Efficacy and Safety of Non-brain Penetrating H_1-Antihistamines for the Treatment of Allergic Diseases

Kazuhiko Yanai, Takeo Yoshikawa, and Martin K. Church

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Abstract H_1 receptor antagonists, known as H_1-antihistamines (AHs), inactivate the histamine H_1-receptor thereby preventing histamine causing the primary symptoms of allergic diseases, such as atopic dermatitis, pollinosis, food allergies, and urticaria. AHs, which are classified into first-generation (fgAHs) and second-generation (sgAHs) antihistamines, are the first line of treatment for allergic diseases. Although fgAHs are effective, they cause adverse reactions such as potent sedating effects, including drowsiness, lassitude, and cognitive impairment; anticholinergic effects, including thirst and tachycardia. Consequently, the use of fgAHs is

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not recommended for allergic diseases. Today, sgAHs, which are minimally sedating and, therefore, may be used at more effective doses, are the first-line treatment for alleviating the symptoms of allergic diseases. Pharmacologically, the use of sedating fgAHs is limited to antiemetics, anti-motion sickness drugs, and antivertigo drugs. The use of histamine H_1-receptor occupancy (H_1RO) based on positron emission tomography (PET) has been developed for the evaluation of brain penetrability. Based on the results of the H_1RO-PET studies, non-brain-penetrating AHs (nbpAHs) have recently been reclassified among sgAHs. The nbpAHs are rapidly acting and exhibit minimal adverse reactions and, thus, are considered first-line drugs for allergic diseases. In this review, we will introduce recent topics on the pharmacodynamics and pharmacokinetics of AHs and make recommendations for the use of nbpAHs as first-line treatment options for allergic diseases.

Keywords Allergic disease · Antihistamines · Efficacy · Histamine H_1-receptor occupancy · Non-brain-penetrating · Pharmacokinetics · Potency

Abbreviations

AHs	Antihistamines
BBB	Blood-brain barrier
Cmax	Maximum plasma concentration
CNS	Central nervous system
EMA	European Medicines Agency
Emax	Maximal response
FDA	Food and Drug Administration
fgAHs	First-generation antihistamines
H_1RO	Histamine H_1-receptor occupancy
hERG	Human ether-a-go-go-related gene
nbpAHs	Non-brain-penetrating antihistamines
OTC	Over-the-counter
PAF	Platelet-activating factor
PET	Positron emission tomography
P-gp	P-glycoprotein
REM	Rapid eye movement
RT	Receptor residence time
sgAHs	Second-generation antihistamines
T½	Half-life
Tmax	Maximum plasma concentration

1 Classification of Antihistamines

H_1 receptor antagonists, known as H_1-antihistamines (AHs), have been used as anti-allergic drugs since their first introduction for clinical use in 1942 (Church and Rihoux 1992; Simons and Simons 2011; Church 2017). In the early stages of development, many first-generation antihistamines (fgAHs), such as promethazine, also served as prototypes of central nervous system drugs such as antipsychotics and antidepressants. In fact, some antidepressants and antipsychotic drugs are the most potent H_1 antagonists (Sato et al. 2013; Sato et al. 2015). Although fgAHs were efficacious against allergic diseases, they caused strong sedating effects owing to blood-brain barrier (BBB) penetration. In addition, their selectivity for H_1-receptors was low, and the frequency of adverse reactions, such as thirst, urinary retention, and tachycardia, was high. To overcome these significant drawbacks, second-generation antihistamines (sgAHs) with high H_1-receptor selectivity, low brain penetrability, and long plasma half-life have been developed (Simons and Simons 1994; Timmerman 2000; Casale et al. 2003). It is reasonable to classify AHs into sedating and non-sedating drugs according to the presence or absence of sedating properties (Yanai et al. 2017; Kawauchi et al. 2019).

In sgAHs, hydrophilic functional groups (-COOH, $-NH_2$) were introduced to decrease the BBB penetrability, thereby lowering the sedating effects. Global guidelines for allergic diseases, including Japanese, American, and European, recommend sgAHs with low central nervous system penetrability as first-line drugs (Holgate et al. 2003; Zuberbier et al. 2009; Church et al. 2010; Bousquet et al. 2020). Carboxyl group-type AHs have high specificity for H_1-receptors (Fig. 1).

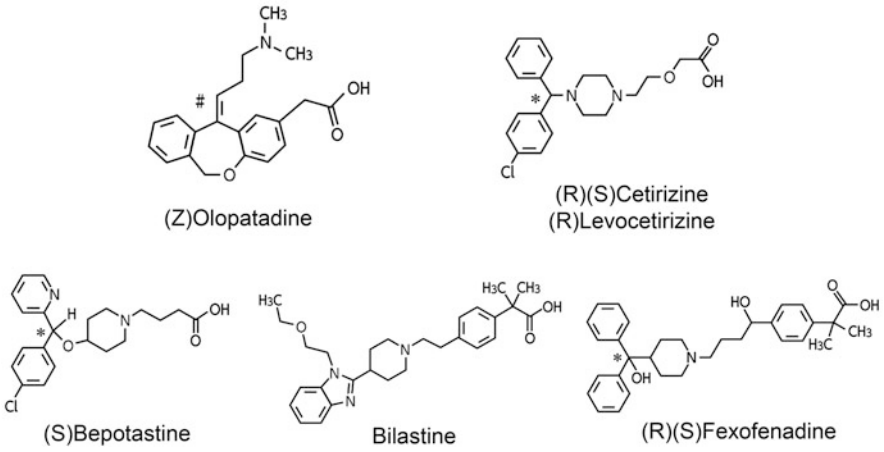

Fig. 1 Carboxyl group-type non-sedating antihistamines (AHs). Carboxyl group-type AHs have high specificity for H_1 receptors and are recommended as first-line drugs for allergic diseases (Yanai et al. 2017; Kawauchi et al. 2019). Asymmetric carbons involved in optical isomerism are marked with an asterisk (*). Although unrelated to optical isomers, double bonds involved in geometric isomers (cis-trans isomers) of different stereo-structures are marked with a hash symbol (#)

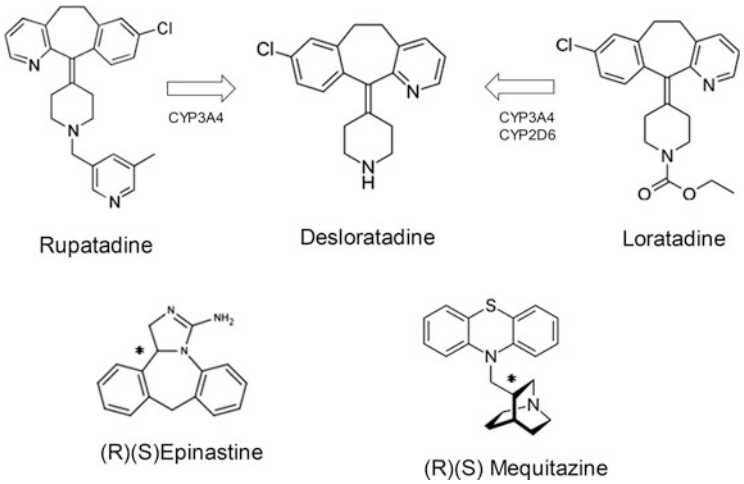

Fig. 2 Non-carboxyl group-type non-sedating antihistamines (AHs). The characteristic feature of non-carboxylgroup-type AHs is that they block not only H_1 receptors but also other receptors (Yanai et al. 2017; Kawauchi et al. 2019). Rupatadine, anti-H_1 + anti-platelet-activating factor (PAF) + anticholinergic effects; desloratadine, anti-H_1 + anticholinergic effects; loratadine, anti-H_1 + anticholinergic effects; epinastine, anti-H_1 + anti-PAF + anti-leukotriene effects, and mequitazine, anti-H_1 + anticholinergic effects. * Asymmetric carbon is involved in the optical isomerism. Peripheral anticholinergic effects may be related to anti-allergic, anti-common cold, anti-gastric acid secretion, anti-gastrointestinal motility, and anti-chronic obstructive pulmonary disease effects, as well as amelioration of overactive bladder, and thus may be clinically useful

Non-carboxyl group-type drugs which have protonated amines at physiological pH, such as mequitazine and desloratadine, have low specificity and block other receptors such as muscarinic receptors (Fig. 2). Drugs such as rupatadine and loratadine are converted to the active metabolite desloratadine in the body. Because loratadine is metabolized by CYP3A4 and CYP2D6, enzymes that are susceptible to drug–drug interactions, the active metabolite desloratadine is often used as an sgAH.

Several studies have suggested hydrophilicity alone is not sufficient to keep drugs from entering the brain but that an active efflux transporter in the BBB 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 (Seelig and Landwojtowicz 2000; Chen et al. 2003). In vitro, studies of P-gp-mediated efflux from caco-2 cells have shown cetirizine, desloratadine, and hydroxyzine to have weak but significant efflux ratios while that of fexofenadine was much greater (Crowe and Wright 2012). 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 (PET) (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

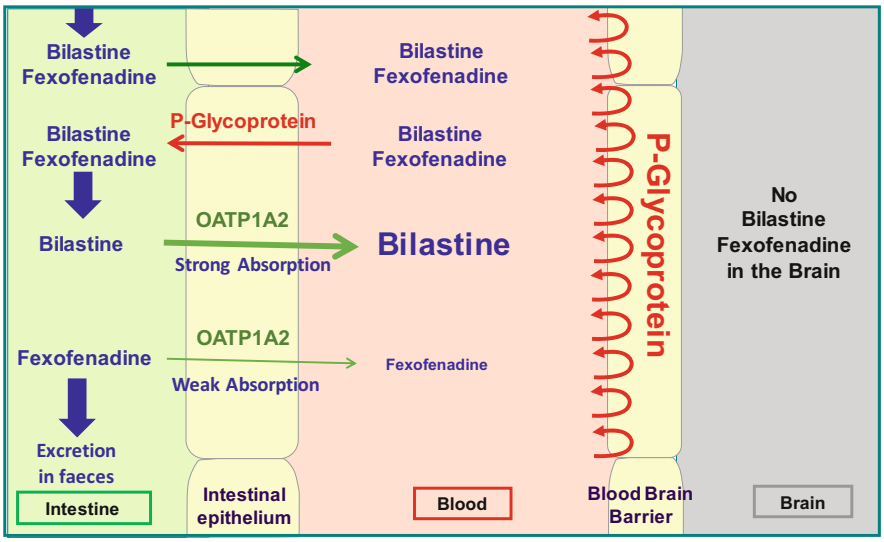

Fig. 3 Absorption, excretion, and prevention of brain penetration of bilastine and fexofenadine. The top left-hand corner shows the passive absorption of both from the intestine into the blood. Both drugs are then partially excreted by the membrane pump p-glycoprotein. Both drugs are then actively absorbed by the transporter OATP1A2, bilastine more effectively than fexofenadine. Both drugs are prevented from entering into the blood and brain by p-glycoprotein

out of the BBB by P-gp as shown in Fig. 3 (Schinkel 1999; Chen et al. 2003; Church 2011; Maurer et al. 2011; Montoro et al. 2011).

2 Constitutive Activity of Histamine H_1 Receptors

In cultured cells, the levels of the H_1 receptor increase in the presence of histamine (Mizuguchi, et al. 2020). In contrast, some AHs decreased the expression levels of the H_1 receptor. In fact, H_1 receptor levels in the nasal mucosa of patients with allergic rhinoconjunctivitis are increased and then decreased with the use of AHs. Signal transduction is considered to begin only when the agonists are bound to receptors. However, with increased receptor expression, signal transduction occurs in the absence of agonists, and this type of receptor activation is known as constitutive activation. When receptors are constitutively activated, AHs act as inverse agonists to inhibit the activated receptors and return to a non-activated state (Bakker et al. 2001; Leurs et al. 2002). Early treatment for allergic rhinoconjunctivitis, in which AHs are administered before the pollinosis season, is provided to directly block histamine and inhibit constitutive activity.

3 Efficacy and Potency of AHs

The binding affinity (potency) of non-sedating AHs toward the H_1 receptor varies widely, and the difference in potency can be $\geq$100 times (Yanai et al. 2011). Although the potency of AHs varies widely, clinical efficacy, which is expressed by the maximal response (Emax), is almost the same when the drug is used at sufficient doses. Therefore, when efficacy is insufficient, non-sedating AHs are to be used at higher doses up to four-fold the standard dose in Europe (Makris et al. 2013). For the clinical use of non-sedating AHs, a better understanding of the pharmacodynamic concepts related to potency and efficacy is necessary. The clinical effectiveness of steroids, AHs, and anti-allergic drugs for the treatment of allergic diseases are different, in the order of steroids > AHs > anti-allergic drugs. A recent randomized controlled study has reported that there are no additive effects with the combined use of AHs and leukotriene antagonists and that monotherapy with AHs will suffice for seasonal allergic rhinoconjunctivitis (Lavorini et al. 2020).

The potency of a drug is generally expressed as binding affinity, which is measured in vitro at equilibrium between receptors and drugs. It is usually measured using radioactive ligands, and the binding of the ligands to the receptors under equilibrium conditions is expressed as the inhibitory binding concentration, K_i (Yanai et al. 2011). As shown in Fig. 4a, the lower the K_i value, the more potent is the binding affinity. The binding affinity of the H_1 receptor to histamine per se is far lower than that of the H_1 receptor to AHs; thus, any AH can sufficiently block the binding of histamine to the H_1 receptor at a clinically useful level. Shimamura et al. (2011) reported the crystal structure of human histamine H_1 receptor complex with doxepin and binding models of AHs. The recently -reported cryo-electron microscopy structure of the human H_1 receptor also improved understanding of the competition of histamine binding sites by AHs (Xia et al. 2021).

Binding affinity can also be measured under kinetic conditions between a receptor and radioactive ligand (Bosma et al. 2017; Bosma et al. 2018). The kinetic method measures the receptor residence time (RT), which is the reciprocal of the rate of dissociation from the receptor at a non-equilibrium state k_{off}. The larger the RT, the higher is the potency. Different AHs have different K_i and RT values, as shown in Fig. 4b. Notably, the in vitro RTs of classical AHs, such as diphenhydramine, are considerably shorter than those of non-sedating sgAHs, indicating that the length of time for which classical AHs act on H_1 receptors is very short. However, as RT was determined in vitro, it might not be applicable to true in vivo conditions. Once they penetrate the brain, the AHs remain for a considerable period (see Fig. 7). It has been reported that the in vivo association and dissociation of [^{3}H]pyrilamine in the brain were much slower than those of in vitro binding at 37°C (Yanai et al. 1990).

Although determination of K_i and RT, indicators of the in vitro potency of an AH, may help in the best selection of candidate AHs, the large differences in the volume of distribution and tissue accumulation in humans may preclude K_i and RT from being a good predictor of clinical efficacy (Church and Maurer 2012).

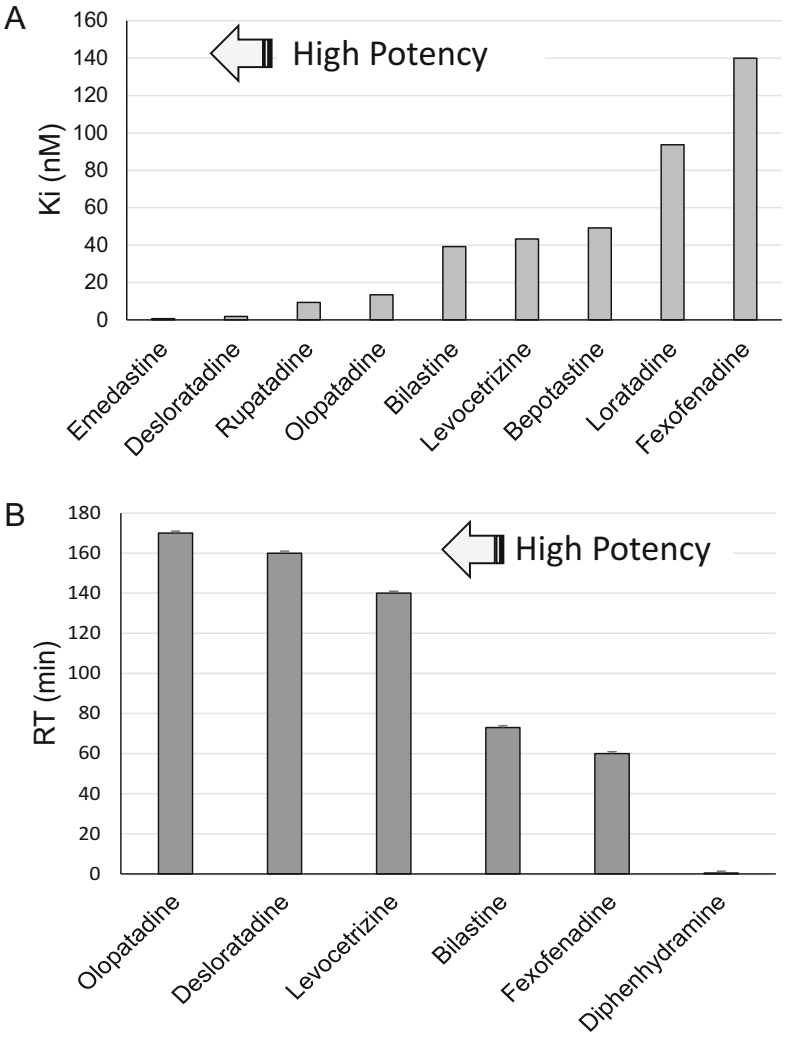

Fig. 4 Potency of antihistamines: Measurement at the equilibrium (**a**) and dynamic states (**b**). (**a**) Binding affinity (Ki value) measured at equilibrium in vitro; (**b**) Receptor residence time (RT) measured by in vitro kinetics. The RT can also be measured based on changes in intracellular Ca^{2+} concentration without the use of radioactive ligands. Note that clinical efficacy does not necessarily depend on the potency of receptor binding. Modified from Yanai et al. (2011) and Bosma et al. (2017, 2018)

4 Functions of the Histaminergic Nervous System in the Brain

There are approximately 64 000 histamine-producing neurons, located in the tuberomammillary nucleus of the human brain. When activated, these neurons stimulate histamine receptors in all the major parts of the cerebrum, cerebellum, posterior pituitary, and spinal cord (Haas and Panula 2003).

The actions of histamine on H_1-receptors in the brain have been implicated in arousal in the circadian sleep/wake cycle, reinforcement of learning and memory, fluid balance, suppression of feeding, control of body temperature, control of cardiovascular system, and mediation of stress-triggered release of ACTH and β-endorphin from the pituitary gland (Brown et al. 2001).

Studies in genetically modified mice have confirmed the stimulatory effects of histamine in the central nervous system (CNS) (Yoshikawa et al. 2021). H_1-receptor knockout mice are less active during the active period, sleep insufficiently during the resting period, and are likely to gain weight (Inoue et al. 1996; Schneider et al. 2014). Obesity owing to atypical antipsychotics and antidepressants with potent H_1-antagonistic activity is caused by the blocking of H_1 receptors (Kim et al. 2007; He et al. 2013; Singh et al. 2019). When the histaminergic nervous system actively acts on H_1-receptors in animals, their eating behavior is suppressed. Interestingly, the sleep-wake cycle and obesity were considered to be completely different phenomena. But they are not. They were found to be closely linked. An article entitled "Sleep it off" which means that increasing sleep is a possible way to control obesity was published in Nature in 2006 (Pearson 2006). Maintaining a normal sleep-wake cycle can prevent obesity.

In addition, H_3 receptor antagonists, which activate the histaminergic nervous system, increase spontaneous motility by raising alertness levels and decrease the amount of food intake (Provensi et al. 2016). Recently, an H_3 receptor antagonist, pitolisant was approved for the treatment of narcolepsy in Europe and the USA (Guevarra et al. 2020).

5 Central Effects of Sedating AHs

The central effects of fgAHs are caused by blocking the functions of the histaminergic and cholinergic nervous systems in the brain. Blockade of the histaminergic pathways leads to the sedating effects of AHs which include sleepiness and impaired performance (Church et al. 2010). However, sleepiness and impaired performance are often confused. Emotion comprises emotional experience and emotional expression (Darwin 1872): sleepiness is an emotional experience, and impaired performance is an emotional expression. Blockade of cholinergic pathways, particularly with long-term use by elderly people increases the risk of developing Alzheimer's disease due to cognitive function decline (Gray et al. 2015).

While prescription of fgAHs by the medical profession is minimal today, their availability as over-the-counter (OTC) drugs for the common cold has become a social problem. Some people become addicted to the foggy feeling resulting from the ingestion of sedating AH-containing OTC drugs and buy a large amount of these drugs. When the histaminergic nervous system is inhibited, the brain reward system, such as the dopamine system, can be activated, resulting in drug dependence similar to that of commonly abused drugs.

The use of sedating AHs in children also requires caution, especially when the drugs are used for a long time. The use of sedating AHs in children with convulsion predisposition induces seizures (Takano et al. 2010; Kim et al. 2021), and their long-term use may lead to obesity (Saad et al. 2020). The frequency of occurrence of sedating effects in children is also high, which decreases learning ability. In fact, an observational study on 7-year-old children revealed that use of sedating AHs may reduce the intelligence quotient by approximately 10 points (Jedrychowski et al. 2013). The US Food and Drug Administration (FDA) states that "sedating AHs must not be used in children for sedating purposes" and has recommended pharmaceutical companies to withdraw sedating AH-containing OTC drugs for common cold for children younger than two years, thus prompting pharmaceutical companies to voluntarily withdraw such products from the market (Hampton et al. 2013). The efficacy of sedating AHs in children has not been verified, and there is a high possibility that these drugs may only cause adverse effects. Therefore, they should not be used in children (Church et al. 2020). The sgAHs, such as levocetirizine and fexofenadine, which can be used in infants aged six months or older, are available.

6 Evaluation of the Sedating Effects via H_1RO

We have been objectively evaluating the sedating effect of AHs by measuring H_1RO using PET (Yanai et al. 1995). The brain H_1ROs for medical drugs with H_1 antagonistic activity are shown in Fig. 5. Cetirizine, for example, penetrates the brain in a dose-dependent manner and binds to a considerably large number of H_1 receptors at a dose of 20 mg, causing mild cognitive impairment (Tashiro et al. 2009). While the sedating fgAHs block 50% or more of the brain H_1 receptors, the sgAHs block 30% or less. Note that even sgAHs penetrate the BBB, but to a lesser extent than fgAHs. We propose to classify AHs according to H_1RO into three categories: sedating, $H_1RO \geq 50\%$; less-sedating, H_1RO 20–50%; and non-sedating, $H_1RO \leq 20\%$. However, there are large differences in H_1RO among non-sedating AHs (Yanai et al. 2017).

The Consensus Group on New Generation Antihistamines (CONGA) conference stated that true "non-sedating antihistamines" do not exhibit a sedating effect even when they are administered in excess of usual doses (Holgate et al. 2003). In view of the relationship between plasma drug concentration and H_1RO, they also added that

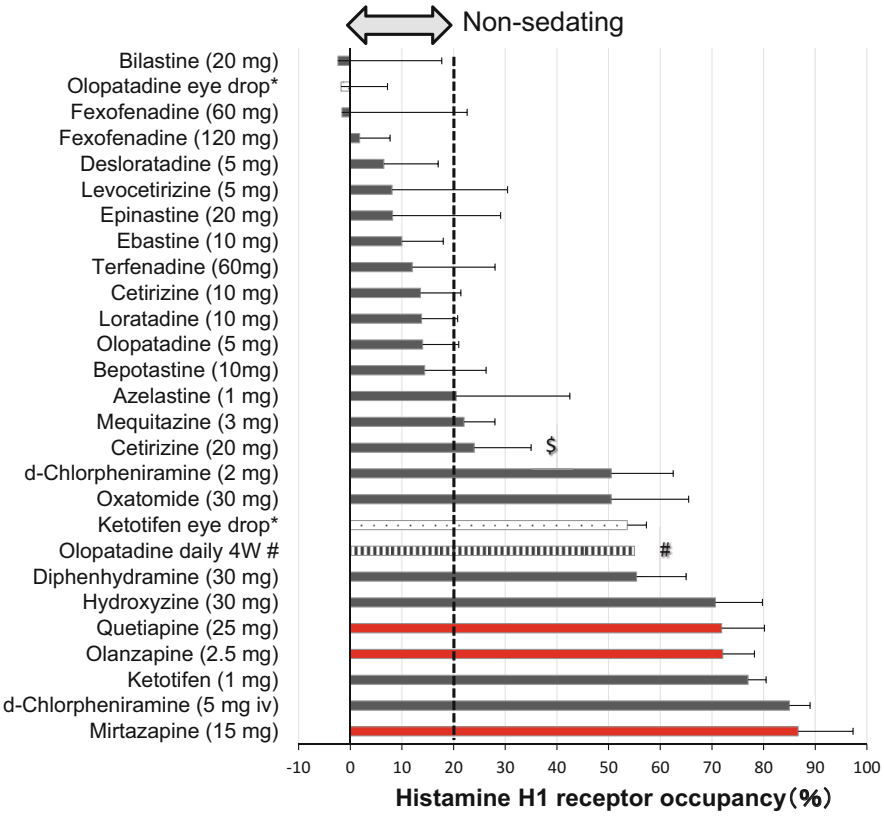

Fig. 5 Histamine H_1 receptor occupancy (H_1RO) in the human brain. Evaluation of the sedating effects of H_1 antagonists based on H_1RO. Antihistamines (AHs) were administered to healthy subjects, and H_1 receptor levels were measured at the maximum plasma concentration (Tmax) using positron emission tomography. The H_1RO data are shown as mean ± SD. As shown in red bars, an antidepressant (mirtazapine) and antipsychotics (olanzapine and quetiapine) showed potent sedating effects and occupied most of the brain H_1 receptors at the minimum doses. Olanzapine 5 mg is also effective against chemotherapy-induced nausea and vomiting. *: eye drop; iv: intravenous injection. # When olopatadine 5 mg was repeatedly administered twice daily (morning and evening) for 4 weeks, the H_1RO increased from 15 to 55%. For the other drugs, a single oral dose was administered. $ Cetirizine has a sedative effect when its dose is increased from 10 mg to 20 mg. Modified from Yanai et al. (2016, 2017) and Nakamura et al. (2019)

"to be truly non-sedating, the drugs should not decrease H_1 receptor binding even when their plasma levels are high." From this viewpoint, non-sedating AHs can be further subclassified into "non-brain-penetrating antihistamines" (nbpAHs) as shown in Fig. 6 (Kawauchi et al. 2019).

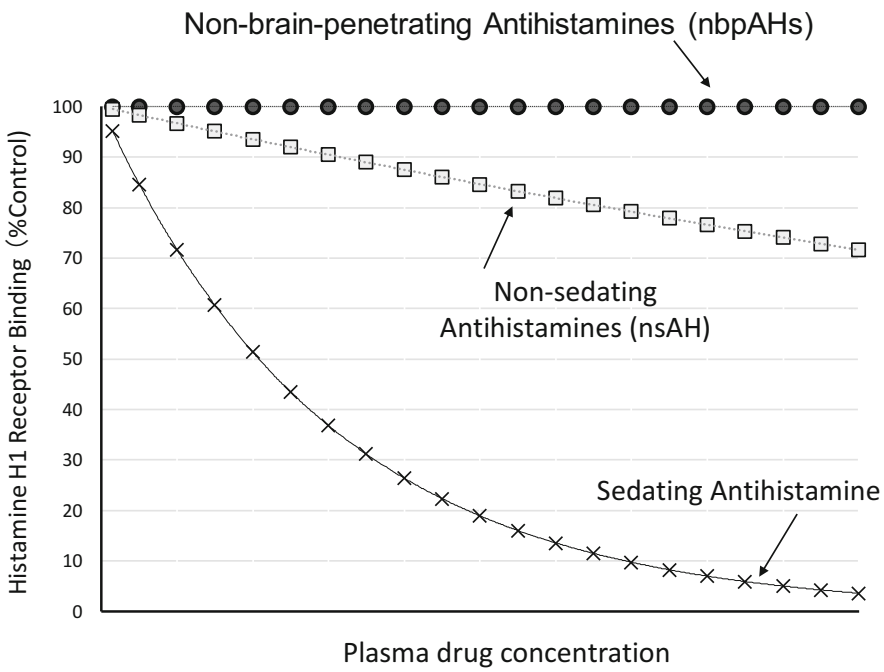

Fig. 6 Conceptual model of "non-brain-penetrating antihistamines (nbpAHs)." The relationship between plasma concentration and H_1 receptor binding after administration of H_1 receptor antagonists is shown. To ensure that sedating effects never occur, it is essential that H_1 receptor binding does not decrease even with an increase in the plasma drug concentration. Some non-sedating AHs can penetrate the brain in a dose-dependent manner after repeated administration, causing sensitive patients to feel drowsy. Sedating AHs rapidly occupied H_1 receptors in a dose-dependent manner, exhibiting a potent sedating effect

7 Recent Topics in the Clinical Pharmacokinetics of AHs

Most H_1-antihistamines are absorbed passively into the blood from the intestine. Peak plasma levels of passively absorbed drugs occur at around 1–4 h (Geha and Meltzer 2001; Simons 2004; Kawauchi et al. 2019). The pharmacokinetics of sgAHs are better than those of fgAHs. The shorter the time to maximum plasma concentration (Tmax), the faster is the treatment effect, and the frequency of administration is determined based on the plasma half-life (T½) as shown in Fig. 7. A remarkable characteristic of sgAHs is that they are affected by several transporters in intestinal absorption and brain penetration through BBB (see Fig. 3). For example, bilastine and to a lesser extent fexofenadine have a more rapid uptake as they are substrates for an organic anion transporting polypeptide, OATP1A2 (Russell et al. 1998; Cvetkovic et al. 1999; Tannergren et al. 2003; Shimizu et al. 2005; Lucero et al. 2012; Church and Labeaga 2017). The role of this transporter is supported by its inhibition by grapefruit juice (Dresser et al. 2005; Crean et al. 2007; Akamine et al.

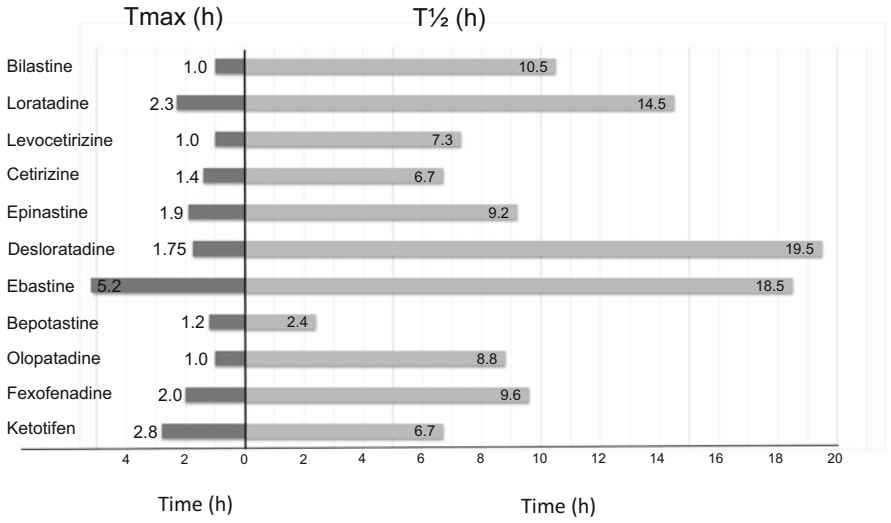

Fig. 7 Plasma pharmacokinetics of antihistamines. The numbers of columns are the respective Tmax and T½ of sgAHs as expressed as hours (h). Equilibrium of plasma concentration is reached at approximately 3–4 half-lives (T½) after continuous administration. The tissue half-life is different from the plasma half-life. The brain half-life is much longer than that of the plasma as shown in Fig. 8

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. Here, we introduce three recent topics regarding the pharmacokinetics of AHs.

7.1 In Vivo Brain RT of AHs in the Human Brain

The next-day residual sedative effect after nighttime administration of the OTC sleep aid diphenhydramine was previously verified by direct PET measurement of H_1RO (Zhang et al. 2010). Figure 8 illustrates how long the sedating AH, diphenhydramine, remains in the brain as determined by PET. The in vivo half-life in the brain can be estimated by examining the changes in H_1RO by measuring the histamine H_1 receptor by PET three times, before, at 3 h, and 23 h after the administration of sedating AHs, in the same subjects. The half-lives of diphenhydramine 50 mg and ketotifen 1 mg in the brain were approximately 30 and 45 h, respectively (Yanai et al. 2016). Because the plasma half-lives of the two drugs were in the range of 6–8 h, their brain RT in vivo was found to be substantially longer. The H_1ROs of AHs in the skin and nasal mucosa are also considered to last long (Gillman et al. 2009).

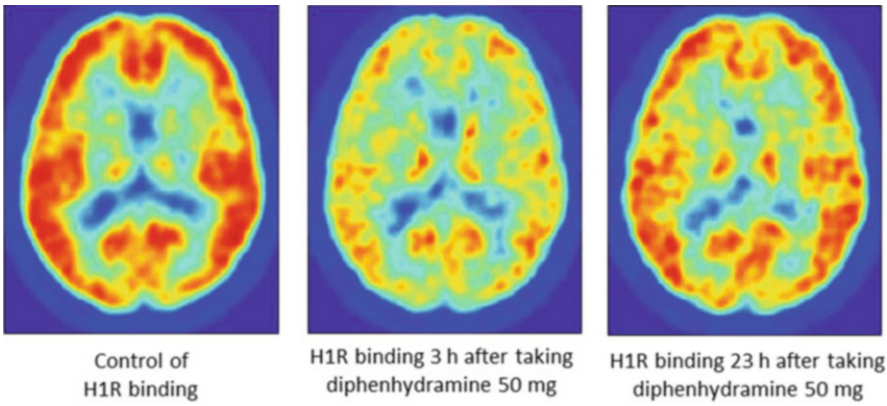

Fig. 8 [^{11}C]doxepin binding to histamine H_1 receptor (H_1R) at baseline (left), 3 h (middle), 23 h (right) after taking diphenhydramine 50 mg in humans. Once the antihistamines (AHs) penetrate the brain, they remain there for a long time. Therefore, a withdrawal period of at least 72 h is necessary after the half-life in the brain has elapsed. The use of sedating AHs at night deteriorates the quality of sleep because they occupy the brain receptors for a long time. Therefore, it is preferable to use non-sedating AHs for allergic diseases at night. Considering the possible hangover effect of over-the-counter AH sleep aids, care needs to be taken during their administration. Modified from Yanai et al. (2016)

7.2 Brain Penetrability of AH in Eye Drops

Eye drops containing AHs are often used to alleviate the eye-related symptoms of pollinosis. The OTC eye drops often contain sedating AHs. However, the risk is not sufficiently communicated to general users. To measure the brain penetrability and obtain H_1RO data for eye drops, histamine H_1receptors in the brain were measured by PET before and after the application of ketotifen eye drops and olopatadine eye drops as a 1-day dose each (Yanai et al. 2016). The H_1ROs after the application of olopatadine and ketotifen eye drops were $-1.8\% \pm 9.0\%$ and $53.6\% \pm 3.7\%$ ($n = 7$), respectively. Thus, although olopatadine eye drops did not affect the brain H_1 receptors, ketotifen eye drops accounted for approximately 50% of the H_1 receptors. With local mucosal administration, drugs are absorbed rapidly. In addition, because there is no first-pass effect, they are likely to rapidly penetrate the brain. The plasma level of ketotifen is nearly zero because of its rapid penetration into the brain. Because eye drops can be absorbed from the nasal mucosa through the nasolacrimal duct, as well as from the cornea and conjunctiva, to measure the H_1 receptor binding by PET, the subjects were instructed to press the upper part of the nose when applying the eye drops. The sgAH-containing eye drops olopatadine, epinastine, and bepotastine, are marketed as medicine. These sgAH-containing eye drops are recommended as first-line treatment for allergic conjunctivitis as they have low brain penetration.

7.3 Transdermal Patch AH Preparation

A transdermal patch containing emedastine difumarate was developed for the treatment of allergic rhinitis in Japan (Okubo et al. 2018; Tanida et al. 2018). Percutaneous absorbable preparations showing systemic effects similar to those of oral drugs have been developed for use as drugs for angina pectoris, asthma, and neurological and psychological diseases; hormone preparations; smoking cessation aids; and narcotic analgesics. Percutaneous absorbable preparations are absorbed more slowly and can maintain constant plasma levels for a longer duration than orally administered drugs. Although emedastine is a potent sedating AH, its percutaneously absorbable preparation might be considered to exhibit less frequent subjective feelings of drowsiness than its oral preparation because the former preparation is absorbed more slowly (Fig. 9). However, because sedating effects appear in a dose-dependent manner, the risky operation of machinery, such as car driving, must be avoided.

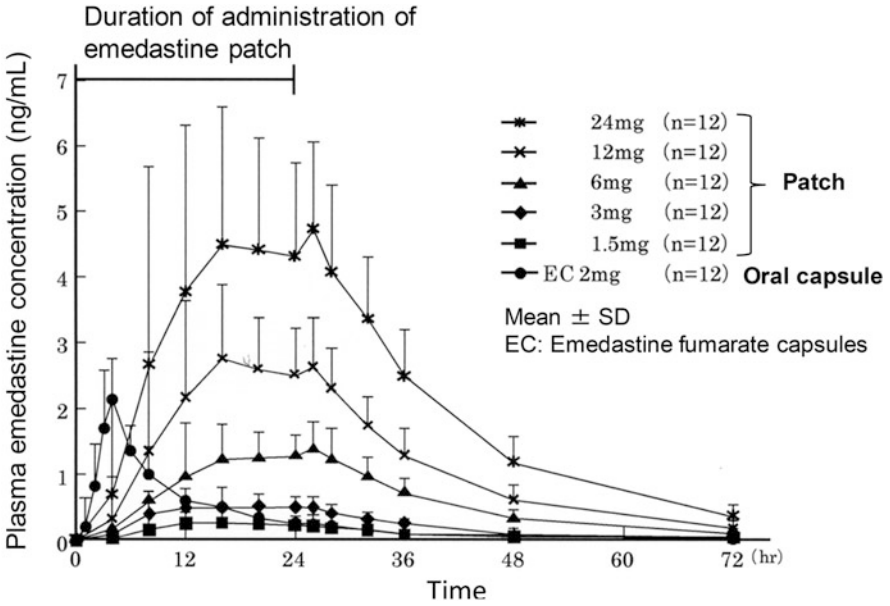

Fig. 9 Changes in plasma concentrations of emedastine administered as percutaneously absorbable and oral preparations. The Tmax of the emedastine patch was 16–20 h, which was approximately 4–5 times longer than that of the oral capsule. In addition, the T½ of the former is approximately twice that of the latter. The maximum plasma concentration (Cmax) of the oral preparations for repeated administration and that of the percutaneously absorbable preparations were adjusted to be the same. Pharmacokinetic data of oral preparations were obtained after a single oral dose of 2 mg. EC: emedastine fumarate capsules. Modified from Tanida et al. (2018)

8 AHs Present in OTC Rhinitis Drugs and OTC Common Cold Drugs

In Japan, epinastine was launched in 2011 as the first OTC allergic rhinitis drug that was less likely to cause drowsiness. Thereafter, OTC allergic rhinitis drugs containing fexofenadine, cetirizine, loratadine, ebastine, and bepotastine were marketed, and the share of non-sedating AHs, which are "less likely to cause drowsiness," has risen to nearly 70% in the market. Impaired performance owing to sedating AHs has become common. In Japan, the only sedating AHs are present in OTC common cold drugs. Several cases of traffic accidents due to the ingestion of OTC common cold drugs have been reported.

Nasal symptoms due to both allergic rhinitis and the common cold involve histamine and acetylcholine as the main chemical mediators. Therefore, antihistamines and anticholinergic drugs that exhibit antagonistic effects on the receptors of these mediators are effective for treating nasal symptoms (De Sutter, et al. 2015). In Japan, non-sedating sgAHs have been used to treat acute upper respiratory inflammation and acute bronchitis in the clinical setting of off-label use. In many countries, sgAH-containing OTC drugs have been approved and marketed for rhinitis and common cold. For example, in the USA and China, as well as in European countries, loratadine is present in rhinitis drugs and common cold drugs.

9 Cardiotoxicity of Sedating AHs

Adverse reactions caused by sedating AHs include cardiotoxicity, lowering of seizure threshold, and obesity, in addition to sedating effects. Several reports appeared in the literature indicating the rare occurrence of a form of polymorphic ventricular dysrhythmia, the "torsade de pointes," after the administration of astemizole or terfenadine. The mechanism most frequently involved in cardiotoxicity induced by several AHs is the blockade of hERG (human Ether-a-go-go-Related Gene, Kv11.1) voltage-gated K^+ channels (Taglialatela et al. 1999; Hazell et al. 2017). It has been pharmacologically verified that non-sedating sgAHs are less likely to cause cardiotoxicity than fgAHs. In particular, the guideline-recommended dose escalation up to four times the usual dose in treatment-resistant patients is considered safe in healthy individuals (Cataldi et al. 2019). The first-generation AH, hydroxyzine, is pro-arrhythmogenic, and the European Medicines Agency (EMA) called attention to this adverse effect in 2015 (Morales et al. 2021). Particular caution should be exercised when hydroxyzine is used in patients with chronic kidney disease because it may cause QT prolongation (Poluzzi et al. 2015; Snitker et al. 2017).

10 Conclusion and Perspectives

In this review, we have looked as fgAHs which penetrate the brain to cause sedation, sgAHs which penetrate the brain poorly and a minimally sedating, and nbpAHs which do not penetrate the brain at all and avoid sedative effects. While the sedative action of fgAHS indicates they are useful as sleep aids, this should be strongly discouraged for two reasons. First is that they have very long half-lives in the brain, some up to 24 h, resulting in hangover in the morning when wakefulness is required. Second is fgAHs increase the latency to the onset of rapid eye movement (REM) sleep and reduce the duration of REM sleep (Boyle et al. 2006; Rojas-Zamorano et al. 2009). This leads to a poor-quality sleep.

Sedating AHs that penetrate the central nervous system have other clinical uses. They are useful as antiemetics, anti-motion sickness drugs, and antivertigo drugs. This is because H_1-receptors and muscarinic receptors are associated with the vomiting center of the brain. Histamine is also involved in nociception, and transmission of noxious stimuli in the ascending pain pathway, such as in the spinal cord (Yanai et al. 2003; Obara et al. 2020). The inhibition of pain associated with migraine, visceral pain, postoperative pain, and cancer pain by sedating AHs has been reported (Worm et al. 2019). However, pain inhibition by non-sedating AHs has not been fully investigated except for irritable bowel syndrome (Wouters et al. 2016). Further studies regarding the utility of AHs for pain control are warranted.

Some basic and epidemiological studies have reported that patients using AHs are less likely to contract COVID-19 than non-users. The University of California examined 219,000 people who were tested for the SARS-CoV-2 infection using PCR and reported that those who were on AHs were significantly less likely to contract the virus (Reznikov et al. 2021). A Spanish study also reported that AH users were more likely to test negative for COVID-19 infection (Vila-Córcoles et al. 2020). Proposed mechanisms for the antiviral effects of AHs include their interactions with the SARS-CoV-2 spike glycoprotein receptor binding domain, sigma-1 receptor, and heparan sulfate (Ennis and Tiligada 2021; Hou et al. 2021). Further research on AHs developed by the Nobel laureate Daniel Bovet should be conducted.

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