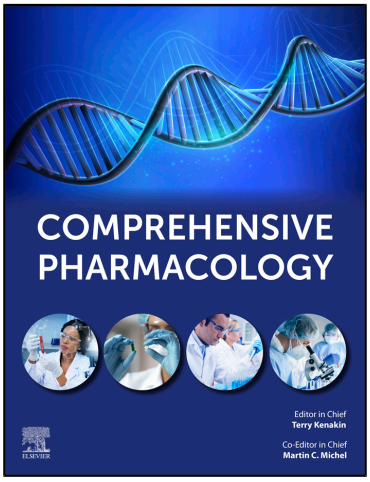

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5.28 The Pharmacology of Antihistamines

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Glossary

Allergic rhinitis Allergic rhinitis is an allergic nasal condition characterized by rhinorrhea and nasal blockage. Rhinorrhea is particularly antihistamine sensitive whereas nice blockage is less sensitive.

Antihistamines Synthetic compounds that prevent activation of histamine receptors. The older first-generation antihistamines have many unwanted effects including sedation. The newer second-generation antihistamines are more effective and have less unwanted effects.

Histamine An organic amine that has a central role in mediating many of the symptoms of allergic disease, such as each in urticaria and rhinorrhea in allergic rhinitis.

Histamine receptors Cell-surface receptors that are activated by histamine. There are four types, H1, H2, H3 and H4. In allergic disease H1 and H4 are mainly responsible for causing the symptoms. H3 receptors are primarily in the brain and H2 mediate gastric acid secretion.

Urticaria Urticaria is an autoallergic skin condition characterized by the occurrence of wheals, angioedema or both. Urticaria can be either spontaneous or inducible. Antihistamines are the primary drug of choice for the treatment of urticaria.

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5.28.1 The effects of histamine in allergic disease

In allergic and associated diseases, histamine has diverse effects, both pro-inflammatory and anti-inflammatory, which are determined by both the histamine receptor subtype and the cells stimulated (Thurmond, 2015). Histamine receptors (H_1-, H_2-, H_3- and H_4-receptors) are characterized by their structure, function, distribution and their affinity to histamine (Leurs et al., 2009; Singh and Jadhav, 2013). The H_1-receptor drives cellular migration, nociception, vasodilatation and bronchoconstriction (Bakker et al., 2001), whereas the H_2 -receptor modifies gastric acid secretion, airway mucus production and vascular permeability (Seifert et al., 2013). The H_3-receptor plays an important role in neuro-inflammatory diseases (Singh and Jadhav, 2013). The H_4-receptor has also been shown to be involved in allergy and inflammation (Thurmond, 2015; Tiligada, 2012). Histamine H_4-receptor-mediated mast cell activation can regulate a powerful inflammatory cascade by releasing several inflammatory mediators including histamine; these mediators may stimulate the migration of different inflammatory cells to the site of inflammation (Jemima et al., 2014). Likewise, the activation of H_1-receptor also regulates allergic responses by enhancing the migration of Th2-lymphocytes towards the allergen during lung inflammation (Bryce et al., 2006).

5.28.1.1 Histamine H_1-receptor effects

The histamine H_1-receptor is expressed in many tissues and cells, including nerves, respiratory epithelium, endothelial cells, hepatic cells, vascular smooth muscle cells, dendritic cells and lymphocytes (Thurmond et al., 2004; Akdis and Simons, 2006). Histamine activates the H_1-receptor through Gαq/11, which then activates phospholipase C and increases intracellular Ca^{++} levels. As a consequence, histamine elicits the contraction of smooth muscle of the respiratory tract, increases vascular permeability, and induces the production of prostacyclin and platelet activating factor by activating H_1-receptors (Simons, 2004). Thus, almost all immediate hypersensitivity reactions, including symptoms observed in the skin, such as erythema, pruritus, and edema, may be elicited by the activation of the H_1-receptor (Schaefer et al., 1999).

Activation of the H_1-receptor can also enhance both Th1- and Th2-type immune responses (Jutel et al., 2001). Similarly, Bryce et al. (2006) demonstrated that allergen-challenged H_1-receptor-deficient mice had attenuated lung allergic responses.

In addition, IL-3 activation can increase H_1-receptor expression on Th1 cells (Horio et al., 2010; Osna et al., 2001), and histamine can enhance B cell proliferation, which is absent in H_1-receptor-deficient mice (Banu and Watanabe, 1999). The role of H_1-receptor activation in asthma is further corroborated by observations showing that use of H_1-antihistamines can significantly decrease asthma symptoms and improve pulmonary function in persistent asthma (Baena-Cagnani et al., 2003; Simons, 1999b, 2004).

The H_1-receptor is also expressed in dermal dendritic cells and keratinocytes in the skin tissue, and histamine increases the proliferation of murine epidermal keratinocytes *in situ* (Maurer et al., 1997) and it increases the nerve growth factor production via the H_1-receptor in human keratinocytes (Kanda and Watanabe, 2003). The secretion of nerve growth factor is caused by the phosphorylation of protein kinase C, extracellular signal-regulated kinases and the activation of activator protein-1 resulting from H_1-receptor stimulation. Similarly, histamine, acting via the H_1-receptor, has also been shown to enhance the production of chemokines, such as GM-CSF, RANTES, and MCP-1in IFN-γ-stimulated keratinocytes. It also up regulates the antigen-presenting capability of dendritic cells, and leads to Th1 polarization through the H_1-receptor (Giustizieri et al., 2004).

Histamine induces IL-31 production, which plays an important and crucial role in pruritus and skin barrier function in allergic dermatitis (Gutzmer et al., 2009). Administration of an H_1-antihistamine decreased IL-31 levels in the serum of atopic dermatitis patients (Mommert et al., 2012). These data, taken together, suggest that H_1-receptor activation by histamine has the ability to induce various symptoms related with allergic and other inflammatory diseases including skin diseases such as chronic urticaria, atopic dermatitis, chronic prurigo, and chronic pruritus.

5.28.1.2 Histamine H_2-receptor effects

The Gαs-coupled H_2-receptor is highly expressed in various cells and tissues, such as B cells, T cells, dendritic cells, gastric parietal cells, smooth muscle cells, and the brain and cardiac tissues. Activation of the receptor can induce airway mucus production, vascular permeability and secretion of gastric acid (Smit et al., 1996). The H_2-receptor is importantly involved in relaxation of the airways, uterus and smooth muscle cells in the blood vessels. Moreover, the H_2-receptor is involved in the activation of the immune system, such as Th1 cytokine production, reduction of basophil degranulation, T-cell proliferation and antibody synthesis (Meiler et al., 2008; Lichtenstein and Gillespie, 1975).

5.28.1.3 Histamine H_3-receptor effects

The H_3-receptor is coupled to Gαi/o and exclusively expressed in neurones. It is important for homeostatic regulation of energy levels, sleep-wake cycle, cognition and inflammation (Dimitriadou et al., 1994). Studies suggest that the H_3-receptor can lead to an increase in severity of neuro-inflammatory diseases and can enhance the expression of IFN-inducible protein 10, MIP 2 and

CXCR3 in T cells (Teuscher et al., 2007). The H_3-receptor has also been associated with rhinitis (Lieberman, 2011). This is likely because it is expressed on presynaptic nerves in the peripheral sympathetic adrenergic system and also on nasal sub-mucosal glands. Stimulation of H_3-receptor suppressed norepinephrine release at pre-synaptic nerve endings and stimulated nasal sub-mucosal gland secretion (Suzuki et al., 2008).

5.28.1.4 Histamine H_4-receptor effects

Many cells express H_4-receptors including neurons, fibroblasts, spleen, intestinal epithelia, lung, synovial tissue and immune cells such as eosinophils, neutrophils, basophils and mast cells (Nicoud et al., 2019; Thangam et al., 2018; Lippert et al., 2004). Signal pathways include a decrease in cAMP accumulation through inhibition of adenylyl cyclase, increase in Ca^{2+} mobilization via IP3, activation of MAPK/ERK, PI3K and SAPK/JNK and inhibition of TGF-β1 signaling pathways and recruitment of β-arrestin (Nicoud et al., 2019).

The H_4-receptor contributes to pain control (Coruzzi et al., 2007; Sanna et al., 2020), has a potential role in cancer progression (Nicoud et al., 2019; Schirmer et al., 2020). It also modulates innate and adaptive immune responses (Nicoud et al., 2019) mediating cell migration and cytokine production (Peng et al., 2019). For example, activation of H_4-receptors has been shown to induce chemotaxis of mast cells, eosinophils and dendritic cells, induction of migration of regulatory T cells and release of mediators including IL-4, -5, -13, -6, -1b, -10, -8 and MCP-1 (Wang et al., 2019; Nicoud et al., 2019).

Histamine H_4-receptor is thought to be involved in allergic diseases and pruritus development and, consequently, is considered as a novel drug target for the treatment of allergy. H_4-receptors are expressed on mast cells, eosinophils, basophils, dendritic and natural killer cells (Thangam et al., 2018; Lippert et al., 2004; Jemima et al., 2014).

Mast cell chemotaxis into sites of allergic inflammation has been shown to be mediated, at least in part, by histamine-activated H_4-receptors. This is prevented by the dual H_3/H_4-antihistamine thioperamide, but not by H_1- or H_2-antihistamines (Hofstra et al., 2003). In another study, JNJ7777120, a selective histamine H_4-antihistamine, effectively reversed the chemotaxis of human lung mast cells induced by the H_4-receptor agonist, JNJ28610244 (Kay et al., 2018).

In human mast cells, H_4-receptor activation leads to intracellular Ca2+ release, degranulation and the production of Th2 and pro-inflammatory cytokines, e.g. IL-13 and RANTES (Ebenezer et al., 2017, 2018). H_4-receptor gene silencing and pretreatment with JNJ7777120 decreased phosphorylation of SAPK/JNK and inhibited the intracellular Ca2+ release and degranulation induced by H_4-antihistamines in the human mast cell line-1 (Ebenezer et al., 2018).

In addition, the H_4-receptor may play a role in IgE-induced FcεRI upregulation and in the sensitization phase of mast cell degranulation. In particular, UR-63325, a selective H_4-receptor antagonist/inverse agonist, inhibited antigen-dependent degranulation of murine bone marrow-derived mast cells and IgE-induced FcεRI upregulation (Mirzahosseini et al., 2013).

Furthermore, H_4-receptor is crucial for the histamine-induced adhesion of eosinophils to endothelial cells. For example, Grosicki and colleagues observed concentration-dependent increase and decrease in the number of eosinophils that adhere to endothelium after activation of H_4-receptors with H_4-agonists and blocking with H_4-antihistamines, respectively (Grosicki et al., 2016).

The H_4-receptor has been reported to be highly expressed on keratinocytes from patients with atopic dermatitis. The stimulation of the H_4-receptor increased proliferation of keratinocytes, which was diminished with JNJ7777120 (Glatzer et al., 2013). In a mouse model of atopic dermatitis, H_4-receptor-deficient mice showed decreases in skin lesions, influx of inflammatory cells and epidermal hyperproliferation at lesional skin sites, and reduced levels of ovalbumin-specific IgE (Rossbach et al., 2016).

Histamine and the selective H_4-agonist, 4-methylhistamine, caused scratching responses in mice, which were almost completely attenuated in H_4-receptor knockout mice or by oral administration of JNJ 7777120 (Dunford et al., 2007). Itch induction may be associated with the intracellular signaling mechanism via the ion channel TRPV1 upon H_4-receptor activation on the dorsal root ganglion neurons (Jian et al., 2015).

Finally, Ohsawa et al. reported that bone marrow-derived basophils preferentially express H_4-receptor mRNA and that the histamine-induced chemotaxis of basophils was blocked by an H_4-antihistamine, but not by an H_1-antihistamine (Ohsawa and Hirasawa, 2012). In a mouse model of allergic rhinitis, mice with H_4R-deficient basophils, H_4-antihistamine-treated wild-type mice, and wild-type mice depleted of basophils failed to develop early or late phase nasal responses following allergen sensitization and challenge (Shiraishi et al., 2013).

5.28.2 The discovery and development of antihistamines

5.28.2.1 H_1-Antihistamines

To understand the strengths and weaknesses of antihistamines, and particularly, H_1-antihistamines, it is necessary to appreciate how they were developed in the 1930s. In his review about his own work (Bovet, 1950), Daniel Bovet wrote "Three naturally occurring amines, acetylcholine, epinephrine, and histamine, may be grouped together because they have a similar chemical structure, are all present in the body fluids, and exert characteristically strong pharmacologic activities. There are alkaloids that interfere with the effects of acetylcholine. Similarly, there are sympatholytic poisons that neutralize or reverse the effects of epinephrine. It seemed possible to me, therefore, that some substance might exist which exerts a specific antagonism toward histamine." It was against this background that Bovet, who was looking for antagonists of acetylcholine, asked his student, Anne-Marie Staub, to test some of these compounds against histamine. Anne-Marie Staub, who was preparing her doctorate thesis in his laboratory, used three

types of laboratory methods for the evaluation of the degree of activity of the various compounds (Bovet, 1950). In the first test, they determined the action against the lethal effects of histamine in guinea pigs. This test they believed to be 'perfectly specific.' In the second test, they determined the protection against histamine administered in the form of an aerosol. Here, they believed that symptoms similar to asthma were produced. In the third test for determining antihistaminic activity, which they believed to be the least specific one, they ascertained the effect of compounds on histamine-induced spasm of the isolated guinea pig ileum. These tests led to the discovery of the first H_1-antihistamine, thymoxyethyldiethylamine (929 F) in 1937 (Staub, 1937).

Although hymoxyethyldiethylamine was too toxic for use in humans, it opened the door for the introduction of the 1st generation H_1-antihistamines into the clinic. These included antergan in 1942 (Halpern, 1942), followed by diphenhydramine in 1945 (Loew et al., 1946) and chlorpheniramine, brompheniramine and promethazine later the same decade (Emanuel, 1999). It should be remembered, however, that these 1st generation H_1-antihistamines (fgAHs) derive from the same chemical stem as cholinergic muscarinic antagonists. Also, early tranquilizers, anti-psychotics, antihypertensive and local anesthetic agents were also developed from this stem. It is hardly surprising, therefore, that fgAHs have poor receptor selectivity and often interact with receptors of other biologically active amines causing anti-muscarinic, anti-α-adrenergic and anti-serotonin effects (Church et al., 2010; Yanai, 2012).

5.28.2.2 H_2-, H_3- and H_4-Antihistamines

While the classical antihistamines discovered in the 1940s and 1950s, such as mepyramine, suppressed the effects of histamine in contracting the smooth muscle of various organs, such as the gut and bronchi, actions such as increased gastric acid secretion, increased heart rate and contraction of the rat uterus were 'mepyramine resistant.' This observation led Ash and Schild (1966) to hypothesize that histamine exerted its effects through more than one receptor and led them to define the classical 'mepyramine sensitive' receptor as the histamine H_1-receptor.

In order to find drugs that antagonized the 'mepyramine resistant' effects of histamine, particularly its stimulation of gastric acid secretion, Sir James Black and his colleagues at The Research Institute of Smith Kline and French Laboratories began in 1964 to synthesize and test over 700 compounds which were closely related to the structure of histamine (Black et al., 1972). This work led to the definition of the histamine H_2-receptor and the discovery of burimamide and cimetidine (Brimblecombe et al., 1975), the forerunners of the H_2-antihistamines for the treatment of gastric ulcers.

Work by Jean-Charles Schwartz and colleagues in Paris in the early 1980s demonstrated that histamine was not only a transmitter in the periphery but also in the brain (Schwartz et al., 1980). However, they also realized that histamine, like other neurotransmitters, may modulate its own release through a presynaptic receptor, an action they suggested to be mediated by a class of receptor, designated as H_3, which was pharmacologically distinct from the previously characterized histamine H_1- and H_2-receptors (Arrang et al., 1983). This discovery and the realization that histamine H_3-receptors are located almost exclusively in the brain has led to the investigation of H_3-antihistamines for the treatment of cognitive disorders and Alzheimer's disease (Brioni et al., 2011).

Using the DNA sequence of the histamine H_3-receptor, several research groups independently identified a previously unexplored G-protein coupled receptor sequence in the human genome as a new histamine receptor, the histamine H_4-receptor (Leurs et al., 2009).

The histamine H_4-receptor was identified in data from human genome databases independently by different scientific groups at the beginning of the millennium. It is a Gαi/o-coupled receptor encoded by the H_4-receptor gene (Nicoud et al., 2019; Oda et al., 2000). The H_4-receptor consists of 390 amino acids, localized on 18q11.2 chromosome and has about 40% homology with the human histamine H_3-receptor (Nakamura et al., 2000; Oda et al., 2000; Nicoud et al., 2019). The identification of histamine H_4-receptors on hemopoietic cells, eosinophils, mast cells and dendritic cells and its potential role in chemotaxis and activation of these cells has stimulated widespread research into the possible use of H_4-antihistamines in allergic disease (Smits et al., 2009).

5.28.3 The histamine H_1-receptor and H_1-antihistamines

5.28.3.1 The histamine H_1-receptor

The histamine H_1-receptor is a member of the superfamily of G-protein coupled receptors (GPCRs). Physically they are composed of seven transmembrane domains coupling the exterior domains to the intracellular activating mechanism (**Fig. 1**). In the way that they work, GPCRs may be viewed as 'cellular switches' that exist as an equilibrium between the inactive or 'off' state and the active or 'on' state (Leurs et al., 2002). To stimulate the receptor, histamine cross links domains III and V to stabilize the receptor in its active conformation or 'on' position (Wieland et al., 1999) (**Fig. 1**). This is a transient event with histamine being rapidly removed. H_1-antihistamines are not structurally related to histamine and do not prevent the binding of histamine but bind to different sites on the receptor and stabilize it in its inactive form. For example, cetirizine cross links sites on transmembrane domains IV and VI to stabilize the receptor in the inactive state and swing the equilibrium to the 'off' position (Gillard et al., 2002) (**Fig. 1**). Binding times for H_1-antihistamines vary from 25 s for diphenhydramine to 60 and 73 min for fexofenadine and bilastine, respectively (Bosma et al., 2018). Thus, H_1-antihistamines are not receptor antagonists but are inverse agonists in that they produce the opposite effect on the receptor to histamine (Leurs et al., 2002). Consequently, the preferred term to define these drugs is 'H_1-antihistamines' rather than 'histamine antagonists.'

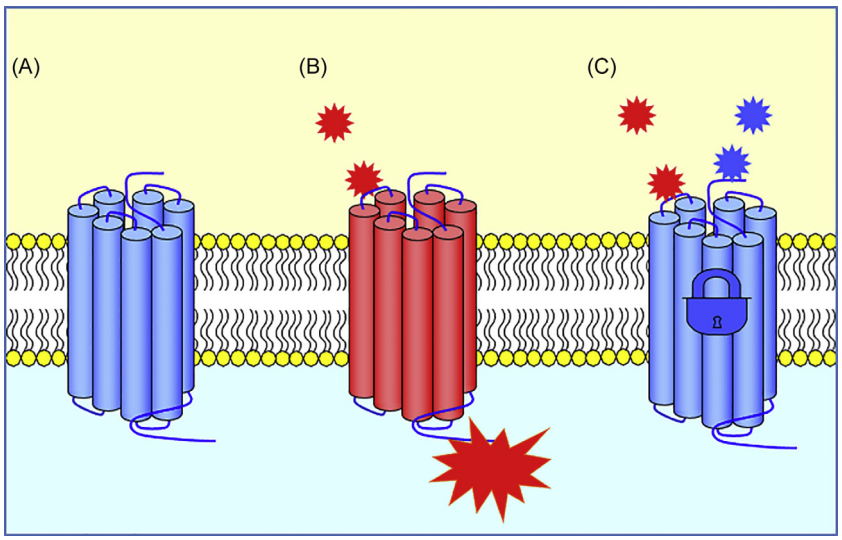

Fig. 1 H_1-antihistamines are inverse agonists not receptor antagonists. (A) unstimulated resting H_1-receptor. (B) Activated H_1-receptor stimulated by histamine (red stars). C H_1-receptor locked in the inactive configuration be an H_1-antihistamine (blue stars) Note that histamine may still bind but cannot stimulate. Data from Leurs R, Church MK, Taglialatela M. (2002) H1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. *Clinical and Experimental Allergy* 32: 489–498.

5.28.3.2 H_1-Antihistamines

There are many efficacious and safe H_1-antihistamines on the market for the treatment of chronic urticaria and allergic rhinitis. It is not the purpose of this chapter to assess and compare individual drugs. However, if readers wish to read the properties of individual drugs, the following reviews are recommended: acrivastine (Bojkowski et al., 1989; Brogden and McTavish, 1991; Gibson et al., 1989), bilastine (Jauregui et al., 2013; Church and Labeaga, 2017; Church, 2011), cetirizine (Spencer et al., 1993; Curran et al., 2004; Broide, 1995), desloratadine (Yuan et al., 2017; Ring et al., 2001; Bachert and Maurer, 2010), ebastine (Van Cauwenberge et al., 2004; Sastre, 2008), fexofenadine (Simpson and Jarvis, 2000; Kawashima et al., 2002), levocetirizine (Singh-Franco et al., 2009; Nettis et al., 2008; Kapp and Wedi, 2004; Ducharme and Weinberg, 2009), loratadine (Monroe, 1996), mizolastine (Lebrun-Vignes et al., 2001; Simons, 1999c), rupatadine (Nettis et al., 2013; Mullol et al., 2008; Metz and Maurer, 2011; Gonzalez-Nunez et al., 2016).

5.28.4 Preclinical pharmacology

5.28.4.1 Efficacy

The efficacy of an H_1-antihistamine is determined by 2 factors: the affinity of the drug for H_1-receptors (absolute potency) and the concentration of the drug at the sites of the H_1-receptors.

The affinity of an H_1-antihistamine for H_1-receptors is determined in preclinical *in vitro* studies. Unfortunately, different methods and target tissues yield differing results so only data from single studies can be compared. In one study using cloned human histamine H_1-receptors, the binding affinities (Ki) in order of potency were; desloratadine 0.4 nM, levocetirizine 2 nM, terfenadine 2 nM, cetirizine 6 nM, fexofenadine10 nM, and loratadine16 nM (Gillard et al., 2003). In human H_1-receptors cloned in Chinese hamster ovary cells the affinities were: desloratadine 0.87 nM, chlorpheniramine 2 nM, hydroxyzine 10 nM, terfenadine 40 nM, cetirizine 47 nM, loratadine 138 nM, and fexofenadine 175 nM, (Limon and Kockler, 2003). Finally, in guinea-pig cerebellum, binding affinities were: fexofenadine 6.62 nM, cetirizine 6.85 nM, bilastine 7.37 nM, and ketotifen 9.34 nM (Corcostegui et al., 2005). Although these are often considered to be fixed values, they may be influenced by temperature and pH, and therefore, they can differ in physiological and pathological conditions. For example, in inflammation the pH of the tissues is reduced (Hunt et al., 2000) from 7.4 to 5.8, leading to a 2- to 5-fold increase in the affinity of fexofenadine and levocetirizine for H_1-receptors but no change in the affinity of desloratadine (Gillard and Chatelain, 2006).

In addition to receptor affinity, the concentration of the drug at H_1-receptors *in vivo* is also crucially important. H_1-receptors are situated on the cellular membranes of cells, including vascular and airways smooth muscle, mucous glands, and sensory nerves, all of which are surrounded by extracellular fluid. Many factors affect the concentration of free drug in this compartment, absorption, volume of distribution and plasma protein binding being of prime importance.

Most H_1-antihistamines are absorbed passively into the blood from the intestine, the exceptions being bilastine and fexofenadine as will be described later. Peak plasma levels of passively absorbed drugs occur at around 2–4 h (Geha and Meltzer, 2001; Simons, 2004). Bilastine, and to a lesser extent fexofenadine, have a more rapid uptake as they are substrates for an organic anion

transporting polypeptide, OATP1A2 (**Fig. 2**) (Shimizu et al., 2005; Lucero et al., 2012; Church and Labeaga, 2017; Cvetkovic et al., 1999; Russell et al., 1998; Tannergren et al., 2003). The role of this transporter is supported by its inhibition by grapefruit juice (Dresser et al., 2005; Crean et al., 2007; Akamine et al., 2015). The mean oral bioavailability of bilastine has been estimated to be around 61% in healthy human volunteers (Lucero et al., 2012), while that of fexofenadine is 30% (Lappin et al., 2010), showing that the affinity for anion pump is stronger with bilastine.

Second is the extent of plasma protein binding which, with H_1-antihistamines, is high, varying from 98% for mizolastine (Simons, 1999c), 96% for cetirizine (Chen, 2008), 90% for levocetirizine (Gillard et al., 2005), 84–90% for bilastine (Church, 2011; Jauregizar et al., 2009), 65% for desloratadine (Gillard et al., 2005) and 60–70% for fexofenadine (Molimard et al., 2004).

Third, and probably most influential, is the apparent volume of distribution, which determines the plasma concentration of a drug after complete body distribution. The apparent volume of distribution is limited for levocetirizine (0.4 L/kg), larger for bilastine (1.29 L/kg) (Church, 2011, Jauregizar et al., 2009) and fexofenadine (5.4–5.8 L/kg) and particularly large for desloratadine (~49 L/kg) (Molimard et al., 2004). The large apparent volume of distribution of desloratadine is primarily due to its extensive intracellular uptake. In the study of Gillard and colleagues (Gillard et al., 2005), the 4-hour plasma concentrations of levocetirizine, desloratadine, and fexofenadine were 28, 1, and 174 nM, respectively.

Because data on the concentrations of H_1-antihistamines in relevant extracellular fluids is generally lacking, the best indirect estimate of efficacy is obtained by calculating receptor occupancy from knowledge of absolute potency and peak drug concentrations in the plasma, usually at ~4 h after a single oral dose (Gillard et al., 2005). This calculation of receptor occupancy after single oral doses of drug shows values of 95%, 90%, and 71% for fexofenadine, levocetirizine, and desloratadine, respectively, indicating that they are all very effective H_1-antihistamines. Receptor occupancy for these drugs appears to correlate with pharmacodynamic activity in skin wheal and flare studies and with efficacy in allergen challenge chamber studies (Gillman et al., 2009; Popov et al., 2006), but is it relevant in clinical practice? Studies in allergic rhinitis suggest that the above 3 drugs are of similar effectiveness (Bachert, 2009; Berger et al., 2006). However, in chronic urticaria, in which local histamine concentrations are high, the differences do seem to be important. For example, in head to head studies in this condition levocetirizine appears significantly more effective than desloratadine (Potter et al., 2009; Staevska et al., 2010).

5.28.4.2 Speed of onset of action

The speed of onset of action of a drug is often equated to the rate of its oral absorption and its duration of action by its plasma concentration. However, this is not strictly correct as the time for a drug to diffuse into the extravascular space to produce a maximal clinical effect is critical. This is seen in **Fig. 3**, which shows the inhibition of the histamine-induced flare response plotted against the concentration of free drug in the plasma. In this study in children (Simons et al., 2007), plasma concentrations of drug were near maximum by 30 min and yet it took an additional 1.5 h for the drug to diffuse into the extravascular space to produce a maximal

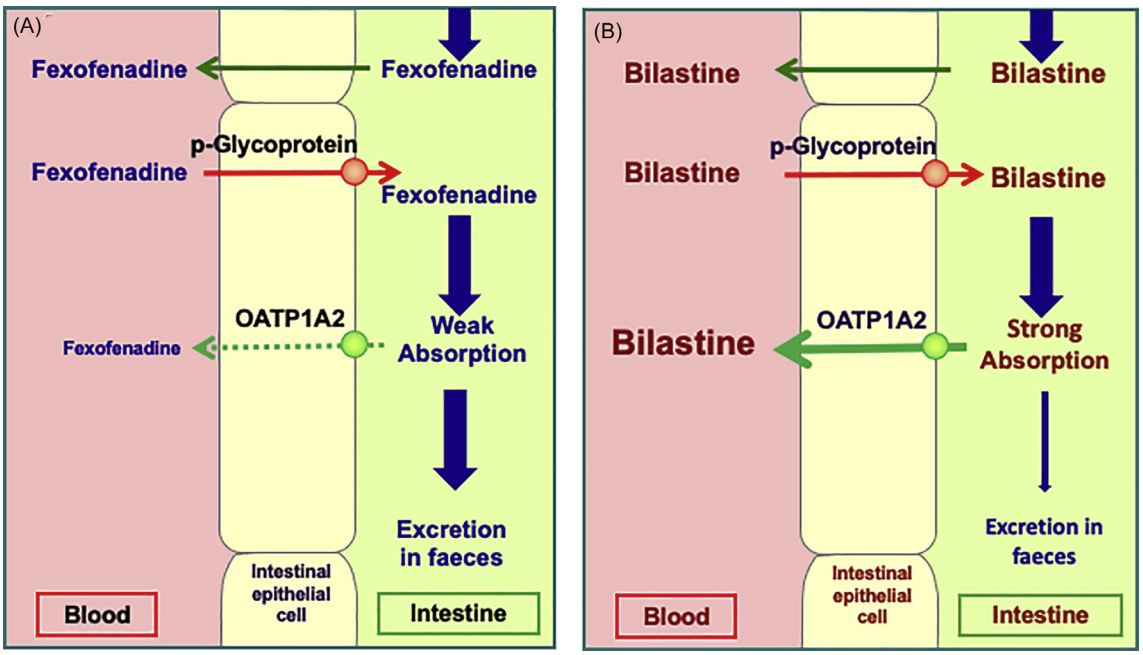

Fig. 2 The roles in of p-glycoprotein in causing active excretion of A fexofenadine and B bilastine from the blood into the intestine and of OATP1A2 in causing their reuptake from the intestine into the blood (Cvetkovic et al., 1999). Reproduced from Church MK and Labeaga L (2017) Bilastine: A new H1-antihistamine with an optimal profile for updosing in urticaria. *Journal of the European Academy of Dermatology and Venereology* 31: 1447–1452.

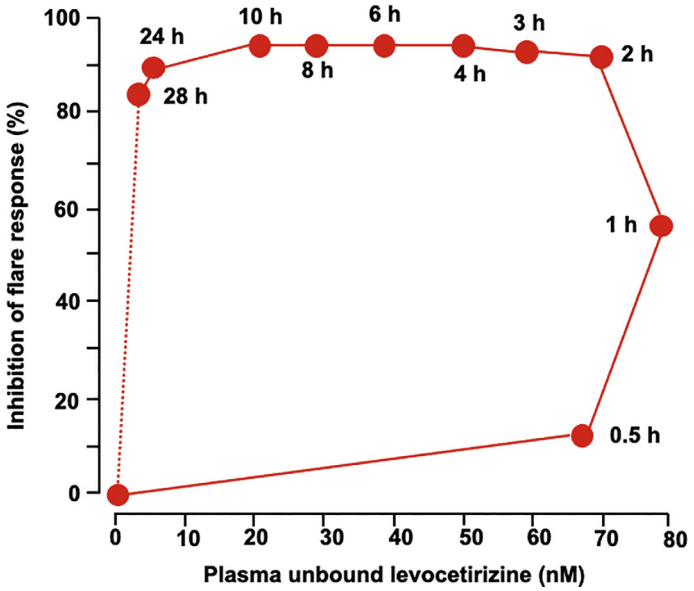

Fig. 3 Hysteresis loop of the inhibition of the histamine-induced flare response plotted against the plasma concentration of unbound levocetirizine after administration of a single 5-mg dose to children. Redrawn from Simons KJ, Benedetti MS, Simons FE, Gillard M, and Baltes E (2007). Relevance of H1-receptor occupancy to H1-antihistamine dosing in children. *The Journal of Allergy and Clinical Immunology* 119: 1551–1554.

clinical effect. In adults, the maximal inhibition of the flare response is usually ~4 h for levocetirizine, fexofenadine, and desloratadine (Grant et al., 2002; Purohit et al., 2003, 2004), but may be longer for drugs, such as loratadine and ebastine, which require metabolism to produce their active moiety (Grant et al., 2002). As mentioned earlier, the absorption of bilastine is facilitated by an organic anion transporting polypeptide. As a consequence, bilastine is more rapidly absorbed than passively absorbed drugs (Church, 2011; Church and Labeaga, 2017). An example of the rates of onset of bilastine and levocetirizine is shown in Fig. 4.

5.28.4.3 Duration of action

The duration of action of H_1-antihistamines is not related to their plasma concentration. This is shown clearly in Fig. 3 in which the duration of action of levocetirizine in inhibiting the histamine-induced flare response is much longer than would be predicted from its plasma concentration (Simons et al., 2007). This is presumably due to "trapping" of the drug by its strong and long-lasting binding to histamine H_1-receptors (Gillard et al., 2002). Although less active in the wheal and flare test, desloratadine has a similarly

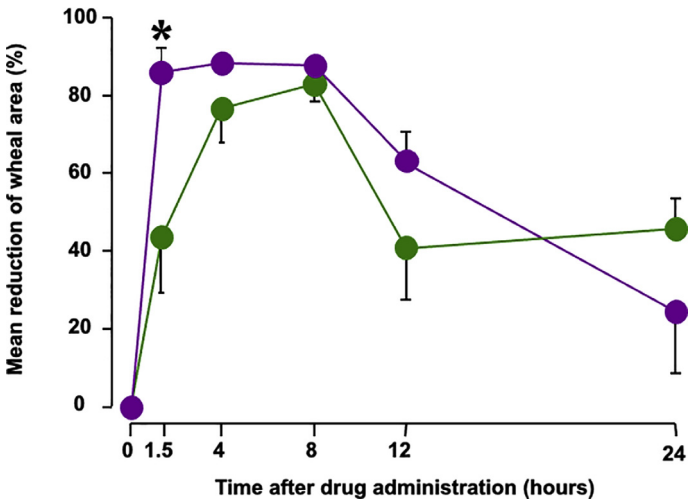

Fig. 4 Inhibition of histamine-induced wheal responses by bilastine 20 mg (purple circles) and cetirizine 10 mg (green circles). *Indicates significance ($P < 0.02$) of difference between bilastine and cetirizine at 1.5 h. Each point is the mean ± SEM of measurements in 12 healthy volunteers. Reproduced from Church MK and Labeaga L (2017) Bilastine: A new H1-antihistamine with an optimal profile for updosing in urticaria. *Journal of the European Academy of Dermatology and Venereology* 31: 1447–1452.

long duration of action (Purohit et al., 2003). However, the duration of action of fexofenadine, calculated in the study of Purohit et al. (2001) as the time for the wheal to be inhibited by at least 70%, is less prolonged, being 8.5 h for 120 mg fexofenadine compared with 19 h for cetirizine. The primary reason for the shorter duration of action of fexofenadine is that it is actively secreted into the intestine and urine by p-glycoprotein (Miura and Uno, 2010). Interestingly, the duration of action of bilastine, which is also a substrate for p-glycoprotein, is much longer because of its active uptake by OATP1A2 (Church and Labeaga, 2017) and because bilastine has an especially long residency time on the H1-receptor (Bosma et al., 2018). Even so, the guidelines recommend that sgAHs should be taken daily and regularly for the treatment of patients with chronic urticaria in order to obtain maximum efficacy (Zuberbier et al., 2018).

5.28.4.4 Elimination

The metabolism and elimination of H_1-antihistamines have been extensively reviewed elsewhere (Molimard et al., 2004; Devillier et al., 2008; Church and Labeaga, 2017). Cetirizine and levocetirizine are not metabolized and are excreted primarily unchanged in the urine (Molimard et al., 2004). Desloratadine undergoes extensive metabolism in the liver. Although this gives the potential for drug-drug interactions, no significant interactions have been reported (Devillier et al., 2008). Fexofenadine, which is also minimally metabolized, is excreted primarily in the feces after its active secretion into the intestine under the influence of active drug–transporting molecule, p-glycoprotein (Devillier et al., 2008). This gives the potential for interactions with agents such as grapefruit juice and St John's Wort, which inhibit these transporters. Although plasma concentrations of fexofenadine may be increased by these agents, no significant resulting adverse reactions have been reported (Devillier et al., 2008).

5.28.4.5 H_1-Antihistamines and the central nervous system

Perhaps the greatest drawback of fgAHs is their ability to cross blood-brain barrier and interfere with histaminergic transmission. Histamine is an important neuromediator in the human brain, which contains approximately 64,000 histamine-producing neurones, emanating from the tuberomamillary nucleus (Haas and Panula, 2003). Stimulation of H_1-receptors in the CNS increases arousal in the circadian sleep/wake cycle, reinforces learning and memory, and has roles in fluid balance, suppression of feeding, control of body temperature, control of the cardiovascular system and mediation of stress-triggered release of ACTH and β-endorphin from the pituitary gland (Brown et al., 2001). It is not surprising then that fgAHs, such as chlorpheniramine, diphenhydramine, hydroxyzine and ketotifen, which, even when given at licensed doses, occupy more than 50% of brain H_1-receptors, interfere with all of these processes (**Fig. 5**) (Yanai et al., 2011).

Physiologically, the release of histamine during the day causes arousal, whereas its decreased production at night results in a passive reduction of the arousal response. When taken during the day, fgAHs, even at the manufacturers' recommended doses, frequently cause daytime somnolence, sedation, drowsiness, fatigue and impaired concentration and memory (Simons, 2004; Juniper et al., 2005). When taken at night, fgAHs increase the latency to the onset of rapid eye movement (REM) sleep and reduce the duration of REM sleep (**Fig. 6**) (Adam and Oswald, 1986; Boyle et al., 2006; Rojas-Zamorano et al., 2009; Church et al., 2010). The residual effects of poor sleep, including impairment of attention, vigilance, working memory and sensory-motor performance, are still present the next morning (Boyle et al., 2006; Kay et al., 1997). This is especially problematic with drugs with a long half-life, such as chlorpheniramine (21–27 h), hydroxyzine (20–25 h) and promethazine (16–19 h).

In adults, first-generation H_1-antihistamines in doses commonly recommended for the treatment of allergic disorders frequently lead to daytime somnolence, sedation, drowsiness, fatigue and impaired concentration and memory (Simons, 1999a, 1994; Juniper et al., 2005; Church et al., 2010). The incidence of subjectively reported somnolence has been reported to vary from 40% with chlorpheniramine or brompheniramine to 80% after hydroxyzine (Druce et al., 1998). However, lack of drowsiness does not mean that an individual is able to drive a vehicle without impairment because subjective somnolence and impairment of the ability to perform tasks are not necessarily correlated, some individuals denying subjective adverse effects despite objective evidence of impairment, while others complain of somnolence and yet are able to perform psychomotor tests adequately (Warren et al., 1981; Simons et al., 1995).

In children, the detrimental CNS effects of fgAHs on learning and examination performance are again well established (Church et al., 2010). Allergic rhinitis reduces learning ability in children and is associated with poor examination performance in teenagers. This situation is exacerbated by fgAHs (Vuurman et al., 1993, 1996; Scadding, 2008). In an analysis of 1834 teenage students in the UK taking national examinations, those with untreated allergic rhinitis were 40% more likely to drop one or more grades compared with healthy teenagers. However, if they took a fgAH this figure increased to 70% (Walker et al., 2007).

A major advance in antihistamine development occurred in the 1980s with the introduction of sgAHs, including loratadine, desloratadine, cetirizine, levocetirizine, ebastine, rupatadine, azelastine and olopatadine, which have high H_1-receptor selectivity, no anti-cholinergic effects, low brain permeability and longer durations of action (Holgate et al., 2003). Unlike fgAHs, sgAHs are amphiphilic in that hydrophilic groups have been introduced into the molecule so that they are always positively or negatively charged and, therefore, have a greatly reduced passage across the blood brain barrier occupying less than 20% of brain H_1-receptors (**Fig. 5**) (Yanai et al., 2011; Hiraoka et al., 2015). Although sgAHs have a much-reduced brain penetration, they may only be referred to as 'minimally sedating' rather than 'non-sedating.' For example, in a study of patients' perspective of effectiveness and side effects of H_1-antihistamine up-dosing in chronic spontaneous urticaria, more than 20% of patients reported sedation as a side effect of sgAHs (Church et al., 2011).

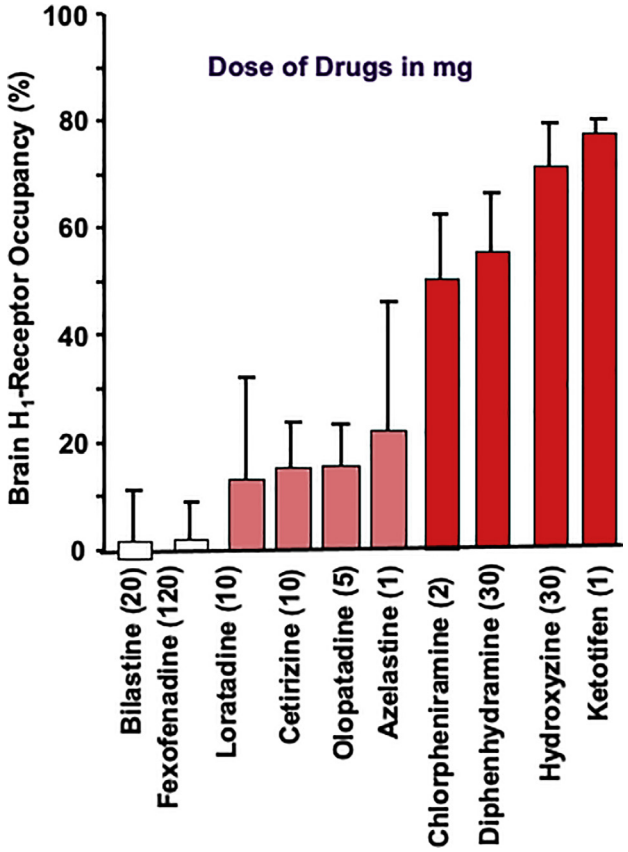

Fig. 5 Percentage occupancy brain H_1-receptors by H_1- antihistamines. First generation agents are colored red, second generation drugs are light red and substrates of p-glycoprotein are white. Data from Yanai K, Zhang D, Tashiro M, Yoshikawa T, Naganuma F, Harada R, Nakamura T, Shibuya K, and Okamura N (2011) Positron emission tomography evaluation of sedative properties of antihistamines. *Expert Opinion on Drug Safety* 10: 613–622 and Farre M, Perez-Mana C, Papaseit E, Menoyo E, Perez M, Martin S, Bullich S, Rojas S, Herance JR, Trampal C, Labeaga L, and Valiente R (2014) Bilastine vs. hydroxyzine: occupation of brain histamine H1-receptors evaluated by positron emission tomography in healthy volunteers. *British Journal of Clinical Pharmacology* 78: 970–980.

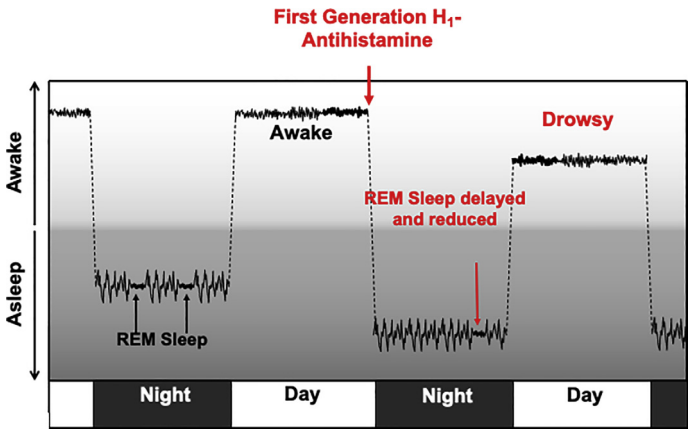

Fig. 6 A theoretical diagram of the sleep/wake cycle and the effects of a first-generation H_1-antihistamine leading to somnolence during the day and abnormal sleep at night. This diagram is reproduced from Church MK, Maurer M, Simons FE, Bindslev-Jensen C, Van Cauwenberge P, Bousquet J, Holgate ST, Zuberbier T, Global A, and Asthma European, N. (2010) Risk of first-generation H(1)-antihistamines: A GA(2)LEN position paper. *Allergy* 65: 459–466.

More recently, studies have suggested hydrophilicity alone is not sufficient to keep drugs from entering the brain but that an active efflux transporter in the blood–brain barrier may be involved. The most extensively studied of the active efflux proteins is P-glycoprotein (P-gp), which is known to efflux a wide variety of structurally dissimilar drugs (Chen et al., 2003; Seelig and Landwojtowicz, 2000). *In vitro*, studies of P-gp-mediated efflux from caco-2 cells has shown cetirizine, desloratadine and hydroxyzine to

have weak but significant efflux ratios while that of fexofenadine was much greater (Crowe and Wright, 2012). More recently, similar studies have shown that bilastine also has a high efflux ratio (Burton et al., 2007; Church, 2011). The failure of bilastine and fexofenadine to enter the brain and occupy histamine H_1-receptors has been confirmed using positron emission tomography (Farre et al., 2014). Thus, these two drugs appear to be truly 'non-sedating' H_1-antihistamines, and the most likely reason for their lack of brain penetration is that they are actively pumped out of the blood–brain barrier by P-gp (**Figs. 5 and 7**) (Maurer et al., 2011; Chen et al., 2003; Schinkel, 1999; Montoro et al., 2011; Church, 2011).

5.28.4.6 H_1-Antihistamines and cardiotoxicity

The effect of H_1-antihistamines in causing cardiotoxicity has been reviewed in detail recently (Cataldi et al., 2019).

The introduction of the sgAHs in the late 1970s and 1980s brought new and unexpected problems, with an increasing number of reports showing an association between the consumption of astemizole and terfenadine and cardiotoxicity. Both of these are essentially pro-drugs that are metabolized by the cytochrome P450 enzyme, CYP3A4, to their active antihistaminic form. However, it was soon realized that if this metabolism was blocked by the concomitant use of inhibitors of CYP3A4, such as ketoconazole, itraconazole and macrolide antibiotics, or by grapefruit juice, which causes post-translational down-regulation of CYP3A4, then this could cause the prolongation of the QT interval, leading to the appearance of polymorphic ventricular arrhythmias, syncope and even cardiac arrest in susceptible individuals (Leurs et al., 2002).

The mechanism most frequently involved in cardiotoxicity induced by sgAHs is the blockade of hERG (Kv11.1) voltage-gated K+ channels; these channels contribute to cardiac repolarization by carrying the I_{Kr} current and, therefore, their blockade causes QT prolongation and ultimately torsade de pointes (Roy et al., 1996; Soldovieri et al., 2008; Taglialatela et al., 1998, 1999, 2000; Suessbrich et al., 1996).

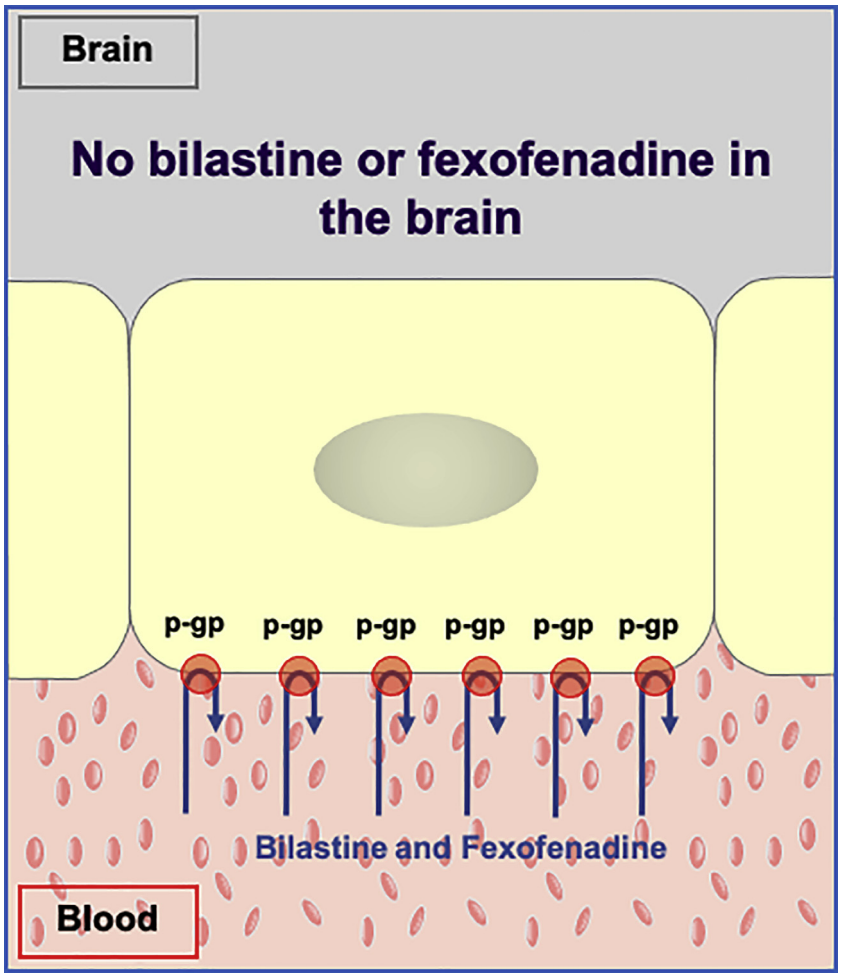

Fig. 7 Diagrammatic representation of the role of p-glycoprotein preventing bilastine and fexofenadine crossing the blood-brain into the brain. Data from Lucero ML, Gonzalo A, Ganza A, Leal N, Soengas I, Ioja E, Gedey S, Jahic M, and Bednarczyk D (2012) Interactions of bilastine, a new oral H(1) antihistamine, with human transporter systems. *Drug and Chemical Toxicology* 35: Supplement 1: 8–17.

Looking at individual H_1-antihistamines, astemizole and terfenadine are no longer approved for use by regulatory agencies in most countries. However, some fgAHs, such as promethazine (Jo et al., 2009), brompheniramine (Park et al., 2008) and chlorpheniramine (Hong and Jo, 2009), may also be associated with a prolonged QTc and cardiac arrhythmias when taken in large doses or overdosed. Today, the concentration of a drug required to produce a half-maximal block of the hERG potassium current (IC_{50}) is used as a surrogate marker for pro-arrhythmic properties of compounds and is the primary test for cardiac safety of drugs (Polak et al., 2009). No clinically significant cardiac effects have been reported for the sgAHs fexofenadine, the metabolite of terfenadine, desloratadine, loratadine, cetirizine, levocetirizine, azelastine, ebastine, mizolastine, rupatadine and bilastine (Ten Eick et al., 2001; DuBuske, 1999; Simons et al., 2003; Hulhoven et al., 2007; Izquierdo et al., 2003; Maurer et al., 2011).

5.28.5 Clinical effectiveness of H_1-antihistamines

5.28.5.1 Speed of onset of action and duration of action

The speed of onset of action of a drug is often equated to the rate of its oral absorption and its duration of action by its plasma concentration at different times. However, this is not strictly correct for drugs which have to diffuse into the extravascular space to produce their maximal clinical effect. In adults, the maximal inhibition of the flare response is usually ~4 h for levocetirizine, fexofenadine and desloratadine (Grant et al., 2002; Denham et al., 2003; Purohit et al., 2004) but may be longer for drugs, such as loratadine and ebastine, which require metabolism to produce their active moiety (Purohit et al., 2004). In contrast, a recent wheal and flare study has suggested that bilastine may have a more rapid onset of action because of its facilitated uptake from the duodenum (Church and Labeaga, 2017).

The duration of action of H_1-antihistamines is also much longer than would be predicted from their plasma concentration and for most is in the vicinity of 24 h (Purohit et al., 2003; Church and Labeaga, 2017). This is presumably due to 'trapping' of the drug by its strong and long lasting binding to histamine H_1-receptors (Gillard et al., 2002). This may be especially so for bilastine, which has an especially long residency time on the H_1-receptor (Bosma et al., 2018). Because it is actively secreted into the bile, intestine and urine by P-glycoprotein (Miura and Uno, 2010), the duration of action of fexofenadine is shorter, around $8^1/_2$ h (Purohit et al., 2001), indicating that it may be best given twice daily. In contrast, bilastine, which is also a substrate for p-glycoprotein, has a duration of action of around 24 h. The reason for this difference is that bilastine is also a substrate for OATP1A, an intestinal pump that facilitates its uptake into the bloodstream (Church and Labeaga, 2017; Lucero et al., 2012). Even so, the guidelines recommend that sgAHs should be taken regularly for the treatment of patients with chronic urticaria in order to obtain maximum efficacy (Zuberbier et al., 2018).

5.28.5.2 Efficacy

A question that is asked repeatedly is how the dose of an antihistamine is determined. The answer is that it is a balance between the effectiveness and the unwanted or side effects of a drug. For fgAHs, it is the degree of somnolence they cause that limits the amount of drug that may be given. With most sgAHs, their ability to penetrate the CNS to cause sedation is also a limiting factor. Drugs such as cetirizine, rupatadine and desloratadine may be minimally sedating at licensed doses, but updosing may cause sedation in susceptible patients. Possible exceptions to this rule are fexofenadine and bilastine which, because they are p-glycoprotein substrates and do not penetrate the CNS, may be updosed without fear of somnolence (Church and Labeaga, 2017; Maurer et al., 2011; Krause et al., 2013).

5.28.5.3 Anti-inflammatory effects of H_1-antihistamines

The early studies of the anti-inflammatory effects of H_1-antihistamines were reviewed by Leurs et al. (2002); Church, 1999). However, current appreciation of the anti-inflammatory mechanisms mediated through the H_1-receptor stems from the observation by Bakker and colleagues (Bakker et al., 2001) that histamine can activate NF-kB, a transcription factor involved in the synthesis of many pro-inflammatory cytokines and adhesion molecules involved in the initiation and maintenance of allergic inflammation. This is supported by the observation that in its treatment of cold-induced urticaria, bilastine reduced the generation of IL-6 and IL-8 (Krause et al., 2013). The clinical implications of this lie in the ability of H_1-antihistamines to reduce nasal congestion and hyper-reactivity (Bachert, 2009), which result from the sensitization of sensory neurons in the nose by allergic inflammation (Grant et al., 2002). However, as nasal congestion is more slowly relieved than other nasal symptoms (Bachert et al., 2004), continuous rather than on demand therapy with antihistamines is required for its treatment (Canonica et al., 2008).

5.28.5.4 H_1-Antihistamines in urticaria

Most types of urticaria, including chronic spontaneous urticaria (CSU) and the majority of inducible urticarias, are mediated primarily by mast cell-derived histamine (Church et al., 2018), which reaches very high concentrations due to the poor diffusibility of substances in the dermis (Petersen et al., 1997; Church et al., 1997). Urticaria is characterized by short-lived wheals ranging from a few millimeters to several centimeters in diameter, which are accompanied by severe itching that is usually worse in the evening or night-time (Maurer et al., 2011).

The latest EAACI/GA^{2}LEN/EDF/WAO guidelines for the management of urticaria (Zuberbier et al., 2018) recommend that the first-line treatment for urticaria should be a 2nd generation, non-sedating H_1-antihistamine. Furthermore, the guidelines state "We recommend aiming at complete symptom control in urticaria, considering as much as possible the safety and the quality of life of each individual patient." Because standard licensed doses of H_1-antihistamines are often ineffective in completely relieving symptoms in many patients (Church et al., 2011), the guidelines state "We suggest updosing sgAHs up to 4-fold in patients with chronic urticaria unresponsive to sgAHs 1-fold" (**Fig. 8**) (Zuberbier et al., 2018). The guidelines also recommend updosing with a single antihistamine rather than using different H_1-antihistamines at the same time. If somnolence is a problem, then either fexofenadine or bilastine should be considered. Thus, it is clear that the attributes that clinicians seek when choosing an H_1-antihistamine, are; a rapid onset of action, good efficacy, a long duration of action and freedom from unwanted effects. While some of these attributes may be predicted from pre-clinical and pharmacokinetic studies, it is only in the clinical environment that they may be definitively established (Church and Maurer, 2012).

For children, many clinicians use sedating fgAHs as their first choice assuming that the safety profile of these drugs is better known than that of the newer sgAHs. However, the guidelines make a strong recommendation to discourage the use of fgAHs in infants and children for the reasons stated above. Thus, in children the same first line treatment and updosing (weight and age adjusted) is recommended as in adults. It should be realized, however, that young children have more body water, as a percentage, than adults. Also, their renal function is fully developed. In contrast, liver enzymes mature more slowly reaching maximum at around 10 years of age. Consequently, in young children, only water-soluble drugs that are excreted renally, such as cetirizine, levocetirizine, fexofenadine and bilastine, should be used.

In elderly patients, fgAHs should also not be used, particularly not in those with dementia as the cumulative use of 1st generation antihistamines with anticholinergic activity is associated with an increased risk for dementia (Gray et al., 2015; Tannenbaum et al., 2012).

5.28.5.5 H_1-Antihistamines in allergic rhinitis

Allergic rhinitis is among the most common diseases globally and usually persists throughout life (Bousquet et al., 2008). The prevalence of self-reported AR has been estimated to be approximately 2% to 25% in children (Asher et al., 2006) and 1% to greater than 40% in adults (Bousquet et al., 2008; Katelaris et al., 2012). The treatment of allergic rhinitis and its impact on asthma (ARIA) guidelines (Brozek et al., 2017) give a comprehensive treatment algorithm.

Clearly, the mast cell histamine-mediated mucus secretion, itching and sneezing are the symptoms that are most sensitive to H_1-antihistamines. H_1-antihistamines are less effective in nasal blockage, which is caused primarily by eosinophil-dominated allergic inflammation, which increases nerve-activated vasodilation in the nose. This symptom is preferentially treated by intranasal corticosteroids (Scadding and Church, 2006).

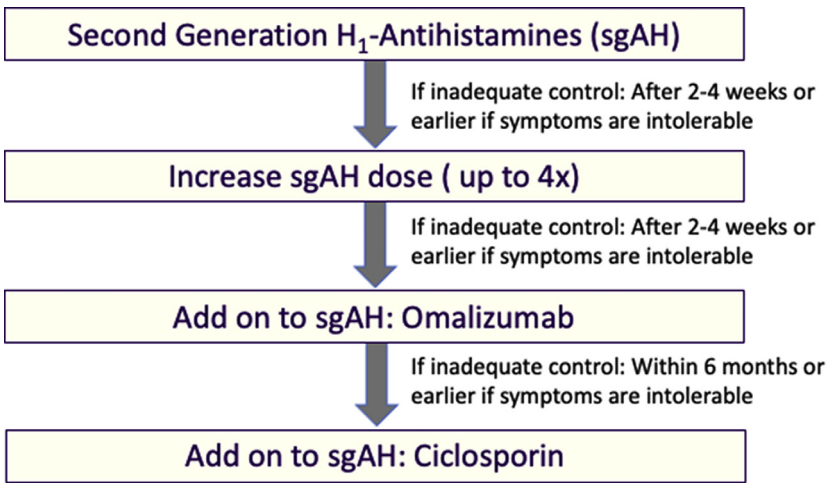

Fig. 8 Recommended treatment algorithm for urticaria from the EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. The 2017 Revision and Update Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, Bernstein JA, Bindslev-Jensen C, Brzoza Z, Buense Bedrikow R, Canonica GW, Church MK, Craig T, Danilycheva IV, Dressler C, Ensina LF, Gimenez-Arnau A, Godse K, Goncalo M, Grattan C, Hebert J, Hide M, Kaplan A, Kapp A, Katelaris CH, Kocaturk E, Kulthanan K, Larenas-Linnemann D, Leslie TA, Magerl M, Mathelier-Fusade P, Meshkova RY, Metz M, Nast A, Nettis E, Oude-Elberink H, Rosumeck S, Saini SS, Sanchez-Borges M, Schmid-Grendelmeier P, Staubach P, Sussman G, Toubi E, Vena GA, Vestergaard C, Wedi B, Werner RN, Zhao Z, and Maurer M (2018) The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy* 73: 1393–1414.

5.28.5.6 H_2-Antihistamines in clinical practice

H_2-antihistamines are widely used for the treatment of acid-peptic disease, including duodenal and gastric ulcers and gastroesophageal reflux disease. H_2-antihistamines bind to H_2 receptors of gastric parietal cells and reduce both stimulated and basal gastric acid production and secretion that is induced by histamine. The first of the four H_2-antihistamines currently used was cimetidine, introduced in the late 1970s, followed by ranitidine, famotidine and nizatidine in the 1980s. All are available for oral use and well-absorbed after oral administration. H_2-antihistamines are generally well-tolerated and side effects are uncommon, but in 2019, several ranitidine products were found to contain the carcinogen N-nitrosodimethylamine (NDMA) with subsequent recalls, suspensions and bans in many countries.

The use of H_2-antihistamines, such as cimetidine and ranitidine, in the treatment of urticaria has been controversial with current evidence not supporting their use (Theoharides, 1989). A detailed review of four studies involving a total of 144 participants concluded that although a measure of relief of symptoms of urticaria and rather minimal clinical improvement in some of the participants, the evidence was weak and unreliable (Fedorowicz et al., 2012). The current EAACI/GA^{2}LEN/EDF/WAO urticaria guideline states that H_2-antagonists and dapsone, recommended in the previous versions of the guideline, are now perceived to have little evidence to maintain them as recommendable in the treatment algorithm (Zuberbier et al., 2018).

In allergic rhinitis there appeared to be a small but statistically significant additive effect of H_2-antihistamines to the clinical response to H_1-antihistamines (Carpenter et al., 1983). H_2-antihistamines are not recommended in the allergic rhinitis guidelines (Brozek et al., 2017).

5.28.5.7 H_3-Antihistamines in clinical practice

H_3-antihistamines, as of now, have not found a place in the treatment of allergic diseases. In an early paper, the addition of an H_3-antihistamine to an H_1-antihistamine in the treatment of urticaria was found to be marginally better than the H_1-antihistamine alone (McLeod et al., 2005). However, this was not followed up.

In allergic rhinitis, the combination of fexofenadine, and PF-03654746 caused a reduction in allergen-induced nasal symptoms. The authors suggested that H_3-receptor antagonism might be a novel therapeutic strategy to further explore in patients with allergic rhinitis (Stokes et al., 2012). In another study, prophylactic treatment with the H_3-antagonist JNJ-39220675 relieved allergen-induced nasal congestion by using standard nasal symptom scoring (Barchuk et al., 2013). H_3-antihistamines are not recommended in either the urticaria or allergic rhinitis guidelines (Brozek et al., 2017; Zuberbier et al., 2018).

5.28.6 H4-Antihistamines in allergic diseases

Several H_4-antihistamines have been developed and some of them are being used in clinical trials for allergic diseases with promising results.

5.28.6.1 JNJ7777120

JNJ7777120 is the first highly selective H_4-antihistamine discovered. It inhibited histamine-induced chemotaxis and calcium influx in mouse bone marrow-derived mast cells, migration of tracheal mast cells from the connective tissue toward the epithelium in mice and neutrophil infiltration in a mouse mast cell-dependent zymosan-induced peritonitis model (Thurmond et al., 2004). JNJ7777120 effects have been extensively evaluated in animal models of allergic skin diseases including atopic dermatitis, contact dermatitis and pruritus.

In a mouse model of atopic dermatitis, treatment with two specific H_4-antihistamines, JNJ7777120 and JNJ28307474, led to a significant reduction in ear edema, inflammation, mast cell and eosinophil infiltration as well as reduction in the levels of several cytokines and chemokines in the ear tissue. Moreover, H_4-antihistamines suppressed lymphocyte proliferation and IL-4, IL-5, and IL-17 levels (Cowden et al., 2010). JNJ7777120 significantly inhibited the production of TH2 chemokines CCL17 and CCL22 in the human monocyte-derived langerhans cells from patients with atopic dermatitis and in antigen-stimulated BMMC (Miyano et al., 2016; Ohsawa and Hirasawa, 2012). NK cell chemotaxis was decreased with JNJ7777120 (Ehling et al., 2016). In another study, combined use of the H_1-antihistamine, cetirizine, and JNJ7777120 decreased serum IgE and levels of IL-4, IL-5 and IL-6 in eczematous lesions (Matsushita et al., 2012).

In addition to its anti-inflammatory effects, JNJ7777120 also significantly inhibited the pruritus in mice, alone (Cowden et al., 2010; Suwa et al., 2011) or in combination with the H_1-antihistamines olopatadine (Ohsawa and Hirasawa, 2012) or cetirizine (Rossbach et al., 2009). In an experimental model of pruritic dermatitis in mice, JNJ7777120 (10 and 30 mg/kg) reduced scratching behavior and ameliorated the skin lesions in a dose-dependent manner and decreased serum IgE levels and numbers of mast cells in skin lesions (Suwa et al., 2011).

JNJ7777120 was effective in chronic allergic contact dermatitis induced by repeated challenge in mice. It suppressed migration of mast cells and eosinophils in skin lesions, decreased serum IgE, IL-4, IL-5 and IL-6 levels and increased levels of interferon-gamma and IL-12 (Seike et al., 2010). JNJ7777120 inhibited extracellular signal-regulated kinase (ERK) activation and spontaneous itching behavior that suggests persistent ERK activation via the H_4R in spinal neurons associated with chronic itch (Huang et al., 2018). In

a mouse model, JNJ7777120 significantly reduced both histamine- and substance P-induced scratching (Yamaura et al., 2009). Pruritus induced by intradermal injection of antigen-specific IgE and antigen stimulation systemically 24 h later was also potently inhibited with JNJ7777120 in H_4R knockout mice (Dunford et al., 2007). Interestingly, the inhibitory effect of JNJ7777120 was greater than those observed with histamine H_1-antihistamines.

Several experimental studies reported the effects of JNJ7777120 in animal models of allergic rhinitis, asthma or peanut allergy.

In an ovalbumin-induced allergic rhinitis rat model, JNJ7777120 significantly improved nasal symptoms, decreased serum levels of IgE, IL-4 and eotaxin in nasal lavage fluid, and increased serum levels of IFN-γ compared with the allergic rhinitis group with no treatment. However, the effect was weak compared with loratadine (Yan et al., 2010). Furthermore, JNJ7777120 dose-dependently inhibited nasal symptoms by single and repeated intranasal and oral administrations in allergic rhinitis in mice. However, the compound decreased serum levels of IgE only by oral administration (Takahashi et al., 2009). JNJ7777120 significantly suppressed nasal symptoms and cough in ovalbumin induced allergic rhinitis which was studied in guinea pigs (Kovacova-Hanuskova et al., 2015).

In ovalbumin-sensitized guinea pigs, JNJ7777120 dose-dependently increased levels of LC-1, reduced allergic asthmatic responses and airway inflammation and lowered levels of PGD2, LTB4 and TNF-α in BAL fluid (Somma et al., 2013). In a mouse model of peanut allergy, combined blockade of H1R (loratadine) and H_4R (JNJ7777120) prevented the development of diarrhea and intestinal inflammation. In addition, the combination of both drugs suppressed dendritic cell functions including antigen-presenting, calcium mobilization and chemotaxis to histamine *in vitro* (Wang et al., 2016). Finally, JNJ7777120 exerted anti-inflammatory and anti-fibrotic effects in an inflammatory mice model of lung fibrosis (Durante et al., 2019).

In summary, JNJ7777120 has been used as the reference tool for studying the functional activity of H_4R in *in vitro* and *in vivo* studies. However, it is considered far from being an ideal antihistamine because of its short *in vivo* half-life and, as reported by Thurmond et al., adrenal toxicity in rats and dogs that prevented its use in clinical studies (Nicoud et al., 2019; Thurmond et al., 2017).

5.28.6.2 JNJ39758979

Another H_4-antihistamine, JNJ39758979, showed a good safety profile in preclinical toxicity studies in rats and monkeys as well as in a phase 1 human volunteer study. After a single oral dose, JNJ39758979 demonstrated a plasma half-life of 124–157 h and dose-dependent inhibition of histamine-induced eosinophil shape change (Thurmond et al., 2014).

In a mouse ovalbumin-induced atopic dermatitis model, mice were treated with the H1R inverse agonist mepyramine, JNJ39758979 or a combination of both. H_1- and H_4-antihistamines provide synergistic anti-inflammatory effects showing decreased scratching behavior, severity of skin lesions, influx of inflammatory cells, reduced epidermal thickening and low levels of IL-33 in lesional skin. Importantly, drugs given alone did not show this strong anti-inflammatory effect (Köchling et al., 2017).

The safety and efficacy of JNJ39758979 on histamine-induced pruritus in healthy subjects were tested in a randomized clinical trial (RCT) (NCT01068223). Volunteers received a single oral dose of 600 mg JNJ 39758979, 10 mg cetirizine, or placebo. Compared with cetirizine, JNJ 39758979 reduced the AUC of pruritus score but did not demonstrate a significant decrease in wheal or flare. Headache and nausea were reported in some patients (Kollmeier et al., 2014).

A phase 2a RCT of an H_4-antihistamine (JNJ39758979) was carried out in Japanese adults with moderate atopic dermatitis (NCT01497119). Patients were randomized to 300 mg, 100 mg of drug or placebo once daily for 6 weeks. Although the study did not meet the primary end-point, improvements in median EASI were observed with 100 mg and 300 mg versus placebo at week 6. Importantly, two patients (both receiving JNJ39758979 300 mg) showed neutropenia that led to premature study discontinuation (Murata et al., 2015).

The efficacy of JNJ 39758979 has been investigated in adults with persistent asthma but no results have not been reported (NCT00946569).

5.28.6.3 Other H_4-antihistamines

Pre-treatment with compounds A and L markedly reduced the H_4R -mediated intracellular calcium release, phosphorylation of ERK1/2, Akt and NF-κB, and Th2 cytokine IL-13 production in human mastocytoma cells-1 (Nagarajan et al., 2017). In an allergic asthma model, compound A pre-treatment (10, 20, 30 mg/kg) led to significant reduction of IgE and Th2 cytokines in BAL fluid, level of inflammatory infiltrates and signaling molecules such as ERK1/2, Akt, SAPK/JNK and NF-κB in lung tissue (Nagarajan and Thangam, 2020).

ZPL-3893787, formerly PF-3893787, is a selective oral H_4-antihistamine, was used daily (30 mg) in adult patients with moderate-to-severe atopic dermatitis in a randomized, double-blind, placebo-controlled, parallel-group study. ZPL-3893787 was well tolerated and showed significant improvement in atopic dermatitis scores (EASI, IGA, SCORAD) compared with placebo group (NCT02424253) (Werfel et al., 2019). Other RCTs in atopic dermatitis patients are ongoing (NCT03517566, NCT03948334).

Effects of several structurally related H_4R ligands of the aminopyrimidine class were evaluated on croton oil-induced ear edema and pruritus in mice. ST-994 and ST-1012 (30 and 100 mg/kg) significantly reduced ear edema. Additionally, ST-994 decreased the inflammatory severity score and in the number of eosinophils in inflamed ear tissue (Adami et al., 2018).

INCB38579 is a pyrimidine-based small molecule antihistamine of the human and rodent H_4R. INCB38579 has good pharmacokinetic properties in rats and mice and showed 80-fold selectivity over the human H_1-H_3R. In *in vitro* experiments, INCB38579 had similar potencies as JNJ7777120 inhibiting histamine-evoked migration of human eosinophils and human and mouse dendritic cells, as well as the shape change of human eosinophils. Furthermore, INCB38579 100 mg/kg were given orally to

CD-1 mice before injection of histamine. INCB38579 and JNJ7777120 significantly reduced the number of scratching bouts. In addition, INCB38579 and JNJ7777120 were able to inhibit carrageenan-induced mechanical hyperalgesia in rats and formalin-induced pain in rats and mice (Shin et al., 2012).

Neumann et al. analyzed the effects of subcutaneous injection of JNJ7777120 in comparison to that of the H_3/H_4-antihistamine thioperamide in a murine asthma model. Thioperamide showed better pharmacokinetics, higher t1/2 values and maximal concentration in lung tissue, but weaker beneficial effects as compared to JNJ7777120. Thioperamide reduced only eosinophilia in bronchoalveolar lavage fluid, while JNJ7777120 was in addition able to decrease serum levels of allergen-specific IgE and inflammatory infiltrations in lung tissue (Neumann et al., 2013).

Efficacy and safety of toreforant (JNJ38518168), an oral selective H_4-antihistamine, was evaluated in 162 patients with uncontrolled, eosinophilic asthma in a phase 2a multicenter randomized controlled trial (NCT01823016). Toreforant was well tolerated but failed to provide therapeutic benefit in this population of patients (Kollmeier et al., 2018).

A940894 is another selective H_4R antagonist that binds to both human and rat H_4R. A940894 showed good half-life and oral bioavailability in rats and mice. *In vitro*, it potently blocked histamine-induced calcium mobilization and shape change of mouse bone marrow-derived mast cells and chemotaxis of human eosinophils. In a mouse mast cell-dependent model of zymosan-induced peritonitis, A940894 markedly suppressed neutrophil influx and decreased intraperitoneal prostaglandin D2 levels (Strakhova et al., 2009).

Effects of VUF6002 (JNJ10191584) were evaluated in the rat model of carrageenan-induced inflammation and thermal hyperalgesia. VUF6002 (10 mg/kg, subcutaneously as well as JNJ7777120 (10 and 30 mg/kg, subcutaneously were able to significantly reduced paw edema and hyperalgesia (Coruzzi et al., 2007).

UR-63325, a selective H_4-antihistamine, inhibited degranulation of bone marrow-derived mast cells (Mirzahosseini et al., 2013) and histamine-induced eosinophil chemotaxis *in vitro*, and 4-methyl-histamine-induced pruritus in rat (Salcedo et al., 2013). It is also demonstrated efficacy in several asthma models in rodents (Salcedo et al., 2013). In healthy volunteers, UR-63325 showed a lineal pharmacokinetic profile suitable for once daily dosing, good safety, and pharmacodynamic results indicating that full H_4R blockage was achieved with single doses up to 100 mg. (Salcedo et al., 2013) Efficacy of UR-63325 was evaluated in a RCT, which included patients with allergic rhinitis, but no results have been published (NCT01260753).

Orally administered compound 48 exhibited strong antipruritic and anti-inflammation activity in several mouse models of atopic dermatitis (Ko et al., 2018).

Several other potent H_4-antihistamines have been reported including A987306 (Liu et al., 2008), A943931 (Zhang et al., 2019), SENS-111 (Petremann et al., 2020) and TR-7 (Popiolek-Barczyk et al., 2018).

5.28.6.4 H_4-Antihistamines in other diseases

Apart from allergic diseases, some H_4-antihistamines showed beneficial effects in other disorders. For example, in a mice model of autism, JNJ7777120 treatment with irradiation exposure increased social interactions in BTBR mice blocking inflammatory cytokine production and transcription factor signaling compared to that in irradiation-exposed BTBR mice (Ahmad et al., 2019). JNJ7777120 was effective in cisplatin-induced anorexia (Yamamoto et al., 2019) and had protective properties in rat models of Parkinson-like pathology, transient cerebral ischemia and age-related macular degeneration (Zhou et al., 2019; Kaneko et al., 2014; Dettori et al., 2018). JNJ39758979 might be a promising medication for diabetic nephropathy (Pini et al., 2018). Toreforant has been administered with limited efficacy in patients with rheumatoid arthritis and psoriasis (Frankel et al., 2018; Boyle et al., 2019). SENS-111, a novel selective oral H_4-antihistamine, improved vertigo symptoms in a translational *in vivo* model of unilateral vestibular loss (Petremann et al., 2020; Venail et al., 2018).

5.28.7 Conclusion

In conclusion, H_1, H_2 and H_3-antihistamines are well established in widespread clinical diseases. In contrast H_4-antihistamines are in the dawn of their development but have a very promising future.

Disclosure of Potential Conflict of Interest

Martin Church: speaker or consultant for Almirall, FAES Pharma, Menarini, Moxie, MSD, Novartis, UCB Pharma, Sanofi-Aventis and Uriach.
Stefan Frischbutter: no conflicts of interest regarding any aspects of this study.
Pavel Kolkhir: personal fees from Novartis and Roche, outside the submitted work.
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See Also: 5.29. Chronic Urticaria

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