



Review

Why are second-generation H₁-antihistamines minimally sedating?

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ABSTRACT

H₁-antihistamines are widely used in treating allergic disorders, e.g., conjunctivitis, urticaria, dermatitis and asthma. The first-generation H₁-antihistamines have a much greater sedative effect than the second-generation H₁-antihistamines. Researchers could not offer a satisfactory explanations until late 1990s when studies showed that second-generation H₁-antihistamines were substrates of P-glycoprotein. P-glycoprotein, expressed in the blood–brain barrier, acts as an efflux pump to decrease the concentration of H₁-antihistamines in the brain, which minimizes drug effects on the central nervous system and results in less sedation. P-glycoprotein is found in the apical side of the epithelium. It consists of transmembrane domains that bind substrates/drugs and nucleotide-binding domains that bind and hydrolyze ATP to generate energy for the drug efflux. This review mainly discusses interactions between P-glycoprotein and commonly used second-generation H₁-antihistamines. In addition, it describes other possible determining factors of minimal sedating properties of second-generation H₁-antihistamines.

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1. Introduction

H₁-antihistamines are the mainstays in the treatment of allergic disorders, particularly seasonal rhinitis, conjunctivitis,

urticaria, dermatitis, and asthma (Chen et al., 2003; Holgate and Polosa, 2008; Pata, 2008). Classical (first-generation) H₁-antihistamines have much stronger sedative effects, e.g., drowsiness, somnolence, fatigue, impairment of cognitive function, memory, and psychomotor performance than second-generation H₁-antihistamines (Church et al., 2010). Non-polar and lipophilic structure of H₁-antihistamines used to be considered as the most significant

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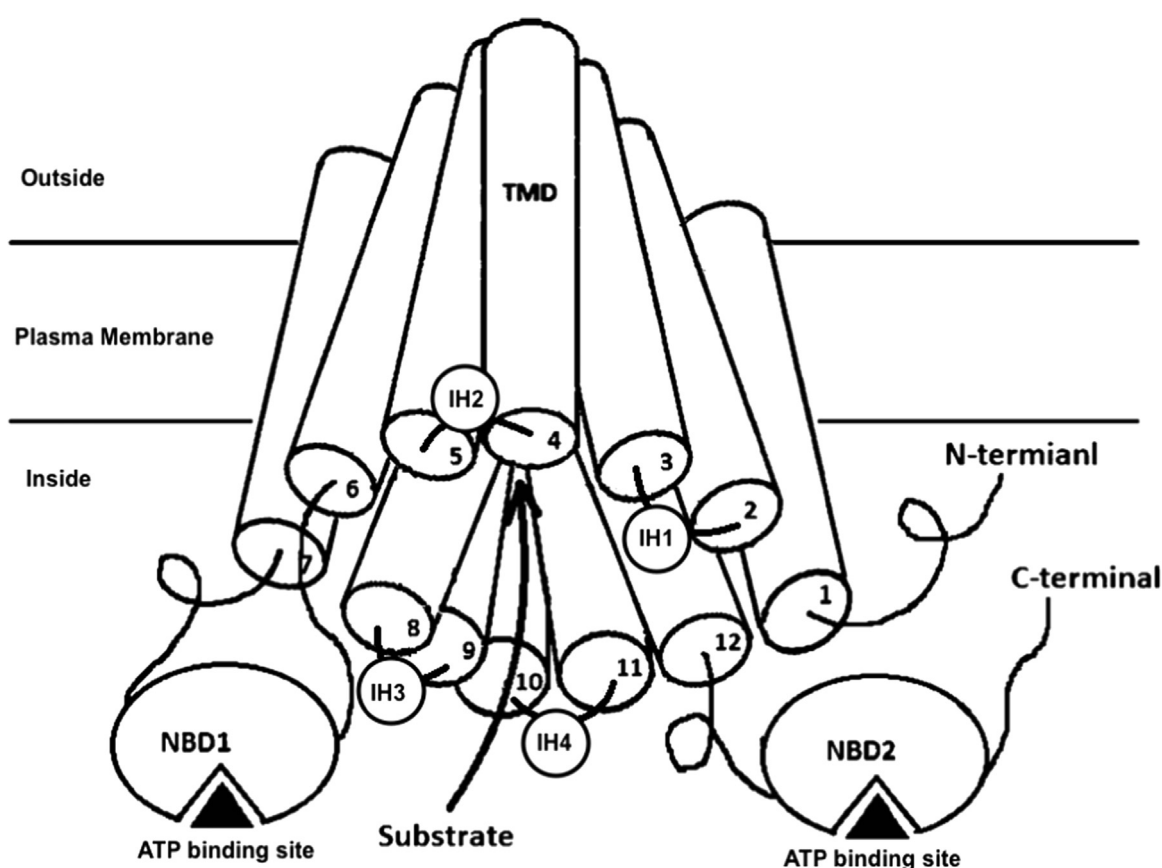


Fig. 1. Structure of P-glycoprotein (Modified from Ward et al., 2013; Linton, 2007; Li et al., 2014; Jin et al., 2012). The basic functional units of P-gp are comprised of four domains. Two cytoplasmic nucleotide-binding domains (NBDs) bind and hydrolyze ATP to generate energy for the drug efflux; two transmembrane domains (TMDs) that consist of six membrane-spanning α -helices which form a substrate membrane-crossing cavity for the drug transport. Intracellular helices (IH) 1–4 are between TMD 1&2, 4&5, 8&9, 10&11, respectively.

factor for sedative effect (Desager and Horsmans, 1995). For now, a satisfactory explanation is that the minimal sedating property of second-generation H_1 -antihistamines is caused by the efflux function of P-glycoprotein (P-gp) (Liu et al., 2008).

P-gp is a 170-kDa transmembrane glycoprotein and acts as a drug efflux pump expressed on the apical side of the epithelium (Silva et al., 2011; Ward et al., 2013; Lopez and Martinez-Luis, 2014). The basic functional units of P-gp are in four domains: two cytoplasmic nucleotide-binding domains (NBDs), binding and hydrolyzing ATP, and two transmembrane domains (TMDs) that consist of six membrane-spanning α -helices which form a substrate/drug binding pocket. Intracellular helices (IH) 1–4 are between TMDs 1&2, 4&5, 8&9, 10&11, respectively (Fig. 1) (Ward et al., 2013; Linton, 2007; Li et al., 2014; Jin et al., 2012). P-gp acts to protect the body against foreign substances and export endogenous chemicals from the blood–brain barrier (BBB), small intestinal mucosa, hepatocytes, and renal tubules (Zhou, 2008). Therefore, P-gp inhibition or induction can alter entry into the central nervous system (CNS), intestinal absorption, and biliary and urinary excretion of the P-gp substrates (Wessler et al., 2013). Many drugs, including second-generation H_1 -antihistamines, antineoplastic drugs, steroids, and antiarrhythmic agents are P-gp substrates or inhibitors (Table 1) (Wessler et al., 2013; Hennessy and Spiers, 2007; Ambudkar et al., 2003).

An increasing number of studies have indicated that most of second-generation H_1 -antihistamines are P-gp substrates and these findings are being applied to clinical practice. This review will emphasize the interaction between P-gp and widely used second-generation H_1 -antihistamines and explain why second-generation antihistamines exert minimal or no sedative effect.

Table 1

P-glycoprotein substrates and inhibitors (Hennessy and Spiers, 2007; Ambudkar et al., 2003).

	Types	Drugs
Substrates	Anti-cancer agents	Doxorubicin, Daunorubicin, Vinblastine, Vincristine, Actinomycin D, Paclitaxel, Teniposide, Etoposide3).
	Immunosuppressant	Cyclosporin A, Tacrolimus
	Antihistamines	Fexofenadine, Loratadine, Desloratadine, Cetirizine
	Steroids	Aldosterone, Cortisol, Corticosterone, Dexamethasone, Spironolactone, Progestins, etc.
	Dopaminergic antagonist	Domperidone
	HIV protease inhibitors	Amprenavir, Indinavir, Nelfinavir, Ritonavir
	Positive inotropic drug	Digoxin
	Anti-emetic	Ondansetron
	Anti-diarrheal agent	Loperamide
	Anti-gout agent	Colchicine
	Antibiotic	Erythromycin
	Antiparasitic agents	Avermectins
	Anti-tuberculous agent	Rifampin
Inhibitors	Immunosuppressant	Cyclosporin A
	Calcium channel blockers	Verapamil, Bepridil, Dihydropyridines
	Progesterone antagonist	Mifepristone (RU486)
	Anti-estrogen r agent	Tamoxifen
	Anti-arrhythmic agent	Quinidine
	Anti-fungal agents	Azoles, e.g., Ketoconazole

2. Pharmacology of H₁-antihistamines

H₁-antihistamines are inverse agonists of the H₁-receptor which is encoded on chromosome 3p and is coupled to G_{q/11}-protein (Leurs et al., 2002; Gushchin, 2010; Laurence et al., 2011). Activation of H₁-receptors stimulates the phospholipase C-IP₃-Ca²⁺ pathway (Gushchin, 2010; Laurence et al., 2011). The increase in cytosolic Ca²⁺ is responsible for excitatory effects of histamine, whereas the release of NO from endothelial cells leads to smooth muscle relaxation and some of the allergic effects, e.g., vasodilatation and edema (Laurence et al., 2011).

First-generation H₁-antihistamines have a highly lipophilic structure that allows them to penetrate BBB and interact with receptors in the CNS. They hold a poor receptor selectivity and block the receptors of other biologic amines, e.g., catecholamine and serotonin (Church et al., 2010; Jáuregui et al., 2013) as well as muscarinic acetylcholine receptors (Kubo et al., 1987). The consequences of blocking these receptors may also contribute to the sedative effect of first-generation H₁-antihistamines (Church et al., 2010).

Lack of CNS effects is a clear difference between second-generation and first-generation H₁-antihistamines (Holgate et al., 2003). In most published articles, second-generation H₁-antihistamines are also called “non-sedating” H₁-antihistamines. Compared with the first-generation H₁-antihistamines that have pronounced side effects, the second-generation H₁-antihistamines are well tolerated by their users. It is particularly true that the second-generation H₁-antihistamines induce much less CNS depression than the first-generation H₁-antihistamines (Mann et al., 2000), while recent research evidence indicates that even second-generation H₁-antihistamines have the potential to produce either or both subjective and objective sedation (Holgate et al., 2003). Thus, in this article, we call second-generation H₁-antihistamines as “minimally-sedating” H₁-antihistamines.

Interestingly, some of the second-generation H₁-antihistamines, such as loratadine, have a lipophilic structure and low pK_a (Table 2), but they still cannot penetrate BBB readily and show minimal sedative effects. Thus, a question is raised: why do the second-generation H₁-antihistamines not exhibit a potent sedative effect as the first-generation H₁-antihistamines do? Findings from further research suggest that second-generation H₁-antihistamines are minimally sedating, because all of them are P-gp substrates.

3. Pharmacology of P-glycoprotein: effects of P-glycoprotein on drug disposition

The P-gp expression in the cells promotes the elimination of drugs (Montesinos et al., 2012). In the BBB, P-gp is expressed at the luminal (apical) membrane of endothelial cells. At this site, P-gp

removes harmful endogenous and exogenous compounds from the brain and thus plays a detoxification role (Demeule et al., 2002). Studies of wild type (WT) and P-gp knockout (KO) mice supported this view. When the KO group was compared with the WT group, KO mice had less efflux of the CNS drug after each group had received the same dose of a P-gp substrate (Chen et al., 2003). Based on these findings, it was concluded that the second-generation H₁-antihistamines may exit from the brain tissue, thereby causing little or no sedation.

P-gp is a member of the ATP-binding cassette (ABC) superfamily of transport proteins. It relies on the energy from ATP hydrolysis to activate the drug efflux pump and thus extrudes the drugs across the cell membrane (Constantinides and Wasan, 2007). The ATPase activity affects drug transport/disposition and concentration on both sides of the cell membrane and reduces the cell exposure to potential toxicants (Demeule et al., 2002).

When substrates bind to P-gp, ATPase activity is increased 3- to 4-fold, even up to 20-fold in some cases. The rate of substrate transport and the increase of ATPase activity are related to the degree of hydrogen bonding between P-gp and its substrates (Omote and Al-Shawi, 2006). Generally, drugs that form few hydrogen bonds with P-gp exhibit a high intrinsic drug efflux rate, whereas drugs that undergo extensive hydrogen bonding display a low intrinsic efflux rate and can be used as P-gp inhibitors. The substrate-induced ATPase activation is usually biphasic with stimulation at low drug concentrations and inhibition at higher drug concentrations (Hennessy and Spiers, 2007).

4. Relationship between P-glycoprotein and minimally-sedating H₁-antihistamines

In the last two decades, many researchers have reported that first-generation H₁-antihistamines hold much stronger CNS side effects, especially sedative effects, than second-generation H₁-antihistamines. Positron emission tomography (PET) measurement of H₁-receptor occupancy is recommended to evaluate drugs' CNS effects (Holgate et al., 2003). The PET scans showed that first-generation H₁-antihistamines penetrated BBB readily, and interfered with histamine binding to H₁-receptors in CNS. However, second-generation H₁-antihistamines, such as fexofenadine, loratadine, cetirizine, ebastine, and bepotastine, are limited to penetrate BBB, and are not able to bind to H₁-receptors in the CNS (Howarth, 2002; Tashiro et al., 2008; Tagawa et al., 2001). The lack of sedative effect of the second-generation H₁-antihistamines is related to the P-gp action that pumps drugs out of the BBB (Timmerman, 1999). Its mechanisms are determined by the P-gp affinity (Obradovic et al., 2007; Conen et al., 2013), MDR gene expression (Ambudkar et al., 2003; Yi et al., 2004; Cvetkovic et al., 1999), and/or energy source (Wang et al., 2001).

Table 2
Pharmacokinetic parameters of H₁-antihistamines.

Generation	Drug name	Half life/h	Protein binding/%	pK _a	C _{max} /μg/ml	T _{max} /h	AUC/μg h/ml (Merlos et al., 1997; Shen et al., 2007)
First	Hydroxyzine (Simons et al., 1984)	20	93	7.82	0.0725	2.1	1.38
Second	Cetirizine (Gandon and Allain, 2002)	8.3	93–98	7.79	0.247	3.8	4.39
Second	Levocetirizine (Simons et al., 1995)	7.8	90	7.49	0.509	0.8	4.09
Second	Loratadine (Zhang et al., 2003)	6	97–99	4.33	17	1.2	0.047
Second	Desloratadine (Zhang et al., 2003)	27	82–87	9.73	16	1.5	0.18
Second	Fexofenadine (Kikuchi et al., 2006)	13.1	60–70	9.01	0.427	1.44	2.68
Second	Carebastine (Yamaguchi et al., 1994)	15	97	10.3	0.98	6	2.37
Second	Bilastine (Scaglione, 2012; Ridolo et al., 2015)	14.5	84–90	–	0.22	1.3	0.99
Second	Bepotastine (Kim and Park, 2013)	2.4	55	–	0.1	1.2	0.39

4.1. Minimally-sedating H₁-antihistamines have a high affinity for P-glycoprotein

Minimally-sedating H₁-antihistamines exit blood–tissue barriers, such as the BBB, because they specifically bind to P-gp (Conen et al., 2013) and are pumped out by P-gp (Timmerman, 1999). The specific binding site is in the drug-binding pocket that consists of two transmembrane domains (TMDs). Different P-gp substrates bind to different residues in the drug-binding pocket, and then are pumped out of the cell membrane. However, the binding sites and residues of H₁-antihistamines have not been identified.

High affinity for P-gp is an important property of second-generation H₁-antihistamines, compared with the classical first H₁-antihistamines that are not P-gp substrates.

4.2. Studies using P-glycoprotein inhibitors

Permeability of H₁-antihistamines was studied by PBMEC/C1-2, an *in vitro* BBB model using a porcine cell line. The results demonstrated that in the presence of verapamil, a P-gp inhibitor, the transport rates of second-generation H₁-antihistamines (cetirizine, fexofenadine, astemizole, and loratadine) increased (Neuhaus et al., 2012).

Table 3 compares different generations of H₁-antihistamines transporting across MDR-MDCK cell monolayers. The MDR-MDCK cell line is a popular model for testing whether a drug is a substrate of P-gp. The H₁-antihistamine permeation was tested in two directions, apical-to-basolateral (A-to-B) and basolateral-to-apical (B-to-A), in the presence or absence of cyclosporin A (CSA), a P-gp inhibitor (Obradovic et al., 2007). The higher the B-A/A-B apparent permeability coefficient (P_{app}) ratio in the absence of CSA, the stronger the P-gp efflux action (Obradovic et al., 2007). P-gp is on the apical side of MDR-MDCK cell monolayers, which may play an essential role in alleviating the sedative effect of H₁-antihistamines. The results of this study showed that P-gp had the greatest impact on cetirizine, which was followed by loratadine and fexofenadine (Obradovic et al., 2007). The apparent permeability coefficient of loratadine, cetirizine, and fexofenadine between the apical and basolateral membranes of the BBB decreased, 1.85, 56.3, and 0.95 fold, respectively (Obradovic et al., 2007).

These studies showed that the ability for second-generation

H₁-antihistamines to cross BBB depended on the affinity of P-gp. Thus, the concentration of second-generation H₁-antihistamines became low in the CNS and caused negligible sedation when clinical doses of the drugs were administered. These findings also indicated that when the P-gp efflux transporter is blocked, there is a decrease in second-generation H₁-antihistamines efflux from the BBB, causing an increase in the cerebral concentration of the drug. A human-based study also showed that during the treatment with a combination of cetirizine and verapamil, participants were less alert than those receiving cetirizine only (Conen et al., 2013). Cetirizine has a high affinity for P-gp that contributes to the lower incidence of drug-induced sedation (Conen et al., 2013).

4.3. P-glycoprotein knockout studies

In a P-gp KO study, it was found that the brain concentrations of cetirizine, loratadine, and desloratadine were low in WT mice, while the cerebral drug concentrations of KO mice were 4-fold, 2-fold, and 14-fold higher than WT mice, respectively (Chen et al., 2003). In contrast, the brain-to-plasma area under the curve ratio between KO and WT was comparable for first-generation H₁-antihistamines hydroxyzine (the precursor of cetirizine), diphenhydramine, and triprolidine (Chen et al., 2003). These findings indicated that second-generation H₁-antihistamines (cetirizine, loratadine, and desloratadine) are P-gp substrates and are pumped out of BBB by P-gp. A study using LLC-PK1 cell line (P-gp KO) and L-MDR1 cell line (P-gp over-expressed) identified that P-gp was a fexofenadine and bepotastine efflux transporter. Little fexofenadine was found inside the L-MDR1 cells when compared with LLC-PK1 cells (Cvetkovic et al., 1999; Ohashi et al., 2006).

4.4. MDR gene expression

In humans, P-gp is encoded by multidrug-resistance genes (MDR) that are located on the long arms of chromosome 7 (7q21) (Hennessy and Spiers, 2007; Ambudlar et al., 2003). MDR1 is associated with the multidrug-resistant phenotype, which affects the disposition and pharmacokinetics of various drugs (Montesinos et al., 2012).

The MDR1 gene determines the structure and function of P-gp. For example, the plasma concentrations of fexofenadine after a single oral administration were lower in persons with 2677AA

Table 3
H₁-antihistamines transport across MDR-MDCK cell monolayers (Obradovic et al., 2007).

Compound	Treatment	Mean P_{app} value $\pm$ SD ($\times 10^{-6}$ cm/s)	B-A/A-B P_{app} ratio
Loratadine	No CSA ^a	A-B: 4.75 ± 1.58 ; B-A: 35.00 ± 4.30	7.4
	With CSA	A-B: 15.52 ± 4.90 ; B-A: 39.64 ± 1.53	2.6
Terfenadine	No CSA	A-B: 0.62 ± 0.08 ; B-A: 11.43 ± 0.68	18.5
	With CSA	A-B: 1.51 ± 0.61 ; B-A: 2.39 ± 0.52	1.6
Fexofenadine	No CSA	A-B: 0.34 ± 0.14 ; B-A: 1.34 ± 0.72	3.9
	With CSA	A-B: 0.13 ± 0.05 ; B-A: 0.27 ± 0.12	2
Hydroxyzine	No CSA	A-B: 26.60 ± 1.20 ; B-A: 38.10 ± 8.30	1.4
	With CSA	A-B: 30.10 ± 1.10 ; B-A: 32.00 ± 3.60	1.1
Cetirizine	No CSA	A-B: 0.29 ± 0.02 ; B-A: 18.30 ± 3.20	63
	With CSA	A-B: 2.30 ± 0.73 ; B-A: 2.46 ± 0.74	1.1

P_{app} : apparent permeability coefficient.

A-B: Apical to basolateral penetration; B-A: Basolateral to apical penetration.

Note that the higher the B-A/A-B P_{app} ratio, the more efflux.

^a CSA: Cyclosporin A, a P-glycoprotein inhibitor.

/3435CC genotype of MDR1 than in persons with other genotypes (Ambudkar et al., 2003; Yi et al., 2004). When [^{14}C]fexofenadine was administered (orally or intravenously) to mice lacking MDR1a-encoded P-gp, a 5–9 fold increase in fexofenadine concentration in both brain and plasma was observed when compared with those of WT mice (Cvetkovic et al., 1999). These findings indicated that fexofenadine efflux is related to the expression of MDR1 gene.

4.5. ATPase activity

ATP binding sites are located in both cytoplasmic nucleotide-binding domains (NBDs). Activity of ATPase affects efflux of second-generation H_1 -antihistamines. Loratadine increases baseline ATPase activity of MDR1/P-gp in a concentration-dependent manner and leads to a 2-fold increase in ATPase activity (Wang et al., 2001). Bepotastine also consumes more energy and increases baseline ATPase activity of P-gp in ATPase activity assay (Ohashi et al., 2006). These findings strongly support the notion that the lack of the sedative effect of loratadine and bepotastine is mediated through P-gp.

5. Other determining factors of minimally-sedating features of H_1 -antihistamines

There is no doubt that P-gp plays a vital role in reducing sedative effects of second-generation H_1 -antihistamines. However, some other factors may help determine the minimally-sedating feature of second-generation H_1 -antihistamines. Cytochrome P450 enzymes, enantiomers, molecular weight, and pK_a may support the minimally-sedating features of second-generation H_1 -antihistamines.

5.1. What are the differences between desloratadine and loratadine? Carebastine and ebastine?

Desloratadine and Carebastine are active metabolites of loratadine and ebastine, respectively, via the action of hepatic cytochrome P450 enzymes.

Desloratadine has a longer plasma half-life (27 h) than loratadine (6 h) (Zhang et al., 2003) and its H_1 -antihistaminic effect is stronger than that of loratadine at the same dose in humans (Chen et al., 2003).

In a P-gp KO study, the brain concentrations of loratadine and desloratadine were lower in WT mice than in KO mice after administration. The brain concentration of loratadine was only 2-fold higher in KO mice than WT mice, while that of desloratadine was 14-fold higher in KO mice than WT mice (Chen et al., 2003). It appears that desloratadine is a stronger P-gp substrate than loratadine in mice. However, the interaction of desloratadine with P-gp was significantly less than that of loratadine in a human P-gp model in which desloratadine inhibited P-gp 4 times less than loratadine (Wang et al., 2001). These findings suggested that desloratadine is a weaker substrate of P-gp than loratadine in humans. These findings further suggested that there is a species difference with regard to the activity of desloratadine as a P-gp substrate. It seems that in humans, the less sedating effect of desloratadine than loratadine is attributable to other properties. Since desloratadine has a high pK_a of 9.73 and it is less lipophilic than loratadine, it is very likely that these properties of desloratadine also play a role in its minimally-sedating feature.

It is intriguing that desloratadine has a much longer plasma half-life (27 h) than loratadine (6 h) (Zhang et al., 2003), but the reason behind this phenomenon is not clear. Based on desloratadine's high pK_a and low lipophilicity, it should have a shorter

plasma half-life than loratadine because these properties inhibit gut absorption and renal reabsorption of the drug. Further studies are needed to determine why desloratadine has a much longer plasma half-life than loratadine.

Ebastine is a prodrug and long-lasting second-generation H_1 -antihistamine. Oral administration of ebastine leads to a negligible plasma concentration of ebastine and a high plasma concentration of carebastine – the carboxylated ebastine. The carboxylation of ebastine occurs in the liver. Carebastine possesses H_1 -antihistamine activity with a half-life of 13.8 to 15.3 h (Yamaguchi et al., 1994) and is a P-gp substrate. In the model of P-gp over-expressing K562/ADM cells, uptake of carebastine was significantly lower than in parental drug-sensitive cell line K562. This decreased uptake of carebastine by K562/ADM can be reversed by verapamil (Tamai et al., 2000).

5.2. Why does cetirizine have a greater sedative effect than other second-generation H_1 -antihistamines?

Among second-generation H_1 -antihistamines, cetirizine shows a more noticeable sedative effect than others (Gandon and Allain, 2002; Kalivas et al., 1990; He et al., 2010; Ozdemir et al., 2014). Although only a small quantity of cetirizine enters the brain after oral administration, and it has minimal anticholinergic and anti-serotonergic activities, cetirizine still induces dry mouth and mild drowsiness (Kalivas et al., 1990). Cetirizine is a racemic mixture that consists of dextrocetirizine and levocetirizine. Compared with cetirizine and dextrocetirizine, levocetirizine holds stronger H_1 -antihistaminic effects in the peripheral system and much less CNS side effects (Ozdemir et al., 2014). However, in a study based on the BBB transport in a guinea pig model, there was no significant difference between these two enantiomers, suggesting that the drug efflux by P-gp is not different between the two (Gupta et al., 2006). It is possible that the cetirizine/dextrocetirizine-induced sedation is species-specific, since cetirizine induces sedation in humans, but may not in guinea pigs. Further studies using cells expressing human P-gp are needed to determine why dextrocetirizine, but not levocetirizine, has noticeable sedative effect.

5.3. Why is the clinical fexofenadine dose 12 times higher than other second-generation H_1 -antihistamines?

The efflux of fexofenadine by P-gp may not be as remarkable as loratadine and cetirizine, as suggested by the data in Table 3. The most commonly used dose of fexofenadine, as an H_1 -antihistamine, is 120 mg per person per day, orally. This dose is 12 times higher than the recommended oral dose of both cetirizine and loratadine (10 mg per person per day). The oral availability of fexofenadine is increased 2.1-fold by the co-administration of erythromycin, a P-gp inhibitor (Kataoka et al., 2011). However, these findings still cannot account for the fact that the clinical dose of fexofenadine is 12 times higher than loratadine and cetirizine. It is very likely that the high pK_a of fexofenadine (9.01) also plays an important role in the membrane transport of this drug (Kikuchi et al., 2006); at pH of 7.4, the ratio between the ionized and non-ionized forms of fexofenadine is 40:1. The high concentration of ionized form of fexofenadine will hinder the membrane transport of this drug. As a result, the gut absorption and the renal re-absorption of fexofenadine are low, even though organic anion-transporting polypeptide (OATP) may help absorb fexofenadine from the gut (Cvetkovic et al., 1999).

6. Conclusions and remarks

P-glycoprotein receives a great deal of attention, because multidrug resistance of P-gp results in therapeutic failure in

clinical practice, particularly drug resistance in chemotherapy. In contrast, this feature becomes an advantage when second-generation H₁-antihistamines are used to treat allergies because of their negligible or minimal sedative effect.

A few studies focusing on the interactions between P-gp and H₁-antihistamines demonstrated that the second-generation H₁-antihistamines have minimal or no sedative effect by serving as P-gp substrates. However, to date, there is no report to present a clear model of tertiary structure of human P-gp. Most of the studies that focus on human P-gp and H₁-antihistamines have been performed at the macroscopic level. Further studies of the minimally-sedating mechanism at the molecular level would be a great contribution to medicine, provided that (1) the human P-gp-related genetic sequence of MDR1 is discovered and (2) the structure-function relationship between P-gp and second-generation H₁-antihistamines is elucidated.

There are additional remarks on second-generation H₁-antihistamines: (1) Why is the dose of fexofenadine 12-times higher than loratadine and cetirizine? (2) Why does desloratadine have much longer half-life than loratadine? (3) Why does cetirizine show more noticeable sedative effect than other second-generation H₁-antihistamines? Further studies are warranted to answer these questions.

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