




Brain histamine H₁ receptor occupancy after oral administration of desloratadine and loratadine

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Abstract

Some histamine H₁ receptor (H₁R) antagonists induce adverse sedative reactions caused by blockade of histamine transmission in the brain. Desloratadine is a second-generation antihistamine for treatment of allergic disorders. Its binding to brain H₁Rs, which is the basis of sedative property of antihistamines, has not been examined previously in the human brain by positron emission tomography (PET). We examined brain H₁R binding potential ratio (BPR), H₁R occupancy (H₁RO), and subjective sleepiness after oral desloratadine administration in comparison to loratadine. Eight healthy male volunteers underwent PET imaging with [¹¹C]-doxepin, a PET tracer for H₁Rs, after a single oral administration of desloratadine (5 mg), loratadine (10 mg), or placebo in a double-blind crossover study. BPR and H₁RO in the cerebral cortex were calculated, and plasma concentrations of loratadine and desloratadine were measured. Subjective sleepiness was quantified by the Line Analogue Rating Scale (LARS) and the Stanford Sleepiness Scale (SSS). BPR was significantly lower after loratadine administration than after placebo (0.504 ± 0.074 vs 0.584 ± 0.059 [mean ± SD], *P* < 0.05), but BPR after desloratadine administration was not significantly different from BPR after placebo (0.546 ± 0.084 vs 0.584 ± 0.059, *P* = 0.250). The plasma concentration of loratadine was negatively correlated with BPR in subjects receiving loratadine, but that of desloratadine was not correlated with BPR. Brain H₁ROs after desloratadine and loratadine administration were 6.47 ± 10.5% and 13.8 ± 7.00%, respectively (*P* = 0.103). Subjective sleepiness did not significantly differ among subjects receiving the two antihistamines and placebo. At therapeutic doses, desloratadine did not bind significantly to brain H₁Rs and did not induce any significant sedation.

Abbreviations: AAL, automated anatomical labeling; AUC, area under the curve; BPR, binding potential ratio; CONGA, Consensus Group on New-Generation Antihistamines; CYRIC, Cyclotron and Radioisotope Center; H₁R, H₁ receptor; H₁RO, H₁R occupancy; LARS, Line Analogue Rating Scale; LC/MS/MS, liquid chromatography/tandem mass spectrometry; MRI, magnetic resonance imaging; PET, positron emission tomography; ROI, regions of interest; SPE, solid phase extraction; SPM, Statistical Parametric Mapping; SSS, Stanford Sleepiness Scale.

*The authors confirm that the PI for this paper is Kazuhiko Yanai and that he had direct clinical responsibility for patients.

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KEYWORDS

brain H₁ receptor occupancy, desloratadine, positron emission tomography

1 | INTRODUCTION

Allergic disorders such as allergic rhinitis, urticaria, and atopic dermatitis are common, affecting up to 30% of the population.¹⁻⁴ Oral histamine H₁ receptor (H₁R) antagonists, the so called antihistamines, are frequently prescribed to treat these allergic disorders.^{5,6} However, first-generation antihistamines, such as chlorpheniramine and diphenhydramine, have sedative properties as a central adverse reaction,⁷⁻⁹ although sedating antihistamines are used as over-the-counter sleep aids. To reduce sedative adverse reactions, second-generation antihistamines such as levocetirizine, fexofenadine, and loratadine have been developed.^{10,11}

The sedative properties of antihistamines are associated with the permeability of the blood-brain barrier to the drug molecules.^{11,12} Brain penetration of drugs was associated with several complex factors including P-glycoprotein, molecular weight, pKa and lipid solubility. H₁Rs in the central nervous system have an essential role in activating the cortices during wakefulness and arousal.^{13,14} Antihistamines penetrating the blood-brain barrier are able to occupy cortical and subcortical H₁Rs, resulting in sedation and impaired psychomotor performance. Positron emission tomography (PET) using [¹¹C]-doxepin as a potent H₁R ligand can quantify the brain H₁R occupancy (H₁RO) of antihistamines *in vivo*.^{9,15} Our previous study clearly demonstrated that a first-generation antihistamine, *d*-chlorpheniramine, caused impairment of the attention system of humans that was positively proportional to H₁RO.¹⁶ On the other hand, H₁RO of most second-generation antihistamines was less than 20% and did not cause sedation.^{10,17-20} Several previous studies reported that H₁RO determined by [¹¹C]-doxepin PET was correlated with the proportional impairment ratio, a parameter used to evaluate the sedative potential of each antihistamine.²⁰⁻²³ Therefore, PET imaging by [¹¹C]-doxepin is recommended by the Consensus Group on

New-Generation Antihistamines (CONGA) as a quantitative method to determine the sedative effects of antihistamines.²⁴

Desloratadine, {8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, CAS 100643-71-8}, a second-generation antihistamine, is a biologically active metabolite of loratadine formed by CYP3A4 and CYP2D6 (Figure 1).²⁵ Desloratadine is approved for the treatment of allergic rhinitis and chronic idiopathic urticaria around the world. A number of clinical studies have demonstrated the therapeutic efficacy of desloratadine in allergic rhinitis. Nayak and Schenkel found that daily administration of 5-mg desloratadine significantly improved nasal congestion and stiffness in patients with intermittent allergic rhinitis compared with placebo.²⁶ A multicentre, randomised, placebo-controlled, double-blind parallel-group trial showed that desloratadine rapidly reduced the symptoms of perennial allergic rhinitis with minimal adverse events.²⁷ Moreover, administration of desloratadine 5 mg once daily was as effective as fexofenadine 180 mg,²⁸ bilastine 20 mg²⁹ or rupatadine 10 mg³⁰ in seasonal allergic rhinitis. Desloratadine also improved symptoms of chronic idiopathic urticaria in a multicentre, randomised, double-blind placebo-controlled study³¹ and in an observational postmarketing surveillance study³² without serious adverse events. Hong et al performed a randomised, double-blind, active-controlled parallel-group pilot trial of 64 patients and found that levocetirizine was more efficacious than desloratadine, but desloratadine had less sedative effect, in the treatment of chronic idiopathic urticaria.³³ Central adverse reactions, such as somnolence, decreased vigilance and impairment of cognitive functions, were less frequent with the use of desloratadine compared with a first-generation antihistamine, diphenhydramine, although diphenhydramine resulted in better improvement in allergic rhinitis symptoms.^{34,35} Desloratadine did not impair psychomotor performance,³⁶ driving performance,³⁶ and tasks associated with flying³⁷ compared with diphenhydramine. Additionally, desloratadine

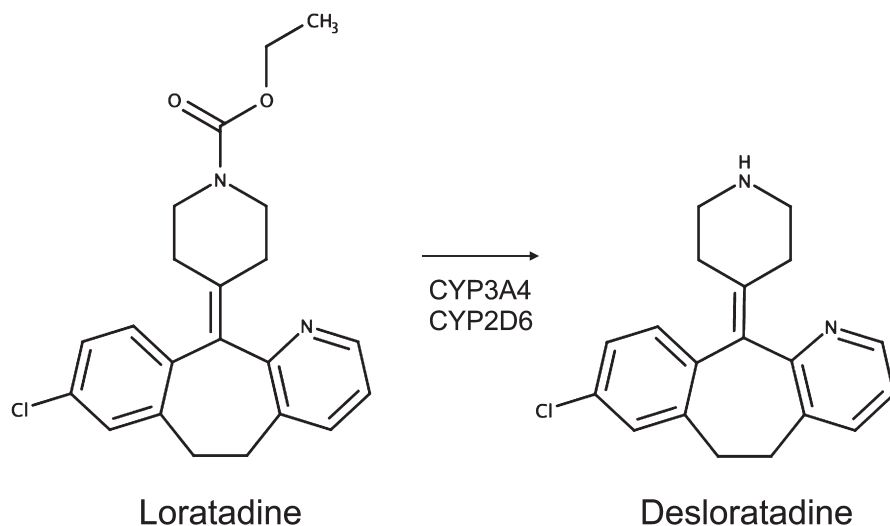


FIGURE 1 Chemical structures of loratadine and desloratadine. *In vivo* formation of desloratadine (descarboethoxylopratadine) is primarily mediated by CYP3A4 and CYP2D6

was associated with fewer cardiovascular adverse events than earlier second-generation antihistamines.³⁸ These studies indicate that treatment of allergic rhinitis and chronic idiopathic urticaria with desloratadine is clinically efficacious, safe, and well tolerated, without serious adverse events in the central nervous and cardiovascular systems.^{39,40}

The binding of desloratadine to brain H₁R has not been previously determined in humans by PET, although the United Kingdom Medicine and Healthcare Products Regulatory Agency in 2001, the US Food and Drug Administration in 2002, and the Japan Pharmaceuticals and Medical Devices Agency in 2016 approved desloratadine, which has been widely used to treat allergic rhinitis and chronic idiopathic urticaria. In the present study, we measured the binding potential ratio (BPR) and H₁RO of desloratadine (5 mg) and loratadine (10 mg) by using [¹¹C]-doxepin PET in healthy male volunteers and investigated the correlation between these parameters and sedative effects quantified as subjective sleepiness. Additionally, we examined the plasma concentrations of each drug after oral administration in relation to BPR and H₁RO.

2 | METHODS

2.1 | Ethical approval

This study was approved by the Ethical Committee on Clinical Investigation at Tohoku University Hospital (Sendai, Japan) and by the institutional review committee of the Cyclotron and Radioisotope Center (CYRIC), Tohoku University (Sendai, Japan) and was performed in accordance with the Declaration of Helsinki. The study was registered in the UMIN Clinical Trials Registry (UMIN 000029704). All experiments were performed at the CYRIC, Tohoku University.

2.2 | Participants

We recruited eight healthy male Japanese volunteers (mean ± SD age, 23.2 ± 1.28 years; mean ± SD body weight, 59.6 ± 5.27 kg) who had provided written informed consent beforehand. None of the participants had any clinical history of physical or psychiatric disease. They were not taking any medications likely to interfere with the study results and had no abnormal findings on brain magnetic resonance imaging (MRI). The participants were required to refrain from smoking, drinking alcohol, and consuming caffeine or grapefruit (including juice) on the day of and the day before PET scanning. No spontaneous adverse events were reported during the study.

2.3 | Trial design

We performed a double-blind, randomised, placebo-controlled three-way crossover PET imaging study. All the participants received single oral administration of desloratadine (5 mg), loratadine (10 mg), or a lactobacillus preparation (6 mg) as placebo. Desloratadine and loratadine were administered according to their

approved and recommended daily doses in Japan. The lactobacillus preparation was used as a placebo and was not associated with any statistically significant differences between pre- and postadministration in previous studies.^{18,19,41} The drugs were administered orally at 9:30 AM on the study day. The minimum washout interval between crossover treatments was 7 days. After drug administration, the participants were asked to remain comfortably seated on a sofa. [¹¹C]-Doxepin containing saline solution was injected intravenously into each participant 90 minutes after oral administration (11:00 AM), at a time close to T_{max} of desloratadine and loratadine.^{6,42-44} Sixty minutes after [¹¹C]-doxepin injection, the subjects were positioned on the couch of the PET scanner (Eminence SET-3000BX; Shimadzu, Kyoto, Japan) for transmission scanning (6 minutes) and emission scanning in the three-dimensional mode for 15 minutes (70-85 minutes after [¹¹C]-doxepin injection). To determine plasma concentrations of desloratadine and loratadine, venous blood samples were collected from each participant before drug administration and 30, 60, 120, and 180 minutes after oral administration. The subjective sleepiness of each participant was also measured before drug administration and 30, 60, 90, 120, 150, and 180 minutes after oral administration using the Line Analogue Rating Scale (LARS)⁴⁵ and the Stanford Sleepiness Scale (SSS).⁴⁶

2.4 | Radiosynthesis of [¹¹C]-doxepin and PET procedures

[¹¹C]-Doxepin was prepared by [¹¹C]-methylation of desmethyl doxepin with [¹¹C]-methyl triflate, as described previously.^{47,48} The radiochemical purity of [¹¹C]-doxepin was >99%, and its specific radioactivity at the time of injection was 198 ± 67.9 GBq μmol⁻¹ (5,355 ± 1,833 mCi μmol⁻¹). The injected dose and cold mass of [¹¹C]-doxepin were 159 ± 11.6 MBq (4.30 ± 0.314 mCi) and 2.42 ± 2.13 nmol, respectively. Each participant received [¹¹C]-doxepin by intravenous injection 90 minutes after oral administration of the drugs (11:00 AM). Sixty minutes later (12:00 AM), transmission and emission PET scans were performed using a PET scanner (Eminence SET-3000BX). The PET scanning covered the entire brain in one scan, taking transmission scan (6 minutes) for scatter and tissue attenuation correction, followed by emission scan in the three-dimensional model lasting for 15 minutes (70-85 minutes after [¹¹C]-doxepin injection) according to a simplified reference tissue model approach (Supporting Information Figure S1).^{48,49}

2.5 | PET imaging analysis

All brain PET images were reconstructed after correction for scatter and tissue attenuation, and standardised uptake values were calculated from emission scan data to obtain static images of the distribution volume (V_d) of [¹¹C]-doxepin.¹⁷⁻¹⁹ Three brain images of each participant, following oral administration of desloratadine, loratadine, and placebo, were spatially normalised with MRI-T1 images of each participant using Statistical Parametric Mapping (SPM12; Wellcome Department

of Imaging Neuroscience, London, UK).⁵⁰ The MRI scan was obtained with a 1.5T MR scanner (Signa EXCITE HD 1.5T; General Electric, Milwaukee, WI) at the Sendai Medical Imaging Clinic, Sendai, Japan. PNEURO tool of PMOD software (version 3.4, PMOD Technologies, Zurich, Switzerland) was used for the placement and evaluation of regions of interest (ROI) as described previously.¹⁷ The automated anatomical labeling (AAL) atlas was applied to all PET images to calculate the mean uptake value of each ROI. Some AAL ROIs were combined into the following seven ROIs, including the frontal cortex, temporal cortex, parietal cortex, occipital cortex and the anterior and posterior cingulate gyrus and cerebellum. The cerebellum was defined as a reference region because the previous study confirmed the negligible H₁R binding in the cerebellum.⁵¹ As a parameter for specific H₁R binding of [¹¹C]-doxepin in each cerebral cortex region, we calculated BPR using a simplified reference tissue model method.⁴⁹ This approach allows for shorter PET scanning times as compared with other methods. The BPR (B_{max}/K_d) of [¹¹C]-doxepin among the three drug treatment conditions was estimated according to the following equation: $BPR = (\text{mean uptake value during the 15-minute scan of each region} / \text{mean uptake value during the 15-minute scan of the cerebellum}) - 1$. Our previous studies demonstrate the rationale behind adopting BPR as a parameter for specific H₁R binding of [¹¹C]-doxepin.^{48,49,52} H₁RO as a percentage of the placebo control was calculated in each ROI by the following equation: $H_1RO = (1 - BPR \text{ of antihistamine} / BPR \text{ of placebo}) \times 100\%$.^{48,49} PMOD software was used to obtain composite PET images of each drug.

2.6 | Measurement of plasma concentrations of desloratadine and loratadine

The plasma concentrations of desloratadine and loratadine were measured by high-performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) (API4000, AB Sciex, Framingham, MA) with an electrospray ionisation method. An internal standard solution (20 µL) and 75% methanol (20 µL) were added to each plasma sample (200 µL). After 700 µL of 10 mmol L⁻¹ ammonium formate was added, the sample mixture was applied onto the conditioned solid phase extraction (SPE) column (OSSIS HLB 96-well plate 30 mg; Waters Corp., Milford, MA), followed by washing. The sample was eluted by 1 mL of methanol from the SPE column, 10 mmol L⁻¹ ammonium formate (200 µL) was added, and then 3 µL of sample preparation was applied to LC/MS/MS. The eluted samples passed through a Cadenza CD-C18 LC column (3 µm, 100 × 3 mm; Imtakt Corp., Kyoto, Japan) at a flow rate of 0.5 mL min⁻¹ and a column temperature of 40°C. The mobile phase consisted of 10 mmol L⁻¹ ammonium formate and a methanol/acetonitrile mixture (3:2 v/v). Detection of desloratadine, loratadine and internal standard was based on fragmentation of the precursor ion ($m/z = 311, 383, 387$ to product ion $m/z = 259, 337, 341$ with collision energy of 29, 33, 33 eV for desloratadine, loratadine and internal standard, respectively) in positive multiple reaction monitoring. The temperature of the ion source was 700°C, the voltage was 4,000 V, the curtain gas pressure (N₂) was 10 psi, the ion source gas pressure (zero grade air) was 70 psi, and the collision gas (N₂) pressure was 8 psi. Chromatographic data for positive multiple reaction monitoring were

collected and analysed by using Analysis 1.6.3 (AB Sciex). The linear range of measurement was 0.1–20 ng mL⁻¹ ($R > 0.999$). The lower limit of quantification of desloratadine and loratadine was 0.1 ng mL⁻¹.

2.7 | Statistical analysis

Differences in changes in subjective sleepiness (the LARS and SSS scores) from preadministration among the three groups were examined by two-way analysis of variance (ANOVA) with the Bonferroni post hoc test. Plasma concentrations were examined by two-way ANOVA with the Bonferroni post hoc test. Differences in BPR among the desloratadine, loratadine, and placebo groups were examined by one-way ANOVA, followed by Bonferroni multiple-comparison correction. Differences in H₁RO between the desloratadine and loratadine groups were examined by a paired Student's *t* test. The relations between BPR and SSS, H₁RO and SSS were examined by Pearson's correlation test. Statistical significance for each analysis was defined as $P < 0.05$. Prism 8 (GraphPad Software, San Diego, CA) was used to perform all statistical analyses. All imaging and statistical analyses were performed by two experts without knowing the three treatment conditions of desloratadine, loratadine, and placebo.

3 | RESULTS

3.1 | Subjective sleepiness

There were no significant differences among the desloratadine, loratadine and placebo groups in subjective sleepiness, as measured by LARS and SSS (Figure 2, left panels). Additionally, we found that total subjective sleepiness, calculated from the area under the curve (AUC) of the subjective sleepiness time course, did not differ significantly among the desloratadine, loratadine, and placebo groups (Figure 2, right panels). These results indicate that oral administration of desloratadine or loratadine did not induce subjective sleepiness.

3.2 | Plasma concentrations of desloratadine and loratadine

Figure 3 shows the time courses of the plasma concentrations of each drug. Loratadine concentration was significantly higher than desloratadine concentration 60 minutes after oral administration (two-way ANOVA, $F = 4.48$; Bonferroni $P = 0.028$). The desloratadine concentration after oral administration of 10 mg loratadine was not significantly different from the desloratadine concentration after oral administration of 5 mg desloratadine.

3.3 | Brain distribution of [¹¹C]-doxepin

The mean [¹¹C]-doxepin BPR images in the eight participants are shown in Figure 4. The red area indicates brain regions where BPR was high. The desloratadine and placebo groups had similar BPRs (mean ± SD desloratadine vs placebo, 0.546 ± 0.084 vs 0.584 ± 0.059 ; one-way ANOVA, $F = 8.20$; Bonferroni $P = 0.250$),

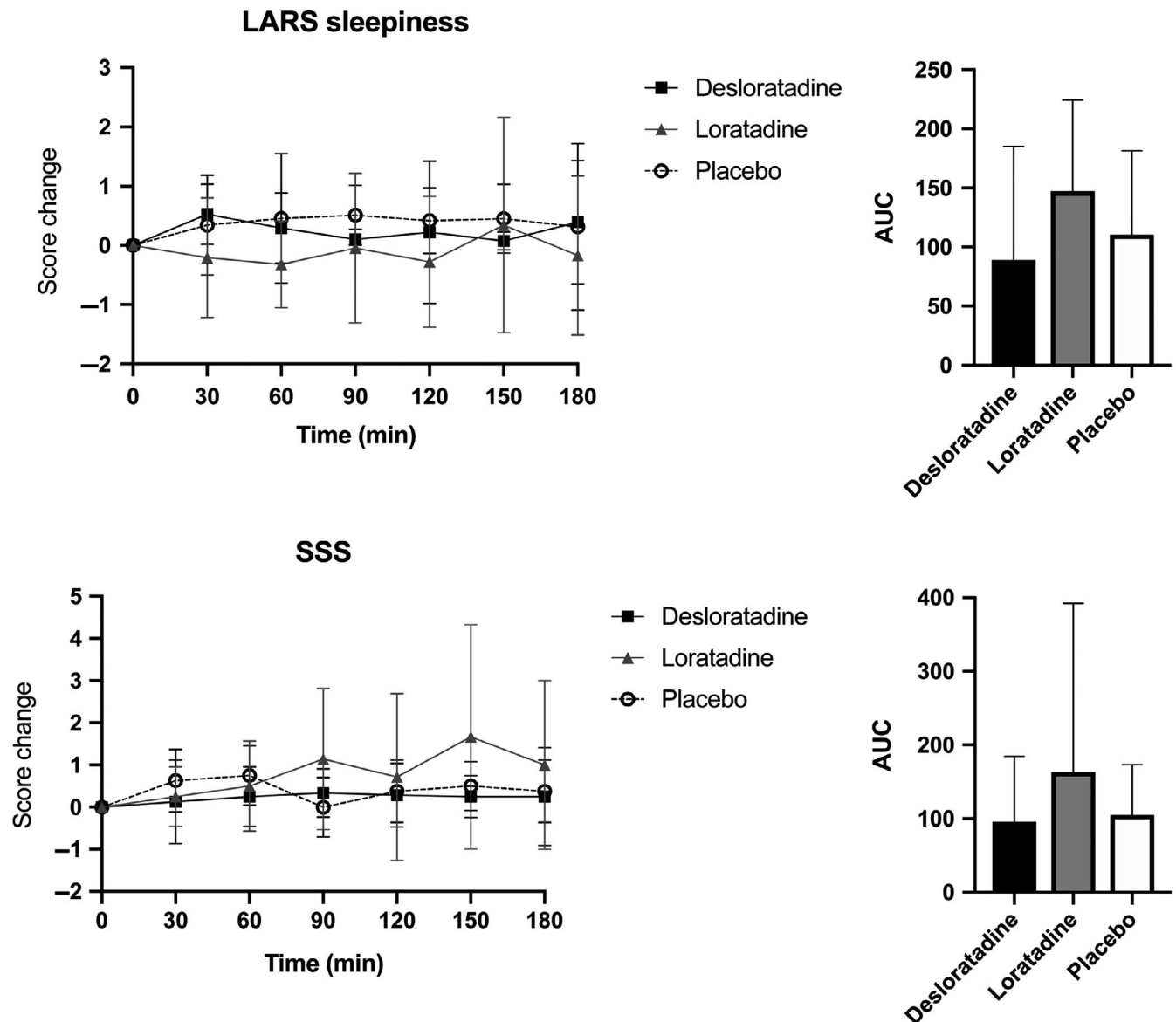


FIGURE 2 Subjective sleepiness after oral administration of desloratadine, loratadine, and placebo. The upper left panel shows the time course of the Line Analogue Rating Scale (LARS) sleepiness (two-way ANOVA; $F = 0.495$, $P > 0.999$). The upper right panel shows total LARS sleepiness, determined by the area under the curve (AUC) of the left panel (one-way ANOVA; $F = 1.36$, $P = 0.229$). The lower left panel shows the time course of the Stanford Sleepiness Scale (SSS) (two-way ANOVA; $F = 0.967$, $P > 0.999$). The lower right panel shows total SSS, determined by the AUC of the left panel (one-way ANOVA; $F = 0.497$, $P = 0.530$)

whereas the loratadine group had lower BPR than the placebo group (mean \pm SD loratadine vs placebo, 0.504 ± 0.074 vs 0.584 ± 0.059 ; one-way ANOVA, $F = 8.20$; Bonferroni $P = 0.002$) (Figure 5, left panel, and Table 1). These results suggest that loratadine permeated the blood-brain barrier slightly and bound to H_1R in the cortices to some extent. On the other hand, desloratadine had minimal binding to brain H_1R .

3.4 | ROI-based comparison of BPR and H_1RO

Table 1 shows the mean BPRs in the cortical regions. The BPRs of the desloratadine group in each region were not significantly different

from those of the placebo group. The BPR of the loratadine group was lower than the BPR of the placebo group in all regions except the anterior cingulate gyrus ($P < 0.05$, one-way ANOVA, Bonferroni's multiple comparisons test), indicating that loratadine might bind H_1R throughout the neocortex especially in the parietal cortex, with more pronounced binding in the posterior cingulate gyrus, and intermediate binding in subcortical structures.

H_1RO following oral administration of desloratadine and loratadine was also calculated using placebo as baseline (0%) (Figure 5 and Table 2). The overall H_1RO in the brain did not differ significantly between the desloratadine and loratadine groups, although H_1RO tended to be lower in the desloratadine group than in the loratadine

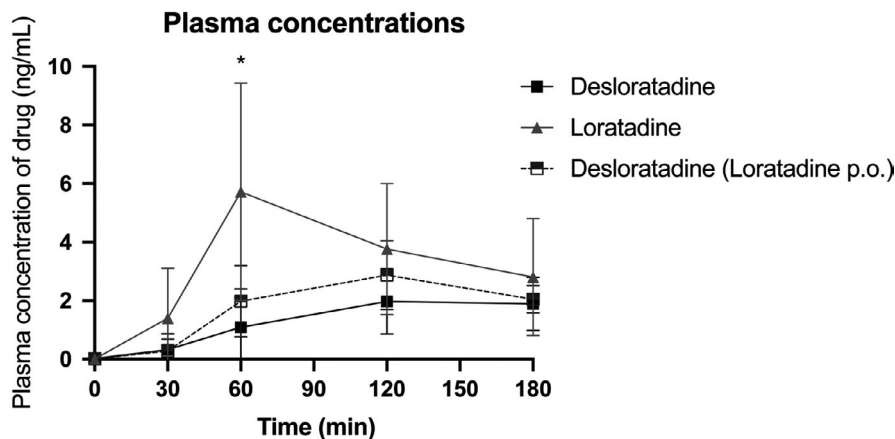


FIGURE 3 Plasma concentrations after oral administration of desloratadine and loratadine. Black squares show the plasma concentration of desloratadine after oral administration of 5 mg desloratadine. Triangles show the plasma concentration of loratadine after oral administration of 10 mg loratadine. Black and white squares show the plasma concentration of desloratadine after oral administration of 10 mg loratadine (desloratadine is an in vivo metabolite of loratadine). Symbols and bars indicate means and errors, respectively. * $P < 0.05$ (two-way ANOVA; $F = 4.48$, Bonferroni $P = 0.0277$)

group (mean \pm SD, $6.47 \pm 10.5\%$ vs $13.8 \pm 7.00\%$; paired t test, $P = 0.103$) (Figure 5, right panel, and Table 2). The H_1RO in each region did not differ significantly between the desloratadine and loratadine groups (Table 2).

3.5 | Relation between subjective sleepiness, plasma drug concentration, and BPR

Subjective sleepiness was not correlated with BPR or H_1RO in either the desloratadine or the loratadine group (Table 3). The plasma concentration of loratadine (AUC, $\mu\text{g mL}^{-1} \cdot \text{min}$) was significantly correlated with overall BPR (Pearson correlation coefficient $R = -0.862$; 95% CI, -0.975 to -0.040 ; $P = 0.006$) (Figure 6, upper panel, and Table 3). These results suggest that loratadine slightly penetrated the blood-brain barrier at the dose of 10 mg. There were no other significant correlations between BPR, H_1RO , and plasma concentrations of the drugs. There was a tendency toward a correlation between the plasma concentration of loratadine and H_1RO , but the relation was not statistically significant because one participant had high H_1RO with low plasma concentration of loratadine (Figure 6, lower panel) (Pearson correlation coefficient $R = 0.585$; 95% CI, -0.204 to 0.913 ; $P = 0.128$).

4 | DISCUSSION

To exhibit pronounced sedative properties, antihistamines need to penetrate the blood-brain barrier and bind with cortical H_1Rs . A previous study reported that clinically observed H_1RO by antihistamines can be estimated by the integration of preclinical data on pharmacokinetic/pharmacodynamics parameters.⁵³ Since the modeling and simulation are incomplete at this moment, brain H_1RO by [^{11}C]-doxepin PET has been utilized as an index of the sedative potential of H_1 antagonists including antipsychotics and antidepressants.^{54,55}

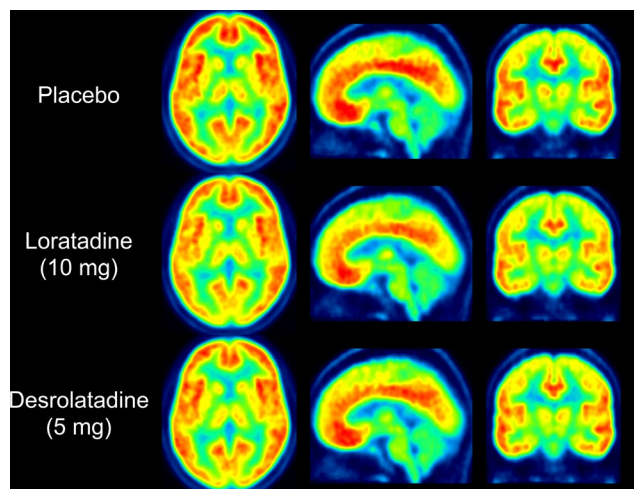


FIGURE 4 Binding potential ratio (BPR) images of [^{11}C]-doxepin in the brain after oral administration of placebo (upper), 10 mg loratadine (middle), and 5 mg desloratadine (lower). The left, middle, and right panels show axial, sagittal, and coronal brain images, respectively. The brain image of each participant was spatially normalised by Statistical Parametric Mapping (SPM12) and averaged across each drug condition to generate the mean images displayed

The H_1RO of first- and second-generation antihistamines has been measured by several PET research groups, and a classification of these drugs has been proposed according to the level of H_1RO .⁹ H_1RO was defined as an important index for evaluating sedating property at CONGA, an expert meeting sponsored by the British Society for Allergy and Clinical Immunology.²⁴ Antihistamines are classified into three groups based on H_1RO after a single oral administration: the nonsedating ($<20\%$), less-sedating (20% - 50%), and sedating ($\geq 50\%$) groups. To cite an example, a study of the second-generation antihistamines fexofenadine and cetirizine reported that the H_1RO of fexofenadine (120 mg) was minimal (-0.1%), whereas

FIGURE 5 Overall binding potential ratio (BPR) (left) and H_1 receptor occupancy (H_1RO) (right) after oral administration of desloratadine, loratadine, and placebo. Symbols indicate participants in the study, and bars indicate means and standard deviations (SD). The left panel shows the BPRs of desloratadine (squares), loratadine (triangles) and placebo (circles): mean \pm SD 0.546 ± 0.084 , 0.504 ± 0.074 and 0.584 ± 0.059 , respectively. The loratadine group had lower BPR than the placebo group (one-way ANOVA; $F = 8.20$, Bonferroni $P = 0.002$). The right panel shows H_1RO after oral administration of desloratadine (squares) and loratadine (triangles): mean \pm SD $6.47 \pm 10.5\%$ vs $13.8 \pm 7.00\%$, t test $P = 0.103$

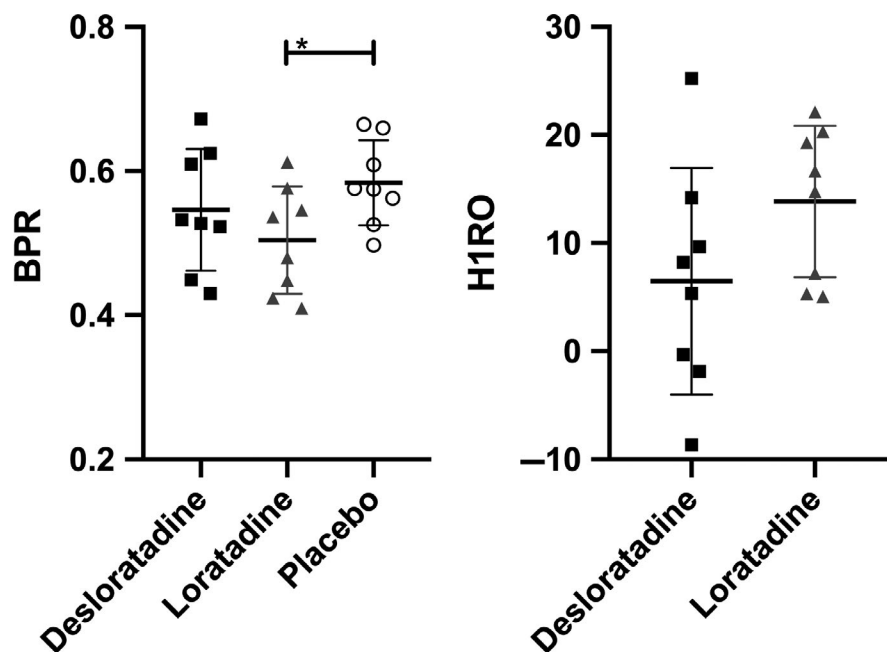


TABLE 1 Binding potential ratio based on region of interest

ROI	Desloratadine		Loratadine		Placebo	
	Mean	SD	Mean	SD	Mean	SD
FC	0.582	0.093	0.546*	0.086	0.630	0.075
TC	0.575	0.084	0.535*	0.086	0.603	0.076
OC	0.474	0.060	0.429*	0.059	0.508	0.033
PC	0.391	0.115	0.343*	0.089	0.425	0.097
ACG	0.607	0.108	0.588	0.113	0.649	0.082
PCG	0.648	0.138	0.582*	0.097	0.687	0.093
All regions	0.546	0.084	0.504*	0.074	0.584	0.059

Abbreviations: ROI, region of interest; SD, standard deviation; FC, frontal cortex; TC, temporal cortex; OC, occipital cortex; PC, parietal cortex; ACG, anterior cingulate gyrus; PCG, posterior cingulate gyrus.

* $P < 0.05$ vs placebo (one-way ANOVA, Bonferroni).

TABLE 2 H_1 receptor occupancy based on region of interest^a

ROI	Desloratadine		Loratadine	
	Mean	SD	Mean	SD
FC	7.74	9.07	13.6	6.14
TC	4.29	11.5	11.2	9.24
OC	6.85	9.07	15.5	10.7
PC	9.18	12.0	19.6	10.0
ACG	6.56	10.7	9.69	10.7
PCG	5.54	15.1	15.4	4.88
All regions	6.47	10.5	13.8	7.00

Abbreviations: ROI, region of interest; SD, standard deviation; FC, frontal cortex; TC, temporal cortex; OC, occipital cortex; PC, parietal cortex; ACG, anterior cingulate gyrus; PCG, posterior cingulate gyrus.
^aThere were no statistically significant differences between desloratadine and loratadine treatment.

that of cetirizine (20 mg) was moderate (26.0%), consistent with its less-sedating property.¹⁸

In the present study, we have determined BPR and H_1RO of desloratadine by using PET for the first time. The mean cortical BPR was 0.546 and H_1RO was 6.47% after oral administration of desloratadine 5 mg (Tables 1 and 2). There was no significant difference in BPR after administration of desloratadine and placebo (mean \pm SD, 0.546 ± 0.084 vs 0.584 ± 0.059). It is obvious from Figure 2 that desloratadine does not induce subjective sleepiness. Previous studies indicated that desloratadine does not impair psychomotor and driving performance.^{36,37} Based on the PET classification of antihistamines and previous evidence, desloratadine is classified as a nonsedating antihistamine at the therapeutic dose.

We compared the measured values of H_1RO of loratadine (10 mg) and desloratadine (5 mg) in this study with those from previous studies. As shown in Supporting Information Figure S2, the mean H_1RO values of loratadine (10 mg) were very similar in the

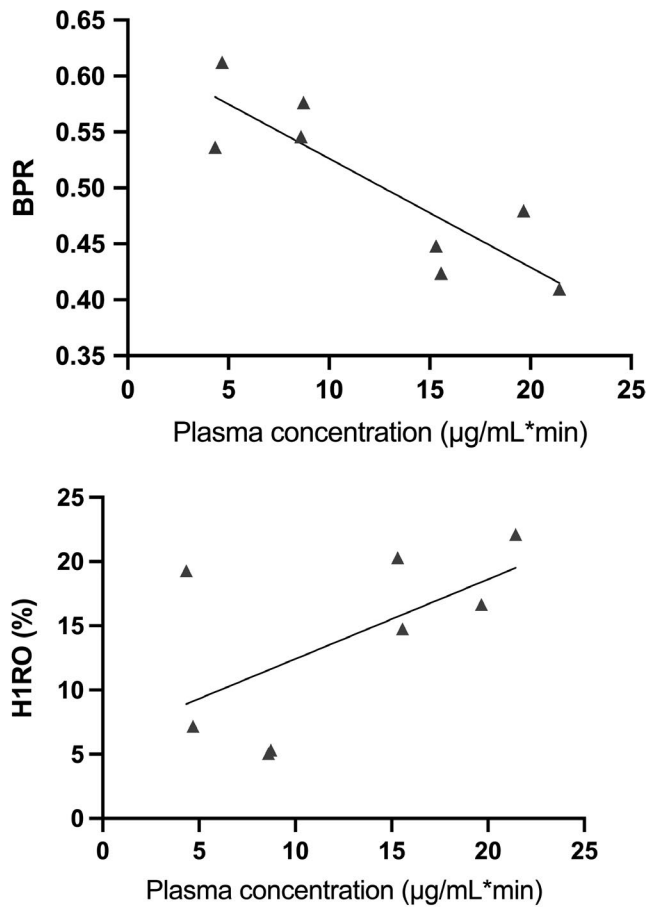


FIGURE 6 Relation between binding potential ratio (BPR), H_1 receptor occupancy (H_1RO) and plasma concentration of loratadine. Each triangle indicates a participant in the study. The upper panel shows the significant relationship between BPR and plasma concentration (area under the curve [AUC], $\mu\text{g mL}^{-1} \text{min}$) (Pearson correlation coefficient $R = -0.862$; 95% CI, -0.975 to -0.040 ; $P = 0.006$). The lower panel shows the relationship between H_1RO and plasma concentration (AUC, $\mu\text{g mL}^{-1} \text{min}$), which is not statistically significant (Pearson correlation coefficient $R = 0.585$; 95% CI, -0.204 to 0.913 ; $P = 0.128$)

present and previous studies (13.8% vs 11.7%, respectively),²⁰ even though these studies were performed in different PET facilities. These data suggest the consistency and relevance of the classification of the sedative properties of antihistamines by H_1RO . On the other hand, we found that the mean BPR after administration of loratadine 10 mg was 0.504 (Table 1). Kubo et al previously reported a mean brain BPR of 0.293 after administration of loratadine 10 mg, a lower value than that in our study.²⁰ These discrepancies could be explained by the following factors. First, our study recruited healthy volunteers as participants, whereas the subjects in Kubo's study were patients with moderate or severe chronic allergic rhinitis. Residual occupancy of antihistamines might have affected the lower BPR in patients. Second, the two studies used different modalities to acquire PET and MRI images. Third, the two studies used different methods of PET data analysis, such as definitions of the ROI and parameter settings for image reconstructions.

TABLE 3 Correlation between H_1R binding (BPR and H_1RO), subjective sleepiness, and plasma concentrations of drugs

Measurement	Desloratadine				Loratadine				Placebo							
	SSS		LARS		SSS		LARS		SSS		LARS					
	R	P	R	P	R	P	R	P	R	P	R	P				
BPR	0.186	0.659	0.251	0.549	0.091	0.829	-0.618	0.102	0.153	0.717	-0.862 ^b	0.006	0.460	0.252	0.423	0.296
H_1RO	-0.549	0.159	-0.360	0.381	0.144	0.735	0.352	0.393	-0.110	0.795	-0.105 ^a	0.804 ^a	-	-	-	-

Abbreviations: SSS, Stanford Sleepiness Scale; LARS, Line Analogue Rating Scale; R, Pearson correlation coefficient; BPR, binding potential ratio; H_1RO , H_1 receptor occupancy.

^aThe lower row in the loratadine plasma concentration column indicates the desloratadine plasma concentration after oral administration of loratadine.

^b $P < 0.05$ (Pearson correlation).

The BPR of desloratadine was similar to that of placebo, whereas loratadine had a significantly lower BPR than placebo (Figure 4 and Table 1). These results indicate that loratadine might induce sleepiness caused by binding to brain cortical H_1 Rs. This is corroborated by the inverse relation between the plasma concentration of loratadine and BPR (Figure 6, upper panel, and Table 3). Furthermore, H_1 RO after loratadine administration, which tended to be proportional to the plasma concentration of loratadine, might reinforce the binding property of loratadine to cortical H_1 R (Figure 6, lower panel). Severe subjective sleepiness was observed in some participants who received loratadine. Based on individual analyses, two participants who showed subjective sleepiness (+6.00 and +4.00 increase of SSS from baseline) had relatively high peak plasma concentrations of loratadine (7.88 and 10.4 ng mL⁻¹), low BPR (0.448 and 0.423), and high H_1 RO (20.3% and 14.8%) after oral administration of loratadine 10 mg. On the other hand, these two participants exhibited slight subjective sleepiness (+1 changes from SSS baseline in both) and peak plasma concentrations similar to the mean values (1.18 and 2.09 ng mL⁻¹) after oral administration of desloratadine 5 mg. These participants had BPRs of 0.532 and 0.449 and H_1 ROs of 5.34% and 9.66% after oral administration of desloratadine 5 mg. The individual data indicate that a clinical dose of loratadine can induce sleepiness due to high plasma concentrations and binding to brain H_1 Rs in some populations. The large variations in plasma concentration and H_1 RO may be related to genetic variance of CYP3A⁵⁶ and P-glycoprotein,⁵⁷ which affect the metabolism and efflux, respectively, of antihistamines. Overall subjective sleepiness, however, as previously reported by Kay and Harris,⁵⁸ was not significant in this study (Figure 2). The current PET data may identify loratadine as a “relatively nonsedating” antihistamine that could induce sedation or impaired performance when used at a higher than therapeutic dose.^{24,59-61}

The BPR and H_1 RO of desloratadine did not correlate significantly with subjective sleepiness (LARS and SSS) or plasma concentrations after administration of desloratadine (5 mg) (Table 3). Plasma concentrations after oral administration of desloratadine (5 mg) and loratadine (10 mg) showed similar time courses without significant differences between these treatments (Figure 3). Fexofenadine, a nonsedating second-generation antihistamine and an active metabolite of the prodrug terfenadine, also did not affect BPR after terfenadine administration.^{17,51} These results indicate that nonsedating antihistamines converted from the absorbed prodrugs in vivo may have no or minimal direct effects on BPR. In general, however, a large number of participants in [¹¹C]-doxepin-PET experiments will be needed to demonstrate correlations of H_1 RO with plasma antihistamine concentrations in the case of lower H_1 RO.

No significant differences were found between test drugs with regard to SSS and LARS, which measure subjective sleepiness; that is, neither desloratadine 5 mg nor loratadine 10 mg showed any potential to cause significant sedation when compared with placebo. The failure to find significant differences may represent a type 2 error due to limited sample size and variability among participants. A large number of participants are needed to demonstrate differences in subjective sleepiness after taking nonsedating antihistamines.

The limitations of this study include the large variations in H_1 RO of desloratadine. One possible explanation for this is due to small number of participants and the simplified protocol used in this study. We did not perform continuous PET scanning and simultaneous arterial blood sampling to calculate the distribution volume of [¹¹C]-doxepin. Instead, we used the BPR, which may indicate [¹¹C]-doxepin binding to regionally specific H_1 R. This was done to relieve the participants from the burden of the long scanning time of PET and sequential arterial blood sampling. Another limitation is the minimum washout interval between crossover treatments. The minimum interval was 7 days; however, this may have been too short to wash out the drug administered in the previous arm. Shibasaki et al reported that the variants of CYP3A, which metabolize loratadine, affected the in vivo metabolism of administered drugs.⁵⁶ In fact, a participant who had low BPR and high H_1 RO from desloratadine treatment may have been affected by loratadine administration a week previously (Figure 5).

In summary, desloratadine does not bind significantly to H_1 R in the central nervous system and does not induce subjective sleepiness at therapeutic doses. The H_1 RO of desloratadine 5 mg was 6.47%, which was lower than that of loratadine (13.8%). These results indicate that desloratadine 5 mg does not penetrate the blood-brain barrier in large amounts enough to induce inhibition of H_1 R signaling resulting in sedation and cognitive impairment.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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