski R, Hull S, Cohn M, Mayleben D, Feldman N, Ereshefsky L, Lankford A, and Roth T (2008) Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in elderly patients with primary insomnia: a randomized, double-blind, placebo-controlled crossover study. *J Clin Psychiatry* **69**:1557–1564.
Schmidt P, Holsboer F, and Spengler D (2001) Beta(2)-adrenergic receptors potentiate glucocorticoid receptor transactivation via G protein beta gamma-subunits and the phosphoinositide 3-kinase pathway. *Mol Endocrinol* **15**:553–564.
Seifert R, Grünbaum L, and Schultz G (1994) Histamine H1-receptors in HL-60 monocytes are coupled to Gi-proteins and pertussis toxin-insensitive G-proteins and mediate activation of Ca2+ influx without concomitant Ca2+ mobilization from intracellular stores. *Naunyn Schmiedebergs Arch Pharmacol* **349**:355–361.
Shan L, Dauvilliers Y, and Siegel JM (2015) Interactions of the histamine and hypocretin systems in CNS disorders. *Nat Rev Neurol* **11**:401–413.
Shayo C, Fernandez N, Legnazzi BL, Monczor F, Mladovan A, Baldi A, and Davio C (2001) Histamine H2 receptor desensitization: involvement of a select array of G protein-coupled receptor kinases. *Mol Pharmacol* **60**:1049–1056.
Shi GP, Bot I, and Kovanen PT (2015) Mast cells in human and experimental cardiometabolic diseases. *Nat Rev Cardiol* **12**:643–658.
Sigterman KE, van Pinxteren B, Bonis PA, Lau J, and Numans ME (2013) Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev* **5**:CD002095.
Simons FE and Simons KJ (2011) Histamine and H1-antihistamines: celebrating a century of progress. *J Allergy Clin Immunol* **128**:1139–1150.e4.
Smit MJ, Leurs R, Alewijnse AE, Blauw J, Van Nieuw Amerongen GP, Van De Vrede Y, Roovers E, and Timmerman H (1996) Inverse agonism of histamine H2 antagonist accounts for upregulation of spontaneously active histamine H2 receptors. *Proc Natl Acad Sci USA* **93**:6802–6807.
Smith AD, Gillen D, Cochran KM, El-Omar E, and McColl KE (1999) Dyspepsia on withdrawal of ranitidine in previously asymptomatic volunteers. *Am J Gastroenterol* **94**:1209–1213.
Snider RM, McKinney M, Forray C, and Richelson E (1984) Neurotransmitter receptors mediate cyclic GMP formation by involvement of arachidonic acid and lipoxygenase. *Proc Natl Acad Sci USA* **81**:3905–3909.
Soehnlein O, Lindbom L, and Weber C (2009) Mechanisms underlying neutrophil-mediated monocyte recruitment. *Blood* **114**:4613–4623.
Solelhac G and Charpin D (2014) Management of allergic rhinitis. *F1000Prime Rep* **6**:94.
Stein T, Souza-Silva E, Mascarin L, Eto C, Fin FE, and Tonussi CR (2016) Histaminergic pharmacology modulates the analgesic and antiedematogenic effects of spinally injected morphine. *Anesth Analg* **123**:238–243.
Takahama H, Asanuma H, Sanada S, Fujita M, Sasaki H, Wakeno M, Kim J, Asakura M, Takashima S, Minamino T, et al. (2010) A histamine H_2 receptor blocker ameliorates development of heart failure in dogs independently of β-adrenergic receptor blockade. *Basic Res Cardiol* **105**:787–794.
Traiffort E, Ruat M, Arrang JM, Leurs R, Piomelli D, and Schwartz JC (1992) Expression of a cloned rat histamine H2 receptor mediating inhibition of arachidonate release and activation of cAMP accumulation. *Proc Natl Acad Sci USA* **89**:2649–2653.
Tubio MR, Fernandez N, Fitzsimons CP, Copsel S, Santiago S, Shayo C, Davio C, and Monczor F (2010) Expression of a G protein-coupled receptor (GPCR) leads to attenuation of signaling by other GPCRs: experimental evidence for a spontaneous GPCR constitutive inactive form. *J Biol Chem* **285**:14990–14998.
Violin JD, Crombie AL, Soergel DG, and Lark MW (2014) Biased ligands at G-protein-coupled receptors: promise and progress. *Trends Pharmacol Sci* **35**:308–316.
Wang YX and Kotlikoff MI (2000) Signalling pathway for histamine activation of non-selective cation channels in equine tracheal myocytes. *J Physiol* **523**:131–138.
Wei H, Ahn S, Shenoy SK, Karnik SS, Hunyady L, Luttrell LM, and Lefkowitz RJ (2003) Independent beta-arrestin 2 and G protein-mediated pathways for angiotensin II activation of extracellular signal-regulated kinases 1 and 2. *Proc Natl Acad Sci USA* **100**:10782–10787.
Weng G, Bhalla US, and Iyengar R (1999) Complexity in biological signaling systems. *Science* **284**:92–96.
Wenzel-Seifert K, Kelley MT, Buschauer A, and Seifert R (2001) Similar apparent constitutive activity of human histamine H(2)-receptor fused to long and short splice variants of G(salpha). *J Pharmacol Exp Ther* **299**:1013–1020.
Xu AJ, Kuramasu A, Maeda K, Kinoshita K, Takayanagi S, Fukushima Y, Watanabe T, Yanagisawa T, Sukegawa J, and Yanai K (2008) Agonist-induced internalization of histamine H2 receptor and activation of extracellular signal-regulated kinases are dynamin-dependent. *J Neurochem* **107**:208–217.
Zappia CD, Granja-Galeano G, Fernández N, Shayo C, Davio C, Fitzsimons CP, and Monczor F (2015) Effects of histamine H1 receptor signaling on glucocorticoid receptor activity. Role of canonical and non-canonical pathways. *Sci Rep* **5**:17476.
Zeng Z, Shen L, Li X, Luo T, Wei X, Zhang J, Cao S, Huang X, Fukushima Y, Bin J, et al. (2014) Disruption of histamine H2 receptor slows heart failure progression through reducing myocardial apoptosis and fibrosis. *Clin Sci (Lond)* **127**:435–448.

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