IV. 4. Neural mechanism of impaired visuomotor coordination by sedative antihistamine: A human PET study

Mochizuki H.*, Tashiro M.*, Kano M.*, Itoh M.**, and Yanai K.*

Department of Pharmacology, Tohoku University School of Medicine*
Cyclotron and Radioisotope center, Tohoku University**

Introduction

The histaminergic system has been considered to maintain general cortical activation during arousal state through the activation of histamine H1 receptors (H1R)\(^1\). The first-generation antihistamines, including d-chlorpheniramine, induce sleepiness by blocking H1R in the central nervous system (CNS). These drugs also impair various cognitive functions such as psychomotor speed and verbal learning due to the H1R blockade\(^2,3\). It was speculated that main factors of the impaired cognition and behaviors after the treatment of antihistamines was related to central nervous system (CNS). So we investigated the mechanism of cognitive and behavioral impairments induced by d-chlorpheniramine in human brain using PET and \[^{15}\text{O} \text{H}_2\text{O}\].

Materials and Methods

Subjects

Sixteen healthy male volunteers, ranging 21-24 years old (mean +/- S.D.: 22.5 ±1.2 y.o.), participated in this study. Written informed consent was obtained from each subject and the study was performed in compliance with the relevant laws and institutional guidelines.

Spatial discrimination task

In the present study, a spatial discrimination task was adopted for evaluation of visuomotor coordination. Subjects were asked to press the button with the left or right index finger promptly when the stimulus appeared in the corresponding side of the display. These stimuli were generated by AV tachistoscope (IS701A, Iwatsu, Japan).
Study design

Sixteen subjects were randomly assigned to the following 2 groups: the chlorpheniramine (CG) and placebo groups (PG). On the experiment day, subjects of the PG received placebo and the CG received 6 mg d-chlorpheniramine (Repetabs). In the first PET scanning session, subjects were asked to gaze a fixation point which appeared in the center of the display. Followed inter-scan interval of about 10min, spatial discrimination tasks were assigned. Reaction time (RT) was measured in order to assess the effect of d-chlorpheniramine during spatial discrimination task. Subjective sleepiness was evaluated just after each scan, using the Stanford Sleepiness Scale (SSS), composed of a 7-level self-report measurement.  

PET measurements and data analysis

The rCBF images were obtained using a 3D-acquisition PET scanner (Shimadzu SET-2400W, Japan).

The rCBF images obtained were realigned, normalized and smoothed by Statistical Parametric Mapping (SPM) software (SPM96; Welcome Department of Cognitive Neurology, London, U.K.). t-Statistics were computed for each voxel for the comparisons: (1) [spatial discrimination task] minus [fixation] in the PG and CG, (2) [the PG] minus [the CG] during spatial discrimination task. For each comparison, voxels with Z-value higher than 3.01 was considered to represent the regions with significant changes in rCBF.

SSS scores and RTs, measured additionally to PET scanning, were also analyzed and compared between the PG and CG with t-statistics. Statistical threshold for each test was defined as p<0.05.

Results

Subjective feeling and objective performance:

Subjective sleepiness measured just after fixation task was significantly higher in the CG (mean ± S.D. of SSS scores: 4.4 ± 0.7) compared to the PG (mean ± S.D.: 3.0 ± 1.2) (p<0.05). Subjective sleepiness just after spatial discrimination task was significantly higher in the CG (mean ± S.D.: 4.4 ± 0.8) compared to the PG (mean ± S.D.: 3.4 ± 0.9) (p<0.05). RT during spatial discrimination task was significantly prolonged in the CG
(mean ± S.D.: 0.28 ± 0.03 sec) compared to the PG (mean ± S.D.: 0.32 ± 0.04 sec) (p<0.05).

**PET studies:**

During the spatial discrimination task, the PG showed the rCBF increase in the right parietal cortex (BA 40), right cingulate gyrus (BA 24) and in the left cerebellum as shown in Fig.1.A and Table1. Changes of brain activities during spatial discrimination were also examined before and after oral administration of d-chlorpheniramine. The comparison revealed that the activation in the BA 24 was significantly increased in the CG than in the PG (p< 0.001 Z> 3.01), and that the activation in the BA 40 was significantly decreased in the CG than in the PG (p<0.001 Z>3.51) (Fig.1.B and C and Table1).

**Discussion**

There are many reports concerning the effect of d-chlorpheniramine, a first generation antihistamine\(^6\). A previous performance study demonstrated that d-chlorpheniramine induced an increased sleepiness, prolonged reaction time, functional deterioration in the visuomotor coordination, learning ability, memory and so on (Nicholson, 1985). The aim of this study was to elucidate the mechanism of the impaired cognition and behavior in sedative condition induced by d-chlorpheniramine using PET with \(\text{[}^{15}\text{O}]\text{H}_2\text{O}\).

The significant activation in PG during spatial discrimination task was observed in the right cingulate gyrus (BA 24), right anterior parietal cortex (BA 40) and in the cerebellum (Fig.1.A).

Activation of BA 40 during spatial discrimination task was significantly weaker in CG than in PG (Fig.1.B). Patients with lesions in the anterior parietal cortex manifested a decrease in regularity of exploratory finger movements\(^7\). It was suggested that activation of BA 40 was associated with finger movements following visual stimuli in spatial discrimination tasks. Deterioration in task performances in CG would be attributed to the decreased activation of BA 40.

On the other hand, activation in BA 24 was more intense in CG than in PG. As shown in Fig.1.C, the enhanced activation of the cingulate cortex was posterior part. Deiber also argued that the posterior region of cingulate gyrus might be associated with selection of correct motor outputs based on spatial attention\(^8\). Thus, the enhanced activation in the
posterior part of BA 24 would reflect compensation mechanism for the deterioration in task performances due to antihistamines.

These findings indicated that the alteration in the cortical activity would be related to the impaired spatial cognition caused by treatment of d-chlorpheniramine.

Acknowledgements

This work was supported by grants-in-aid from the Ministry of Education, Science, Sports and Culture, and the Ministry of Health and Welfare, Japan. We appreciate technical assistance of Mr. M. Miyake, Y. Ishikawa and S. Watanuki in PET studies.

References


Table 1. Brain regions related to spatial discrimination task, and alteration of their activity after the administration of d-chlorpheniramine.

<table>
<thead>
<tr>
<th>Brain regions</th>
<th>BA</th>
<th>axis (x,y,z)</th>
<th>Z score</th>
<th>The effects of d-chlorpheniramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>left cerebellum</td>
<td>52</td>
<td>-69 -25</td>
<td>6.17</td>
<td></td>
</tr>
<tr>
<td>right cingulate cortex</td>
<td>24</td>
<td>22 -16 36</td>
<td>5.29</td>
<td>increase 3.01</td>
</tr>
<tr>
<td>right parietal cortex</td>
<td>40</td>
<td>61 -60 38</td>
<td>4.75</td>
<td>decrease 3.50</td>
</tr>
</tbody>
</table>
Fig. 1. (A) The significant increases of rCBF during spatial discrimination task. Decreased (B) and increased (C) activations related to spatial discrimination task after the administration of d-chlorpheniramine.