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**CURRENT KNOWLEDGE AND PERSPECTIVES FOR HISTAMINE H₁ AND H₂ RECEPTOR
PHARMACOLOGY. FUNCTIONAL SELECTIVITY, RECEPTOR CROSSTALK AND
REPOSITIONING OF CLASSIC HISTAMINERGIC LIGANDS.**

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Abbreviations: AML, acute myeloid leukemia; ATP, adenosine triphosphate; GTP, guanosine triphosphate; AC, adenylyl cyclase; IP, inositol phosphate; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FRET, fluorescence resonance energy transfer; GPCR, G-protein coupled receptor; GR, glucocorticoid receptor, GRK-2, G protein coupled receptor kinase 2; H₁R, histamine H₁ receptor; H₂R, histamine H₂ receptor; H₃R, histamine H₃ receptor; H₄R, histamine H₄ receptor; IFN γ , interferon γ ; IL-2, interleukin 2; PGE₂, prostaglandine E₂; HDC, histidine decarboxylase; PI3K, phosphoinositide 3- kinase; PKB, protein kinase B; NF- κ B, nuclear factor κ B; NADPH, nicotinamide adenine dinucleotide phosphate; PLC, phospholipase C; RGS, regulator of G-protein signaling; ROS, reactive oxygen species; Th1, T helper 1; CHO, Chinese hamster ovary; CNS, central nervous system; SNC suprachiasmatic nucleus; REM, rapid eyes movement; KO, knock out; 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.

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. The aim of the present article is to focus on novel aspects of the pharmacology and molecular mechanisms of histamine receptors that should be contemplated for either optimizing current therapies, repositioning histaminergic ligands for new therapeutic uses or even for including agonists of the histaminergic system in the treatment of different pathologies as leukemia or neurodegenerative disorders. In the last years there have been described new signaling phenomena related to H₁R and H₂R 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 appears as a pharmacological feature that can be exploited to look into non-traditional 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. We hope that the molecular mechanisms discussed in the present review contribute to a better understanding of the different aspects involved in histamine receptor pharmacology, which in turn shall contribute to increase drug efficacy, avoid adverse effects or reposition histaminergic ligands.

INTRODUCTION

Histamine is a biogenic amine that exerts its physiological action by binding to receptors belonging to the superfamily of seven transmembrane G protein coupled receptors (GPCRs). Until now, there have been described four different types of histamine receptors: H₁, H₂, H₃ and H₄ histamine receptors (H₁R, H₂R, H₃R and H₄R) (Panula *et al.*, 2015).

Most of the studies carried out in the last decades were mainly focused on the newly described H₃R and H₄R; while H₁R and H₂R were originally characterized many years ago. However, the H₁R and H₂R are the only histamine receptors with approved drugs for human treatment. They still are effective targets for the treatment of allergies and some forms of gastric acid-related conditions and belong to the top 18-used-drug-classes between 1999 and 2012 (Kantor *et al.*, 2015; Simons and Simons 2011; Iwakiri *et al.*, 2016).

Histamine receptors' pharmacology was comprehensively reviewed in numerous excellent articles that have been recently published (Panula *et al.*, 2015; Haas, 2016). However, based on the enormous costs for developing new drugs, the aim of the present article is to discuss different aspects of histamine receptors function that have been more recently characterized and can be considered for repositioning histaminergic ligands for new therapeutic uses or for optimizing the usage of the ones that already exist (Nosengo, 2016). In this regard, novel or potential applications of old histaminergic drugs as well as the potential therapeutic implications of functional ligand selectivity and crosstalk will be exhaustively reviewed.

H₁ AND H₂ RECEPTORS SIGNALING.

H₁R canonical signaling involves activation of the Gq/11 protein and its effector phospholipase C (PLC), with the consequent increase in inositol phosphates (IPs) and intracellular calcium levels in most systems, as well as the activation of small G-proteins Rac and RhoA (Gutowski *et al.*, 1991;

Notcovich *et al.*, 2010). Alternatively, in native and heterologous H₁R expression systems it has been described its signaling via Gi/o, activation of phospholipase A2 (PLA2) and production of cGMP and nitric oxide (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 CHO cells, activation of the H₁R may also stimulate adenylyl cyclase (AC) with the consequent intracellular cAMP production (Marley *et al.*, 1991; Keogh and Marley, 1991). Aside from the signaling events triggered by ligand binding, it has been described that the H₁R displays high levels of spontaneous receptor activity in the absence of agonists. Both, IP₃ production and modulation of gene expression under the control of the nuclear factor kappa B (NF-κB), had shown to be constitutively activated by the H₁R (Bakker *et al.*, 2001; Fitzsimons *et al.*, 2004). Based on these observations, all clinically relevant H₁R ligands were reclassified as H₁R inverse agonists (Bakker *et al.*, 2000). However, since all marketed antihistamines are actually inverse agonists, it cannot be discriminated whether this pharmacological property is therapeutically more relevant than neutral antagonism or histamine receptor blockade.

In most tissues where it is expressed, H₂R couples to G_s protein so its activation stimulates adenylyl cyclase (AC) mediated cAMP production (Alewijnse *et al.*, 1998; Monczor *et al.*, 2003; Panula *et al.*, 2015). Its coupling to G_s proteins was demonstrated by agonist- induced photoaffinity labeling, studies with GPCR-G_s fusion proteins, [³⁵S]GTPγS binding as well as steady-state GTP hydrolysis (Leopoldt *et al.*, 1997; Kelley *et al.*, 2001; Wenzel-Seifert *et al.*, 2001). It has been proved to display lower affinity for histamine than the receptor subtypes H₃ and H₄ and to present high constitutive activity towards cAMP production (Panula *et al.*, 2015).

In some H₂R native or heterologously expressing cells, besides the classical signaling through G_s protein, it can also couple to Gq/11 proteins, leading to IP₃ synthesis and the consequent increase in intracellular Ca²⁺ concentration (Panula *et al.*, 2015). It has been described that H₂R stimulation by

histamine can potently inhibit the activity of PLA₂, triggering the synthesis of arachidonic acid (Traiffort *et al.*, 1992). Interestingly, some actions mediated by the H₂R as modulation of cell proliferation and gene expression have proved to involve the modulation of signaling cascades that are usually associated to tyrosine kinase receptors as the extracellular signal-regulated kinases (ERK1/2) or the phosphoinositide 3- kinase (PI3K) pathway (Leopoldt *et al.*, 1997; Mettler *et al.*, 2007; Bonini *et al.*, 2011; Luo *et al.*, 2013; Alonso *et al.*, 2016). In addition, it has been established that histamine or H₂R agonists inhibit, in myeloid cells, the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, the enzyme responsible for the generation of reactive oxygen species (ROS) (Aurelius *et al.*, 2012).

All clinically used H₂ receptor antagonists, including cimetidine, famotidine and ranitidine, behave as inverse agonists (Smit *et al.*, 1996; Monczor *et al.*, 1998). However, as for the H₁R ligands, whether or not inverse agonism is relevant for their therapeutic action still needs to be elucidated. After long lasting or repetitive stimulation, G protein coupled receptor kinase 2 (GRK-2) was proved to be the principal kinase that participates in both H₁R and H₂R desensitization. Besides receptor phosphorylation by GRK-2, H₁R and H₂R desensitization was described to also involve the inactivating action of the RGS (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 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 demonstrating unique signaling complexities that may account for their effects on biological systems, and that may provide the basis for yet unexplored therapeutic strategies. In the following sections of this work we will discuss more recently described features of the signaling molecular mechanisms of H₁R and

H₂R and their potential therapeutic implications.

BIASED SIGNALING AT H₁ AND H₂ HISTAMINE RECEPTORS.

The ever growing evidence showing the multiplicity of signaling events associated to a unique GPCR led to the identification of ligands that after binding the receptor, favors some specific signaling events among the texture of receptor possibilities. A critical assumption is that the heterogeneity of active receptor conformations spontaneously exist and that the ligand stabilizes a particular conformational subset that although fails to evoke some of the responses it may stimulate other signaling events of the receptor that bounds (Rajagopal *et al.*, 2010; Kenakin, 2004). This process of “stimulus trafficking” has also been referred to as biased agonism or functional selectivity and 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). It was demonstrated that biased agonism is a phenomenon that also occurs for several GPCRs including the H₁R and H₂R in native and recombinant systems (Moniri *et al.*, 2004; Reher *et al.*, 2012a; Alonso *et al.*, 2014; Alonso *et al.*, 2015).

Biased signaling for H₁ receptor ligands.

The development of agonists acting at H₁R has been disregarded for a long time and all the efforts were focused in the development of ligands that block histamine allergic action mediated by H₁R. In spite of the fact that histamine possesses several physiologic and pathophysiologic effects acting at the 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 the H₁R. Two H₁R ligands of the same class that mainly differed with regard to stereochemistry: (6)-*cis*-5-phenyl-7-dimethylamino-5,6,7,8-tetrahydro-9H- benzocycloheptane (*cis*-PAB) and (2)-*trans*-1-phenyl-3- dimethylamino-1,2,3,4-tetrahydronaphthalene (*trans*-PAT); displayed functional heterogeneity at modulating PLC/IPs versus AC/cAMP signaling pathways of H₁R. While PAB presented partial agonism at activating PLC/IPs cascade and no efficacy at AC/cAMP pathway, PAT behaved in the opposite way, stimulating cAMP production and blocking IPs formation (Moniri et al., 2004; Moniri and Booth, 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. It has been reported that this differential activation of AC/cAMP and in consequence tyrosine hydroxylase by H₁R ligands in mammalian brain and adrenal tissues, could have implications in the treatment of several neurodegenerative disorders that will be discussed further below (Moniri and Booth, 2006).

Biased signaling for H₂ receptor ligands.

As mentioned before H₂R blockers used in clinic for treatment of gastric acid related disorders, as cimetidine, famotidine and ranitidine, are well known inverse agonists regarding cAMP production (Smit *et al.*, 1996; Monczor *et al.*, 1998). Interestingly, in spite of diminishing cAMP production, all these ligands (and also tiotidine, the classic reference ligand used in research) behave as full agonists regarding H₂R desensitization and internalization. Although the extent and rate of H₂R internalization induced by inverse agonists were similar to that of agonist-promoted endocytosis, it resulted to be independent of GRK-2-mediated phosphorylation. Moreover, protein partner profile and receptor fate once it is endocytosed remarkably contrasts when the desensitization/internalization processes are triggered by agonists or inverse agonists (Alonso *et al.*, 2014). On the other hand, cimetidine, famotidine, ranitidine and tiotidine also present a biased profile towards activation of

ERK1/2 signaling pathway over cAMP production. But again, although inverse agonists as well as histamine or H₂R agonists have positive efficacy increasing ERK1/2 phosphorylation, the underlying mechanisms are different. While H₂R agonist-stimulated ERK1/2 phosphorylation is mediated by dynamin; cimetidine, ranitidine and tiotidine lead to an increase in phospho-ERK levels by a mechanism independent of dynamin or even H₂R internalization but mediated by Gβγ (Xu *et al.*, 2008; Alonso *et al.*, 2014; Alonso *et al.*, 2016). Notably, it has been proved that ERK1/2 modulation is involved in the regulation of the expression of histidine decarboxylase, the enzyme responsible for histamine synthesis (Colucci *et al.*, 2001).

Biased agonism has also been described for the H₂R in neutrophils and eosinophils. These cells are chemoattracted and migrate to the focus of infection releasing a diversity of cytotoxic enzymes, cytokines and reactive oxygen species playing a pivotal role in host defense against microbes and viruses (Pincus *et al.*, 1982; Burde *et al.*, 1989; Adamko *et al.*, 2002; Soehnlein *et al.*, 2009; Rothenberg and Hogan, 2006; Sadik *et al.*, 2011; Reher *et al.*, 2012b). Activation of H₂R results in inhibition of granulocyte superoxide release (Gespach and Abita, 1982; Burde *et al.*, 1989; Ezeamuzie and Philips, 2000). Although cAMP increments were related to inhibition of ROS release, substantial evidence showed that H₂R agonists, dimaprit and impromidine, are biased ligands towards 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 for the clinic, as discussed further below.

HISTAMINERGIC REGULATION OF THE SIGNALING OF OTHER RECEPTORS

Considerable progresses over the past years in biochemistry and molecular biology allowed a significant change in how cellular signaling is study and how the experimental results are

interpreted. Traditionally, studies have 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). Nevertheless, holistic analyses of signaling pathways in cell systems revealed that signals do not necessarily disseminate in a linear manner. Alternatively, cellular signaling networks are comprised of modules that can not 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 (Di Riberto *et al.*, 2016, Jordan *et al.*, 2000, Bockaert *et al.*, 2003).

H₁R and H₂R interfere in the activity of other GPCRs.

There have been described several ways in which GPCRs functionally interact with other pathways. In particular, it has been proved that some inverse agonists of histamine receptors interfere with the response of other GPCRs that shared the same signaling pathway. Tiotidine, after binding to H₂R, impaired the signaling of other Gs-coupled GPCRs as the β -Adrenergic, calcitonin and PGE₂ receptors (Monczor *et al.*, 2003, Tubio *et al.*, 2010). Furthermore, the mere overexpression of the H₂R interfered with the signaling of these GPCRs and H₂R knock-down potentiated their response (Tubio *et al.*, 2010). In the same way, mepyramine binding to H₁R interferes with the signaling of the Gq-coupled ATP receptor. These ligands were thought to stabilize a conformation of the receptor that although is inactive it may couple and recruit G-protein making it less available for other unrelated receptors that signal through the same pathway (Fig. 1 top panel). This interpretation also explains that after G-protein overexpression the phenomenon of interference is no longer observed (Tubio *et al.*, 2010; Fitzsimons *et al.*, 2004).

H₁R and H₂R cross-regulation.

The H₁R and H₂R are coexpressed in most cell types such as neurons, airway and vascular smooth muscle cells, granulocytes, monocytes/macrophages, dendritic cells, lymphocytes as well as endothelial and epithelial 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 these (or even more) subtypes of histamine receptors.

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

H₁R and H₂R modulation of the activity of nuclear receptors.

Crosstalk between signals triggered by membrane receptors are 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 to regulate the transcriptional activity of glucocorticoid receptor (GR) through the modulation of GPCR-mediated signaling. Adrenaline and noradrenaline acting on β 2-Adrenergic receptor enhance GR activity via a G $\beta\gamma$ /PI3K/PKB pathway (Schmidt *et al.*, 2001). On the other hand, somatostatin and melatonin receptors' activation suppress GR activity through G $\beta\gamma$ and Gai 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. In a recent paper, it has been observed that histamine, as well as antihistamines, are able to potentiate GR activity. When H₁R is stimulated by histamine, a complex dual process triggers. On the one hand, Gαq/PLC signaling inhibits GR response to dexamethasone. On the other hand, Gβγ dimer enhances GR response to dexamethasone through Jun kinase mediated phosphorylation of the receptor. The balance of both regulatory pathways results in the activation of GR activity. However, since H₁R inverse agonists, potentially inhibit Gαq/PLC signaling they also lead to potentiation of GR response to dexamethasone (Fig. 1 bottom panel) (Zappia *et al.*, 2015). This potentiating effect of histamine and antihistamines on GR activity has proven to alter the expression of endogenous genes related to inflammatory processes, transactivated and transrepressed by dexamethasone (Zappia *et al.*, 2015). This somehow paradoxical effect, in which antihistamines actually behave as partial agonists concerning GR activity, has profound clinical consequences that will be discussed further below. All the above information regarding histamine receptors signaling is summarized in Table 1.

PHARMACOLOGY OF H₁ AND H₂ HISTAMINE RECEPTORS: FROM CLASSICAL 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/or as over-the-counter drugs. Therapeutically relevant H₁R drugs are inverse agonists: loratadine, azelastine, fexofenadine, desloratadine, levocetirizine, cetirizine and olopatadine. These ligands are widely used in the treatment of hay fever, allergic rhinitis and conjunctivitis, and hives (Simons and Simons, 2011). Antihistamines have been also formulated for local application to the mucosa or skin diminishing the symptoms caused by localized or systemic histamine (Solelhac and Charpin, 2014; Ostrom

2014).

On the other hand, the H₂R antagonists cimetidine, ranitidine, nizatidine, and famotidine are classic treatments for patients presenting gastric or duodenal ulcers, dyspepsia or gastro-esophageal reflux disease (Hershcovici and Fass, 2011; Sigterman *et al.*, 2013). Since the launch of antibiotic therapies for *Helicobacter* infections and the discovery of proton pump inhibitors, the anti-secretory H₂R antagonists have been overtaken for gastroesophageal symptomatic treatment (Marshall and Warren, 1984; Marshall *et al.*, 1988; Olbe *et al.*, 2003). However, there is a renaissance in the use of antagonists of H₂R to prevent gastrointestinal ulcers in patients taking non-steroidal anti-inflammatory drugs (Koch *et al.*, 1996; Rostom *et al.*, 2002). For example, an association between ibuprofen and the H₂R antagonist, famotidine (DUEXIS) is available for the treatment of arthritis (Laine *et al.*, 2012).

Based on that, and taking into account the more recently described functional selectivity and crosstalk of H₂R, it is necessary to consider these phenomena in the context of the clinical use of H₂R blockers. The inhibition of acid gastric secretion is achieved by blocking the canonical AC/cAMP signaling pathway of the H₂R. However, it has been described that some H₂R inverse agonists increase p-ERK levels mimicking the effects of histamine (Alonso *et al.*, 2015). As mentioned before, ERK activation induces the expression of histidine decarboxylase (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 parietal cell response to histamine and develops tolerance to the treatment with H₂ antagonists. This was explained by an increase in receptor membrane expression due to structural stabilization of the H₂ receptor 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 may also explain why these ligands produce an increased hypersecretion of gastric

acid after withdrawal (Smith *et al.*, 1999). Being this the case, an H₂R neutral antagonist or inverse agonist that fails to induce HDC expression should avoid such undesired effects.

On the other hand, it was mentioned above the existence of G protein scavenging by H₁ or H₂ inverse agonists. We could not find in the literature examples 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 repurpose of classic H₁ receptor ligands.

Despite the extensive study and clinical applications of histamine H₁R and H₂R pharmacology, there are novel and proposed uses for repositioning histaminergic ligands. Since 2011, the National Institutes of Health has augmented activities to facilitate the repurposing of existing drugs (Huang *et al.*, 2011). In this context, histaminergic ligands are low-cost drugs, with a very good established safety profile and no patent protection, which allows fast tracking for human trials.

Based on the recently described crosstalk between H₁R signaling and GR activity, antihistaminic antiallergic ligands could be potentially repositioned as adjuvants for corticoid therapies in order to diminish corticoid adverse effects. As mentioned above, H₁R inverse agonists are able to modulate the transcriptional activity of GR by potentiating transactivation and transrepression of key genes in the inflammatory response (Zappia *et al.*, 2015). The existence of relevant cell types co-expressing both receptors, such as endothelial cells, dendritic cells, monocytes, neutrophils, T and B cells and microglia, suggests that this interaction may have implications for regulation of inflammation in several systems (Lu *et al.*, 2006; Panula *et al.*, 2015). In the search of strategies to improve the beneficial/undesired effect ratio in the clinical administration of glucocorticoids, the add-on therapies have brought very good results. These therapies consist in the combination of corticoids

with other drugs that potentiates corticoid effect by a different mechanism of action, allowing by this way, to decrease the dose of corticoid administered and in consequence corticoid's adverse effects. By this approximation, corticoids have been used in combination with β 2-adrenoreceptor agonists, teophylline or with antagonist of leukotriene receptor, montelukast to treat asthma (Louis *et al*, 2012). In this regard, combination therapy of glucocorticoids and antihistamines may not only be beneficial for patients having concomitant allergic and inflammatory processes, but also may allow a reduction in the doses of corticoids by antihistamine potentiating effects.

Supporting this hypothesis it has been shown *in vivo* that the antihistamine olopatadine enhanced prednisolone inhibition of scratching and skin symptoms on an atopic dermatitis murine model (Kagawa *et al.*, 2010). Likewise, the H₁R blocker azelastine can reduce the frequency of administration of inhaled corticosteroids without loss of pulmonary function on a clinical trial on patients with chronic asthma (Busse *et al.*, 1996).

Repositioning of antihistaminergic ligands is also proposed by taking advantage on the generalized actions that are mediated by histamine throughout the body and the ubiquitous expression of H₁R. Novel clinical applications for these ligands are being investigated with different degrees of success.

Action of H₁R in the central nervous system (CNS) 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 and considerable evidence indicates that several H₁ blockers are indeed analgesic agents (McHugh and McHugh, 2000; Mobarakeh *et al.*, 2000; Sakurada *et al.*, 2004). Recent data indicate that cetirizine potentiates the analgesic and antiedematogenic effects of morphine (Stein *et al.*, 2016), suggesting an unexplored use for classic antihistamines in the relief of pain.

H₁R antagonists are also proposed as beneficial in the treatment of neurodegenerative disorders that have a neuroinflammatory component as Parkinson's and amyotrophic lateral sclerosis (Dong *et al.*, 2014; Rocha *et al.*, 2014). Concerning this, chronic treatment with clemastine enhances neuronal survival and modulates the expression of inflammatory genes in microglia (Apolloni *et al.*, 2014). It has also been suggested that the blockade of histamine-induced dopaminergic neuronal toxicity, would help to neuronal protection with potential clinical application for Parkinson's disease (Rocha *et al.*, 2016).

Histaminergic neurons are active during the wakeful state and are inhibited during REM sleep by GABAergic neurons located in the hypothalamus (Shan *et al.*, 2015). On that base, antihistamines with central action, such as diphenhydramine and doxylamine, are being widely used for insomnia therapy, although their use is not recommended for long periods due to rapidly developed tolerance (Krystal, 2015). FDA approved the use of 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 H₁ antagonism or an nonspecific action over muscarinic M₁ receptors, this possibility has been rule out by the observation that low doses of doxepin (that act solely on H₁R) showed a significant improvement in total sleep time and efficiency with no evidence of morning residual impairment or sedation (Krystal, 2015; Scharf *et al.*, 2008; Krystal *et al.*, 2010; Krystal *et al.*, 2011)

Potential repurpose of classic H₂ receptor ligands.

Besides the classic gastric acid secretion regulation, H₂R signaling has also been implicated in the development of cardiovascular disease. High histamine concentrations are found in cardiac tissues

and its positive inotropic effects mediated by H₂R stimulation may be important in the pathophysiology of cardiovascular disease (Shi *et al.*, 2015; Hattori, 1999 Eckel *et al.*, 1982; Kirch *et al.*, 1992). In fact, the blocking of histamine release or H₂R antagonism prevented heart failure in rabbits with doxorubicin-induced cardiomyopathy and dogs with sustained atrial tachycardia (Takahama *et al.*, 2010). Consistently, H₂R^{-/-} KO 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, in a decreased responsiveness of β -Adrenoreceptor due to scavenging of G α s protein by the H₂R. A prospective study conducted in a cohort from the MESA study (Multi-Ethnic Study of Atherosclerosis) with more than 6000 cases, concluded that the use of H₂R antagonists prevent the onset of chronic heart failure (Leary *et al.*, 2016). Based on this evidence, H₂R ligands are being repurposed as reliable drugs to provide benefits to patients with chronic heart failure.

Besides these more clear attempts for repositioning classic histaminergic ligands, they are also being considered for improving diabetic condition, treating infections and cancer (for review see Pini *et al.*, 2016; Deva and Jameson, 2012; Pantziarka *et al.*, 2014).

Biased signaling and novel drugs of the classic histaminergic system.

Several worldwide marketed drugs act on receptors that demonstrate biased agonism (Kenakin and Miller, 2010). Although there is a clear theoretical advantage of this pharmacological complexity about GPCRs signaling, currently there are no drugs approved for their use in base of their biased therapeutic profiles (Kingwell, 2015). In general, biased ligands could surmount on-target undesirable events circumventing certain pathways, or enhance their therapeutic efficacy by avoiding or stimulating specific negative or positive feedback loops in their signaling pathways.

The recent development of some new drugs has taken advantage of this signaling multiplicity of ligands with promising results (Violin *et al.*, 2014).

This functional heterogeneity has been described for H₁ and H₂ histamine receptors as mentioned above. In the brain, by acting through the presynaptic H₁R, histamine not only signals through the canonical Gq/calcium pathway but also stimulates AC/cAMP signaling. Neuronal activation of cAMP pathway leads to tyrosine hydroxylase activity and dopamine synthesis. Interestingly, this behavior, dependent of 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 (Moniri *et al.*, 2004; Galeotti *et al.*, 2004). This biased behavior may be of possible value to treat neurodegenerative or neuropsychiatric disorders involving dopamine synthesis.

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

In this regard, histamine dihydrochloride (HDC, Ceplene®) has been approved for the treatment of patients suffering from acute myeloid leukemia (AML) and H₂R agonists are being extensively studied as promising drug candidates for the treatment of AML and inflammatory diseases (Martner *et al.*, 2010; Burde *et al.*, 1989, 1990; Jutel *et al.*, 2009). By inhibiting ROS production, H₂R ligands allow that agents which stimulate the immune system (e.g. IL-2) effectively activate cytotoxic cells, improving the death of tumor cells (Hellstrand, 2002). Based on this, combined histamine and IL-2 post-remission therapy significantly prevents AML relapse (Buyse *et al.*, 2011; Aurelius *et al.*, 2012).

As mentioned above, it has been reported that in myeloid cells H₂R agonists inhibit the generation of ROS by a mechanism that is not mediated by cAMP accumulation. Indeed, dimaprit and

impromidine were described as H₂R biased agonists towards ROS inhibition in neutrophils and eosinophils (Reher *et al.*, 2012a). These results suggest that H₂R biased signaling towards the inhibition of ROS production may present a beneficial effect by allowing cytotoxic cells to kill leukemic cancer cells (Monczor *et al.*, 2016). All the data presented concerning the current and potential clinical applications of histaminergic ligands is summarized in Table 2.

FINAL CONSIDERATIONS

Getting a drug to market, takes 13–15 years and between 2-3 billion dollars on average; while repositioning a drug costs almost one tenth of it and takes less than a half of that time (Nosengo, 2016). The aim of the molecular pharmacology studies relies on the ultimate understanding of the effects of a given ligand on a biological 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, a refresh in the understanding of the whole picture of histamine actions may help to repurposing classic histaminergic low cost ligands with novel therapeutic uses. In an attempt to understand the pharmacology of a ligand, there is always a risk regarding the election of the *experimental eyes* 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 biological response or to interfere in the response of other receptors, widening the 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 time ago by Sir James Black (Black *et al.*, 1972), we hope that the mechanistic aspects discussed in the present review help to understand the histaminergic system as well, aiding to repurpose classic ligands of the histaminergic system, increase drug efficacy and avoid adverse

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effects.

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Authorship Contributions

Monczor, F. and Fernández, N. wrote the manuscript.

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FOOTNOTES

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LEGEND FOR FIGURE.

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

TABLES

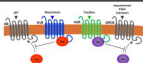
Table 1. Histamine H₁ and H₂ receptors. Signaling pathways, receptor cross-talk and ligands.

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

Table 2. Clinical uses of histaminergic ligands according to their molecular mechanisms of action. Current, proposed, and non-traditional.

Histamine receptor							
Molecular mechanism of action	H ₁			H ₂			
	Therapeutic use	Pharmacological effect	References	Molecular mechanism of action	Therapeutic use	Pharmacological effect	References
Gq/11 activity blockade; NF-kB inhibition	Current	Antiallergic	Panula <i>et al.</i> , 2015; Bakker <i>et al.</i> , 2001	Gs/AC/cAMP inhibition	Current	Gastric acid secretion regulation	Panula <i>et al.</i> , 2015
	Repositioning	Analgesia; neurodegenerative disorders; sleep disorders; stress induced hypertension	Stein <i>et al.</i> , 2016; Apolloni <i>et al.</i> , 2014; Rocha <i>et al.</i> , 2016; Shaun <i>et al.</i> , 2015; Krystal <i>et al.</i> , 2011; de Almeida <i>et al.</i> , 2015.		Repositioning	Chronic heart failure; diabetes; colorectal cancer	Leary <i>et al.</i> , 2016; Pini <i>et al.</i> , 2016; Pantziarka <i>et al.</i> , 2014.
Biased agonism; glucocorticoid receptor crosstalk	Non traditional	Neuroprotection; anti-inflammatory potentiation;	Moniri <i>et al.</i> , 2004; Zappia <i>et al.</i> , 2015	Biased agonism	Non traditional	Gastric acid secretion rebound; AML treatment	Alonso <i>et al.</i> , 2014; Alonso <i>et al.</i> , 2015; Reher <i>et al.</i> , 2012.

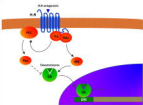
MECHANISMS OF CROSSTALK MEDIATED BY H1R AND H2R AND THEIR POTENTIAL IMPLICATIONS IN THERAPY



Scavenging of inactive G protein



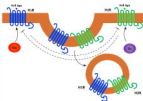
Drug-drug interactions



Modulation of nuclear receptors



Potential of Glucocorticoids' action



H1R and H2R cross-desensitization and cross-internalization



Long term receptor down-regulation