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Invited review

Cherry-picked ligands at histamine receptor subtypes

Bassem Sadek [a, *], Holger Stark [b]

[a] Department of Pharmacology and Therapeutics, College of Medicine & Health Sciences, United Arab Emirates University, PO Box 17666, Al Ain, United Arab Emirates
[b] Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University, Universitaetsstr. 1, 40225 Düsseldorf, Germany

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ABSTRACT

Histamine, a biogenic amine, is considered as a principle mediator of multiple physiological effects through binding to its H_1, H_2, H_3, and H_4 receptors (H1–H4Rs). Currently, the HRs have gained attention as important targets for the treatment of several diseases and disorders ranging from allergy to Alzheimer's disease and immune deficiency. Accordingly, medicinal chemistry studies exploring histamine-like molecules and their physicochemical properties by binding and interacting with the four HRs has led to the development of a diversity of agonists and antagonists that display selectivity for each HR subtype. An overview on H1-R4Rs and developed ligands representing some key steps in development is provided here combined with a short description of structure–activity relationships for each class. Main chemical diversities, pharmacophores, and pharmacological profiles of most innovative H1–H4R agonists and antagonists are highlighted. Therefore, this overview should support the rational choice for the optimal ligand selection based on affinity, selectivity and efficacy data in biochemical and pharmacological studies.

This article is part of the Special Issue entitled 'Histamine Receptors'.

1. Introduction

Histamine is a biogenic neurotransmitter, and since 1907, when it was first synthesized, is still in the center of general interest as it plays an important role in the regulation of several (patho)physiological conditions in central nervous system and peripheral tissues (Hough, 2001). The precise effects of histamine are exerted through stimulation of four different G-protein coupled receptor (GPCR) subtypes, namely H1–H4R (Fig. 1) (Arrang et al., 1988, 1987, 1983, 1985a; Hill, 1990; Hill et al., 1997; Leurs et al., 2005; Lovenberg et al., 1999). The most characteristic roles for H1R activation are smooth muscle contraction and increases in vascular permeability, and many of its functions contribute to allergic responses. Thus, H1R antagonists have been very efficacious drugs for the treatment of allergies (Baraniuk, 1997). The H2R has been confirmed to function as a key modulator for gastric acid secretion, and H2R antagonists are largely used for the treatment of gastrointestinal ulcers (Arrang et al., 1988; Soll and Walsh, 1979). The H3R is primarily expressed in the human central nervous system (Arrang et al., 1988; Lovenberg et al., 1999). It functions as a presynaptic release-controlling receptor that regulates histamine, and also, as a hetero-receptor on non-histaminergic neurons modulating the release of norepinephrine, serotonin, GABA, acetylcholine, and other neurotransmitters (Arrang et al., 1988, 1983; Blandina et al., 1996; Harada et al., 2004; Hill, 1990; Schlicker et al., 1993, 1989, 1990; Yokoyama et al., 1993).

Activation of the H1R leads to the mobilization of intracellular Ca^{2+} by activating the G_q family of G-proteins (Hill, 1990). The H2R signals through Gs G-proteins and receptor activation cause significant increases in cAMP, whereas the H3R couples to $G_{i/o}$, leading to moderate decreases in cAMP (Fig. 1) (Lovenberg et al., 1999; Nakamura et al., 2000). Also, signaling of H2R has been described to act through PLC/IP3 pathway by activating Gq family of G-proteins leading to mobilization of intracellular Ca^{2+} (Mitsuhashi et al., 1989; Smit et al., 1996b; Wellner-Kienitz et al., 2003). Recently, H4R was identified and showed a 35% amino acid homology with the H3R and much lower homologies to H1Rs and H2Rs (Liu et al., 2001; Morse et al., 2001; Nakamura et al., 2000; Nguyen et al., 2001; Oda et al., 2000; Zhu et al., 2001). The knowledge on the physiological and pathophysiological function based on H4R

* Corresponding author.
E-mail address: bassem.sadek@uaeu.ac.ae (B. Sadek).

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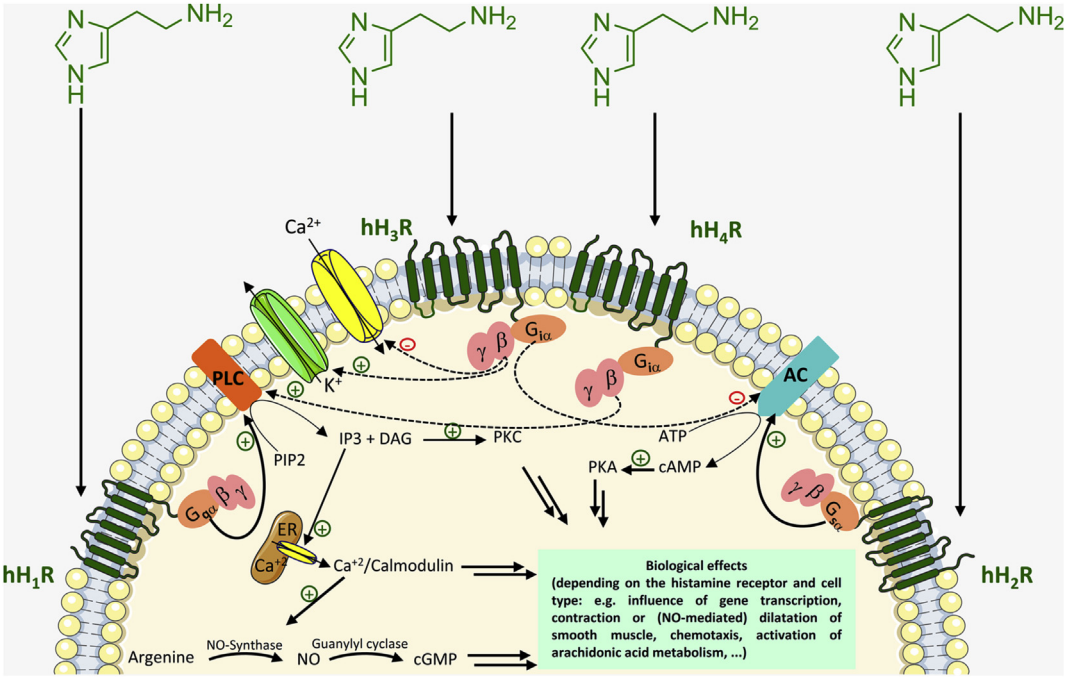

Fig. 1. Signal transduction for histamine receptor subtypes H1R, H2R, H3R and H4R. Figure modified after Strasser et al., 2015 (Strasser and Buschauer, 2015).

modulation is steadily increasing (Jablonowski et al., 2004, 2003; Schneider and Seifert, 2016). However, preclinical data strongly suggest its potential therapeutic exploitation in allergy, inflammation, autoimmune disorders and possibly cancer. Hence, H4R can mediate chemotaxis and calcium influx in mast cells and eosinophils (Hofstra et al., 2003; O'Reilly et al., 2002; Stark et al., 2004; Walter and Stark, 2012).

Taken together, the four HRs couple with several different signaling pathways modulating various G-proteins (Fig. 1).

2. Histamine H1R

The H1R, including many other biogenic amine receptors, is one of the GPCR family members (see for a complete list e.g. http://www.gpcr.org/7tm/ or http://tools.gpcr.org/visualise/proteinselection) for which a tremendous input with the solved crystal structures has been done so far. In the early 1990s, a significant contribution to targeted research of H1R ligands has been provided by the cloning of the human H1R protein consisting of 487 amino acids (gene locus 3q25). Specifically synthesized antagonists could then be investigated and characterized in comprehensive binding studies on various species. Furthermore, the X-ray crystallization of H1R has succeeded in 2010 with the slightly modified and stabilized mutant human H1R in complex with the first generation H1R antagonist doxepin (**11**) (Shimamura et al., 2011). Interestingly, it has been found that the binding pocket of doxepin comprises the highly conserved Asp107 in the transmembrane region 3 (TM3) and aromatic residues in TMs 5 and 6, e.g. Phe424, Trp428 and Phe432 (Fig. 2A) (Panula et al., 2015; Shimamura et al., 2011). In addition, it has been shown that the strong hydrophobic interactions of the aromatic moieties of doxepin withTrp428 may inhibit movement of helix 6, which is commonly described of being one of the important features in GPCR activation. Moreover, it has been observed that doxepin is capable of binding deeply in the pocket expressed by TM3, 5, and 6. Furthermore, a complementary phosphate-anion binding site was observed and described at the entrance of the ligand-binding pocket and described as a unique feature in the x-ray structure. Accordingly, the phosphate anion was found to be matched with Lys179, Lys191 and His450 and this binding pocket is proposed to be crucial for the interaction with zwitterionic H1R antagonists of the second generation antihistamines (Panula et al., 2015; Shimamura et al., 2011). Consequently, possible interactions of the basic amine with the phosphate can affect the stability of the ligand receptor binding, so that the residence of zwitterionic compounds at the receptor ($1/K_{off}$) can be significantly increased (Shimamura et al., 2011). Contrary, understandings of the molecular features governing agonist induced H1R activation await the resolution of an active H1R x-ray structure and presently still rely on molecular modeling and/or mutagenesis studies (Jongejan et al., 2005; Ohta et al., 1994; Sansuk et al., 2010; Strasser et al., 2008). However, histamine is thought to bind the H1R with its protonated ethylamine side chain via Asp107 (Ohta et al., 1994), whereas the imidazole ring is believed to interact with Asn198 and Lys191 (Leurs et al., 1995, 1994). Also, the protonated side chain with Asp107 allows possibly for the release of Ser3.36 tolerating it to function as a closing switch and to interconnect with Asn7.45 positioned at the receptor in its active state (Jongejan et al., 2005; Panula et al., 2015).

3. H1R agonists

Despite the fact that histamine (**1**) regulates various physiological and pathophysiological effects via H1Rs, the research area of the corresponding agonistic active compounds has been neglected for a long time (Fig. 3). Interestingly, two major structural elements can be differentiated in the histamine molecule, namely the imidazole ring and the aminoethyl side chain. A diversity of structural modifications in both parts has earlier been described (Gerhard and Schunack, 1980a, b; Hepp and Schunack, 1980; Stark and Schubert-Zsilavecz, 2004; Vickers et al., 1982; Walter et al., 2011). Hence, introduction of substituents in the ethylene side chain of histamine has not provided interesting H1R agonists, since methylation of the