P-GLYCOPROTEIN LIMITS THE BRAIN PENETRATION OF NONSEDATING BUT NOT SEDATING H1-ANTAGONISTS

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ABSTRACT:
The present study evaluates the impact of P-glycoprotein (P-gp) on plasma-brain disposition and transepithelial transport of sedating versus nonsedating H1-antagonists using multidrug-resistant (mdr) gene 1a and 1b (mdr1a/b) knockout (KO) mice and human MDR1-transfected Madin-Darby canine kidney (MDCK) cells. Three nonsedating (cetirizine, loratadine, and desloratadine) and three sedating (diphenhydramine, hydroxyzine, and tripolidine) H1-antagonists were tested. Each compound was administered to KO and wild-type (WT) mice intravenously at 5 mg/kg. Plasma and brain drug concentrations were determined by liquid chromatography-mass spectrometry analysis. Mean pharmacokinetic parameters (CL, Vss, and t1/2) were obtained using WinNonlin. In addition, cetirizine, desloratadine, diphenhydramine, and tripolidine (2 μM) were tested as substrates for MDR1 using MDR1-MDCK cells. The bidirectional apparent permeability was determined by measuring the amount of compound at the receiving side at 5 h. The brain-to-plasma area under the curve (AUC) ratio was 4-, 2-, and >14-fold higher in KO mice compared with WT mice for cetirizine, loratadine, and desloratadine, respectively. In contrast, the brain-to-plasma AUC ratio between KO and WT was comparable for hydroxyzine, diphenhydramine, and tripolidine. Likewise, the efflux ratio between basolateral to apical and apical to basolateral was 4.6- and 6.6-fold higher in MDR1-MDCK than the parental MDCK for cetirizine and desloratadine, respectively, whereas it was approximately 1 for diphenhydramine and tripolidine. Our results demonstrate that sedating H1-antagonists hydroxyzine, diphenhydramine, and tripolidine are not P-gp substrates. In contrast, nonsedating H1-antagonists cetirizine, loratadine, and desloratadine are P-gp substrates. Affinity for P-gp at BBB may explain the lack of central nervous system side effects of modern H1-antagonists.

Antagonists of H1 histamine receptors (H1-antagonists) are the mainstays of treatment for a number of allergic disorders, particularly rhinitis, conjunctivitis, dermatitis, urticaria, and asthma. Two generations of H1-antagonists have been developed so far. The first generation H1-antagonists such as diphenhydramine (Benadryl), tripolidine (Actifed), or hydroxyzine (Atarx) produce histamine blockade at H1-receptors in the central nervous system (CNS1) and frequently cause somnolence or other CNS adverse effects (Simons, 1999). Therefore, the first generation H1-antagonists are also referred to as sedating antihistamines. The second generation H1-antagonists such as cetirizine (Zyrtec), loratadine (Claritin), fexofenadine (Allegra), or desloratadine (Clarinex) represent an advance in therapeutics; in man, the manufacturers’ recommended doses, they produce relatively little somnolence or other CNS side effects (Kay and Harris, 1999). Therefore, the second generation H1-antagonists are frequently referred as nonsedating antihistamines. Evidence for this improvement in tolerance profile resulting from reduced CNS penetration has been limited (Yanai et al., 1999). Therefore, it is worthwhile to study the underlying mechanisms limiting brain penetration of the second generation H1-antagonists, if any, to develop the next generation of H1-antagonists that are devoid of CNS side effects.

One potential mechanism for the limited CNS exposure and consequently CNS side effects for nonsedating H1-antagonists is P-glycoprotein (P-gp)-mediated efflux. P-gp, which is encoded by the multidrug resistance gene 1 (human MDR1 and rodent mdr1a and mdr1b), exists in various normal tissues such as intestinal epithelium, liver bile canallicula, and brain endothelium (Borst et al., 1999). Numerous studies have shown that brain endothelium P-gp can pump xenobiotics with diverse structures out of the brain, thereby reducing unwanted or undesired CNS effects (Schinkel et al., 1994, 1997; Schinkel, 1998; Chen and Pollack, 1999; Cvetkovic et al., 1999; Yokogawa et al., 1999; Elmquist and Miller, 2001). These studies have been mainly conducted using mdr1a knockout (KO) mice. The mdr1a KO and mdr1a/1b double KO mice are unique in vivo models to study the P-gp’s effect on the blood-brain disposition of xenobiotics (Schinkel et al., 1994, 1997; Schinkel, 1998; Chen and Pollack, 1999; Cvetkovic et al., 1999; Yokogawa et al., 1999; Elmquist and Miller, 2001). For compounds that are P-gp substrates, the brain-to-plasma concentration ratio at steady state or brain-to-plasma area under the curve (AUC) ratio is significantly higher in KO mice compared with the genetically competent counterpart (Chen and Pollack, 1999).

Limited evidence has shown that P-gp may reduce the CNS exposure of nonsedating but not sedating H1-antagonists. For example, terfenadine (Seldane), the first nonsedating H1-antagonist, was shown to inhibit P-gp in vitro (Hait et al., 1993; Raeissi et al., 1999; Chishty...
P-GLYCOPROTEIN REDUCES BRAIN PENETRATION OF NONSEDATING H1-ANTAGONISTS

et al., 2001) and as a P-gp substrate (Kim et al., 1999). No study has been conducted to show that terfenadine has limited CNS exposure due to P-gp. Two separate studies showed that fexofenadine, another nonnosing H1-antagonist and an active metabolite of terfenadine, is a P-gp substrate (Cvetkovic et al., 1999; Soldner et al., 1999). Cvetkovic et al. (1999) identified P-gp as a fexofenadine efflux transporter using the LLC-PK1 cell, a polarized epithelial cell line lacking P-gp, and the derived cell line (L-MDR1), which overexpresses P-gp. In the same study oral and i.v. administration of [14C]fexofenadine to mice lacking mdr1a-encoded P-gp resulted in an approximately 2-fold higher brain-to-plasma concentration ratio at 4 h postdose in mdr1a KO compared with WT mice. Consistent with results from Cvetkovic et al. (1999), Soldner et al. (1999) demonstrated P-gp-mediated efflux of fexofenadine using the recombinant vaccinia expression system that contains overexpressed P-gp or MDR1-transfected Madin-Darby canine kidney (MDCK) cells. Although limited, the data suggest that P-gp may prevent nonnosing H1-antagonists from accessing the brain.

The present study was undertaken to test the hypothesis that nonnosing H1-antagonists are P-gp substrates, thereby reducing CNS exposure, whereas sedating ones are not. Three sedating (hydroxyzine, diphenhydramine, and triprolidine) and three nonnosing [cetirizine, the active metabolite of hydroxyzine (Paakkari, 2002), loratadine, and desloratadine, the active metabolite of loratadine (Radwanski et al., 1987)] H1-antagonists were used in the study. The plasma-brain disposition of these H1-antagonists was examined in mdr1a/b KO and WT mice after intravenous administration. In addition, two sedating (diphenhydramine and triprolidine) and two nonnosing (cetirizine and desloratadine) H1-antagonists were tested as P-gp substrates using MDR1-MDCK cells.

Materials and Methods

Materials. Hydroxyzine, triprolidine, and diphenhydramine were obtained from Sigma-Aldrich (St. Louis, MO). Loratadine and desloratadine were extracted and purified from prescribed capsules with purity of >99%. Compounds A and B were synthesized at Pfizer Inc. (Groton, CT). All the other chemicals and reagents were the highest grade available from commercial sources.

Animals. Male FVB (control) and mdr1a/b KO mice, 4 to 5 weeks of age (Taconic Farms, Germantown, NY), were housed in a group of 20 and 2, respectively, with free access to food and water and were maintained on a 12-h light/dark cycle.

Plasma-Brain Disposition of H1-Antagonists in WT and KO Mice. Mice were administered each individual compound intravenously at 5 mg/kg through tail vein injection (<100 μl in less than 30 s). Blood and brain samples were harvested at 2, 5, 15, 45, 120, 240, 480, and 1440 min postdose (n = 3 mice/time point). Plasma samples were obtained by centrifuging the blood samples at 13,000 rpm for 2 min. Brain was rinsed with saline and blotted dry and weighed. Samples were stored at −20°C before analysis by liquid chromatography-mass spectrometry.

Quantitation of H1-Antagonists in Plasma and Brain. Sample pretreatment. Loratadine and triprolidine plasma samples were extracted using liquid-liquid extraction. Briefly, to 100 μl of sample was added 10 μl of internal standard (i.s.) Compound A (Fig. 1) and diphenhydramine were used as the i.s. for loratadine and triprolidine, respectively. The samples were extracted by adding methyl-t-butyl ether (500 μl) using a HPLC Autosampler (PerkinElmer Sciex Instruments, Thornhill, ON, Canada). An aliquot of the reconstitute (20 μl) was injected to an Asahipak ODP C18 column (2.6 i.d. × 20 mm; Shimadzu, Kyoto, Japan) at 20°C. The analytes and is were eluted with a mobile phase composed of solvent A (95% water/5% acetonitrile, containing 0.01% acetic acid) and B (5% water/95% acetonitrile, containing 0.01% acetic acid) under the following gradient: 0 to 0.20 min, 100% of solvent A; 0.20 to 0.30 min, linear gradient from 100% solvent A to 100% solvent B; and then keep at 100% of solvent B for up to 1.5 min. The analyte and i.s. were monitored based on the ion pair (parent and daughter) that is specific to each compound at a collision energy of positive 40 V. The ion pairs (parent and daughter) under the current mass spectrometry conditions for diphenhydramine, hydroxyzine, triprolidine, cetirizine, loratadine, and desloratadine were 255.3/136.1, 374.9/202.2, 278.4/ 208.2, 388.9/202.2, 383.0/383.1, and 310.8/259.2, respectively. The peak areas of the analyte and i.s. were obtained using MacQuan (PerkinElmer Sciex)
The ratio between the dose and AUC0-$\infty$ analysis was used to estimate the pharmacokinetic parameters (Gibaldi and Vos). The quality control samples provided values within 20% of the added value for brain homogenate. Validation of the analytical procedure was carried out and the limits of quantitation were 1 to 10 ng/ml for plasma and 1 to 500 ng/ml for brain homogenate. Instruments. The limits of quantitation were 1 to 10 ng/ml for plasma and brain homogenate. Validation of the analytical procedure was carried out and the quality control samples provided values within 20% of the added value throughout calibration range of 1 ng/ml to 10 μg/ml.

**Estimation of Pharmacokinetic Parameters.** Noncompartmental model analysis was used to estimate the pharmacokinetic parameters (Gibaldi and Perrier, 1982) such as systemic clearance (CL, which was calculated based on the ratio between the dose and AUC0-$\infty$), volume of distribution at steady state ($V_{ss}$), and terminal half-life ($t_{1/2}$, which was calculated using a minimal of the last three concentration-time data). Only AUC0-$\infty$ was calculated for the brain concentration-time data for each compound. All calculations were based on the mean concentration-time data; each data point was the mean of three animals. Therefore, the pharmacokinetic parameter estimates are expressed only as mean. The brain partition of each H1-antagonist was estimated based on the brain-to-plasma AUC ratio, and the in vivo P-gp function was defined as the ratio of brain-to-plasma AUC ratio between KO and WT mice (Adachi et al., 2001).

**Metabolism of Loratadine and Hydroxyzine in Vivo.** Cetirizine and desloratadine, the major metabolites postdosing of hydroxyzine and loratadine, respectively, in mice were identified using LC-MS-MS with the aid of the standard of cetirizine and desloratadine. The plasma samples were pooled and were pretreated in the same way as for quantitation as described previously.

**Transepithelial Transport of Two Sedating H1-Antagonists Triprolidine and Diphenhydramine and Two Nonsedating H1-Antagonists Ceti-**

![Figure 2](image_url)  
**Fig. 2. Plasma (a) and brain (b) concentration-time profiles of diphenhydramine after a 5-mg/kg i.v. administration to KO (open symbols) and WT (solid symbols) mice.**

Data are presented as mean ± S.D. ($n = 3$).

In contrast to the sedating H1-antagonists, the nonsedating H1-antagonists exhibited different brain disposition between the KO and WT mice. The brain concentration-time profiles for cetirizine, loratadine, and desloratadine are shown in Figs. 4, II-III.b, 5I.b, and Fig. 5III.b, respectively. In general, for the nonsedating H1-antagonists, the brain-to-plasma AUC ratio is much higher in KO than WT mice because of the much higher brain AUC but comparable plasma AUC in KO compared with WT mice (Table 2). For cetirizine, brain concentration-time profile in KO mice differed greatly from that of WT postdosing either cetirizine (Fig. 4III.b) or its precursor hydroxyzine (Fig. 4II.b). After dosing hydroxyzine, KO mice showed slightly higher plasma cetirizine AUC than WT mice (418 versus 287 μg/ml × min). However, KO mice had a brain AUC of 67 μg/ml × min, whereas WT mice had a brain level of below the limit of quantitation of the current assay (1 ng/ml) (Fig. 4II.b). After dosing...
cetirizine, the brain $C_{\text{max}}$ value was 0.09 and 0.28 $\mu$g/ml for WT and KO mice, respectively. The brain-to-plasma AUC ratio was 4-fold higher in KO than in WT mice (Table 2).

Likewise, loratadine also had a higher brain-to-plasma AUC ratio in KO compared with WT mice (2.8 versus 1.4). The brain concentration of loratadine peaked at 2 min postdose and had a $C_{\text{max}}$ value of 14.7 and 6.9 $\mu$g/ml for KO and WT mice, respectively. However, it cleared from the brain very efficiently with more rapid clearance from brain in WT than KO mice (Fig. 5I.b). The active metabolite of loratadine, desloratadine, was also determined in plasma and brain tissue post-dosing of loratadine. No significant difference in the formation of desloratadine in the two strains of mice was observed in plasma (Fig. 5II.a). The AUC was 25 and 30 $\mu$g/ml $\times$ min for WT and KO, respectively. Additionally, no detectable brain concentration of desloratadine was observed postloratadine administration in either strain of mice. However, when desloratadine was dosed directly to mice, no brain concentration was detected in WT mice except at 5 min post-dose, whereas a high level of desloratadine was found in KO mouse brains (Fig. 5III.b). The brain AUC of desloratadine in KO mice was 3548 $\mu$g/ml $\times$ min.

Metabolism of H1-Antagonists in Vivo. The active metabolite for hydroxyzine and loratadine was cetirizine and desloratadine, respectively. This was confirmed with LC-MS-MS fragmentation of the metabolite compared with that of the corresponding standard (data not shown).

Transepithelial Transport of the Two Sedating H1-Antagonists Triprolidine and Diphenhydramine and the Two Nonsedating H1-Antagonists Cetirizine and Desloratadine in MDR1-MDCK and parental MDCK Cells. Initial experiment showed that transporter was linear within a 5-h incubation time period (data not shown). Therefore, 5 h was used as the duration for the transporter study. As shown in Table 2, both cetirizine and desloratadine showed asymmetric permeability with an efflux ratio of 5.8 and 9.1, respectively. The efflux was primarily associated with MDR1 as indicated by the low efflux in the parental MDCK cells. In contrast, the efflux ratio for triprolidine and diphenhydramine was approximately 1 in either MDR1-MDCK or parental MDCK cells. The positive controls quinidine and prazosin showed an efflux ratio of 26.5 and 4.3 in MDR1-

![Fig. 3. Plasma (a) and brain (b) concentration-time profiles of triprolidine after a 5-mg/kg i.v. administration to KO (open symbols) and WT (solid symbols) mice.](image)

Data are presented as mean ± S.D. ($n = 3$).

![Fig. 4. Plasma (a) and brain (b) concentration-time profiles of hydroxyzine (I) and its active metabolite cetirizine (II and III) after a 5-mg/kg i.v. administration of hydroxyzine (I and II) and cetirizine (III) to KO (open symbols) and WT (solid symbols) mice.](image)

Data are presented as mean ± S.D. ($n = 3$).
MDCK and 2.3 and 1.9 in parental MDCK cells, respectively (Table 2).

Discussion

It is well known that first generation H1-antagonists are sedating and the second generation H1-antagonists are either nonsedating or less sedating. Factors such as physical-chemical properties (mol. wt., log D, and ionization), and active transporters (uptake and efflux) at the blood-brain barrier (BBB) may determine the blood-brain translocation of xenobiotics. Difference in the physical-chemical properties may play a role in determining the extent of brain penetration and CNS exposure of these compounds. For example, sedating H1-antagonists in general have smaller mol. wt. (<350) compared with that of nonsedating H1-antagonists (340–502). However, mol. wt. alone cannot explain the difference in brain penetration. For example, desloratadine, the active metabolite of loratadine, has a comparably small mol. wt. (338.9) to that of hydroxyzine (347.9), yet no desloratadine versus ~8 μg/ml hydroxyzine was observed in brain tissue of WT mice 2 min after the same i.v. dose. Few studies have been conducted to examine whether there is a difference in plasma-brain translocation of sedating versus nonsedating H1-antagonists and if there is a difference, whether the difference is due to certain active transporters at BBB.

One potential active transporter system at BBB is P-gp. P-gp has been shown to decrease brain penetration of a variety of compounds with diverse structures (Schinkel et al., 1994, 1997; Schinkel, 1998; Chen and Pollack, 1999). There has been some speculation about a potential link between nonsedation of second generation H1-antagonists and P-gp efflux nature (Timmerman, 1999, 2000). However, only a few studies have shown that nonsedating H1-antagonists are P-gp substrates, thus reducing their brain penetration, which may limit their CNS side effects. Fexofenadine is the only nonsedating H1-antagonist that has been shown to be a P-gp substrate in both in vitro such as MDR1-MDCK transfected systems and in vivo mdr1a/b KO mice (Cvetkovic et al., 1999; Soldner et al., 1999). The present study was conducted to investigate the plasma-brain translocation and the role of P-gp in brain penetration of sedating and nonsedating H1-antagonists using mdr1a/b KO mice. Additionally, we tested two sedating and two nonsedating H1-antagonists in in vitro MDR1-MDCK cells.

In general, the brain-to-plasma AUC ratio, which reflects brain penetration, is much higher for the sedating H1-antagonists (3.80–9.00) compared with the nonsedating ones (0.02–1.65) in WT mice whose brain endothelium contains P-gp. The significant reduction in brain penetration for nonsedating H1-antagonists compared with sedating ones in WT mice is consistent with the fact that P-gp acts as an efflux pump that extrudes its substrates. The partitioning of P-gp substrates to the brain in mdr1a/b KO mice should no longer be restricted by P-gp and more governed by their physical-chemical properties. Therefore, a ratio of brain-to-plasma AUC ratio of approximately 1 between KO and WT mice for sedating H1-antagonists diphenhydramine, triprolidine, or hydroxyzine was observed, suggesting nonsedating H1-antagonists are not P-gp substrates. In contrast, a 2.0-, 4.4-, and >14-fold higher brain-to-plasma AUC ratio was observed in KO compared with WT mice for nonsedating H1-antagonists loratadine, cetirizine, and desloratadine, respectively, indicating that nonsedating H1-antagonists are P-gp substrates.

The fact that nonsedating H1-antagonists cetirizine and desloratadine are P-gp substrates was further substantiated by the results after dosing their precursors hydroxyzine and loratadine, respectively. The formation of cetirizine from hydroxyzine did not differ with mouse strains as indicated by the similarity of systemic exposure of cetirizine posthydroxyzine administration. Yet, significant cetirizine was measured in the brains of KO but not WT mice. Likewise, formation of plasma desloratadine was comparable between KO and WT mice, even though there was no detectable brain concentration of desloratadine after dosing loratadine in WT or KO mice. This may be due to low plasma desloratadine concentration, and subsequently even lower brain concentration, which may be below the limit of quantitation of the current assay for desloratadine (1 ng/ml). It has been shown that cetirizine (Paakkari, 2002) and desloratadine (Clissold et al., 1989) are

![Figure 5](https://example.com/figure5.png)
the active metabolite in humans for hydroxyzine and loratadine, respectively. The metabolism of loratadine to desloratadine in humans is mainly mediated by a combination of cytochrome P450 2D6 and 3A4 (Yumibe et al., 1996). In contrast, it is not known regarding the specific enzyme that is responsible for the formation of cetirizine from hydroxyzine (Paakkari, 2002). Regardless of the enzymes involved in the formation of active metabolite from hydroxyzine and loratadine, a comparable systemic exposure of the active metabolite for hydroxyzine and loratadine between KO and WT mice suggests the similarity in these metabolizing enzymes between the two strains of mice.

Consistent with the in vivo mouse data, which strongly indicate that P-gp mediates the brain-to-plasma efflux of nonsedating but not sedating H1-antagonists, the in vitro MDR1-MDCK results also demonstrate a significant MDR1-associated efflux for the two nonsedating but not for the two sedating H1-antagonists. The MDR1-MDCK data suggest that nonsedating H1-antagonists are, whereas sedating H1-antagonists are not MDR1 substrates, consistent with results from the in vivo mouse study.

In contrast to our finding, Wang et al. (2001) showed that desloratadine failed to significantly increase in basal ATPase activity, suggesting that desloratadine is unlikely a P-gp substrate under the experimental conditions. Unlike the MDR1-MDCK cell assay that directly measures transport of potential P-gp substrates, ATPase assay is a generic readout on the release of inorganic phosphate and does not directly measure transport (Scarborough, 1995; Polli et al., 2001). Polli et al. (2001) demonstrated that there was no instance of a compound that was positive in the ATPase assay and negative in other assays, including transport assay using MDR1-MDCK cells. In contrast, the opposite was true. For example, daunorubicin showed a significant efflux in MDR1-MDCK cells with an efflux ratio of 14.2 but an ambiguous readout in the ATPase assay (Polli et al., 2001). Therefore, the ATPase assay may provide false negative results in the case of desloratadine. Although the clinical implications are unknown and worthy of further study, the present study provides the first direct evidence that desloratadine is a P-gp substrate using both KO and WT mice.

In summary, the present study has demonstrated for the first time that sedating H1-antagonists hydroxyzine, diphenhydramine, and triprolidine are not P-gp substrates; they show equal brain penetration between mdr1a/b KO and WT mice and equal bidirectional (A-to-B and B-to-A) permeability in MDR1-MDCK cells. In contrast, nonsedating H1-antagonists cetirizine, loratadine, and desloratadine are P-gp substrates; they exhibit significantly reduced brain exposure in WT compared with KO mice and significant MDR1-associated efflux in MDR1-MDCK cells. Our results at least partially explain the reduced or devoid CNS side effects for nonsedating H1-antagonists and suggest that optimization of affinity toward H1-receptor and P-gp may be a useful strategy to select H1-antagonists with desired potency and without potential CNS sedating effect.

Acknowledgments. We thank Ralph Davidson and Dr. Dennis Pereira for helping with the MDCCK assay of the two sedating and two nonsedating H1-antagonists.

References


### TABLE 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ratio of Brain to Plasma AUC Ratio between KO and WT Mice</th>
<th>Efflux Ratio in MDR1-MDCK (P&lt;sub&gt;B-to-A&lt;/sub&gt;/P&lt;sub&gt;A-to-B&lt;/sub&gt;)</th>
<th>Efflux Ratio in MDCCK (P&lt;sub&gt;B-to-A&lt;/sub&gt;/P&lt;sub&gt;A-to-B&lt;/sub&gt;)</th>
<th>P-gp Substrate</th>
<th>Sedating?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetirizine</td>
<td>4.4 (0.80/0.12)</td>
<td>5.6 ± 0.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.3 ± 0.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>No (Kay and Harris, 1999)</td>
</tr>
<tr>
<td>Loratadine</td>
<td>2.0 (3.80/1.60)</td>
<td>N.D.</td>
<td>N.D.</td>
<td>Yes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No (Kay and Harris, 1999)</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>&gt;14 (14.1/&lt;1)</td>
<td>9.1 ± 0.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.4 ± 0.2</td>
<td>Yes</td>
<td>No (Kay and Harris, 1999)</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>1.24 (7.95/0.8)</td>
<td>N.D.</td>
<td>N.D.</td>
<td>No</td>
<td>Yes (Simons, 1999)</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>1.09 (4.29/0.2)</td>
<td>0.9 ± 0.2</td>
<td>1.2 ± 0.2</td>
<td>No</td>
<td>Yes (Simons, 1999)</td>
</tr>
<tr>
<td>Triprolidine</td>
<td>0.6 (6.05/0.2)</td>
<td>0.9 ± 0.3</td>
<td>1.1 ± 0.4</td>
<td>Yes</td>
<td>No (Kay and Harris, 1999)</td>
</tr>
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</table>

N.D., not determined.

<sup>a</sup> The values in the parentheses are the brain-to-plasma AUC ratio for the KO and WT, respectively.

<sup>b</sup> Data were from Polli et al. (2001).

<sup>c</sup> Significantly higher efflux ratio compared with the parental MDCK-II cells (P < 0.05).

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