

Effects of Levocetirizine and Diphenhydramine on Regional Cerebral Glucose Metabolism and Hemodynamic Responses during Cognitive Tasks

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Introduction

Histamine plays important roles in various brain functions, such as arousal, attention, and cognition^{1,2}). On the other hand, antihistamines often have sedative side effects. The adverse effects are mainly due to the ability of antihistamines to penetrate the blood–brain barrier, blocking neuronal transmission in the histaminergic nervous system in the brain. We have studied brain functional changes because of sedative effect of antihistamines. This time, we investigated the regional brain activity during cognitive tasks after administration of sedative and non-sedative antihistamines in terms of cerebral glucose metabolic changes and examined its relationship with regional hemodynamic response.

Materials and Methods

Eighteen healthy young volunteer (21.7 ± 0.8 years) participated in the study. This study used a double-blind, placebo-controlled, three-way, crossover design. Single doses of levocetirizine 5 mg, diphenhydramine 50 mg, and placebo (lactobacillus tablets) were administered orally with 100 mL water. Treatment periods were separated by a washout period of at least 6 days. The first PET scan (PET1) was performed in the resting state before oral administration (baseline) and the second PET scan (PET2) was done at 120 min post-administration (Fig. 1). The cognitive testing battery consisted of the word fluency test (Task1), two-back test (Task2), and Stroop test (Task3), all of which were prepared to activate the prefrontal cortex. Each of the three tasks took 60 s and each task was separated by 20-s-

long pre-task and post-task resting phases. A session including the three tasks was repeated six times, taking 30 min in total (Fig. 1). Also, assessment of subjective sleepiness was performed with the Stanford Sleepiness Scale (SSS) and the line analog rating scale (LARS); (Fig. 1).

We investigated cerebral glucose metabolic changes using positron emission tomography (PET). Brain scans were performed by the Eminence STARGATE PET scanner (Shimadzu Corp., Kyoto, Japan). Subjects were first scanned in the "resting" control condition (PET1) and later in the "task" condition (PET2) to compare the regional brain metabolic changes due to antihistamines (Fig. 1). PET brain images were transformed into those reflecting standardized uptake values (SUVs), normalized by body weight and by injected radioactivity of FDG. These SUV images were analyzed to identify regional changes in glucose consumption using a software package, Statistical Parametric Mapping (SPM8; Functional Imaging Laboratory, London, UK)³, which performed voxel-by-voxel analysis. During the cognitive tasks, hemodynamic responses were recorded as changes in oxygenated hemoglobin concentrations (Δ Oxy-Hb) in the frontal cortex using the OMM-3000 System (Shimadzu Corp., Kyoto, Japan). In the present study protocol, the first cognitive task (word fluency task: Task1) was initiated after the pre-task resting period and lasted for 60 s; this was followed by other post-task and pre-task resting periods and then the second task (20 s each). Then, the second (two-back task: Task2) and the third (Stroop task: Task3) tasks were assigned in a similar manner. Thus, the set of three cognitive tests was repeated six times (Fig. 1). The cerebral hemodynamic response pattern was examined for each task and for each drug treatment condition. For NIRS data analysis in the present study, we focused on the increase of oxy-Hb concentration which is considered as an estimate of regional brain activation. The oxy-Hb data were also corrected baseline offset (zero) to the task-starting time ($t=0$) and were transformed into Δ Oxy-Hb data, and were averaged to demonstrate hemodynamic responses in bilateral prefrontal areas during tasks for the three drug treatment conditions. Δ Oxy-Hb waveforms values were averaged throughout the task phase (0 to 60 s) for statistical examination.

For statistical analyses, we used SPSS 22.0 (Japanese version). For the subjective sedation, SSS and LARS scores were both examined by applying non-parametric examinations such as the Friedman test and Wilcoxon signed rank test (two-tailed; $p \leq .05$). All results of cognitive tests, including word counts in word fluency tests and accuracy and reaction time in two-back and Stroop tests, were also examined between drug treatments using non-parametric methods such as the Friedman test and Wilcoxon signed rank test (two-

tailed; $p \leq .05$). For the statistical analyses of PET images, the repeated ANOVA option of the SPM8 software package was applied because normal distribution and equal variance were confirmed. Significant findings were additionally examined by post hoc multiple pairwise treatment comparisons using a Bonferroni test (two-tailed; $p \leq .05$). For the statistical analyses of NIRS data, non-parametric examinations such as the Friedman test and Wilcoxon signed rank test (two-tailed; $p \leq .05$) were applied because normal distribution and equal variance were not confirmed. Significant findings were additionally examined by post hoc multiple pairwise treatment comparisons using the Wilcoxon signed rank test (two-tailed; $p \leq .05$). Details are described in our published paper⁴.

The ethics committee of the University Graduate School of Medicine approved the study protocol.

Results and Discussion

Subjective feelings were no significant differences between placebo and treatment conditions. Performance in Stroop test (accuracy) was significantly impaired after treatment with the sedative antihistamine compared with both the placebo ($p = .008$) and levocetirizine treatment ($p = .001$).

FDG-PET analysis using SPM8 revealed significant regional brain changes in glucose consumption during cognitive tasks (PET2) compared with the pre-treatment resting images (PET1) for each drug treatment condition (Fig. 2). Notably, the activation in Broca's area (Brodmann area: BA44/45), BA9, and BA10 was observed in all treatment conditions. Regional energy consumption was more prominent and more extensive with antihistamine treatments than with placebo in the following order: diphenhydramine > levocetirizine > placebo.

Hemodynamic responses were examined in the prefrontal regions that showed significant activation in FDG-PET (BA9, -10, and -44/45). Prefrontal activation ($\Delta\text{Oxy-Hb}$) was much more prominent during Task1 than during the other tasks. Thus, activation during Task2 and Task3 was much less prominent. In terms of temporal analysis, cortical activation patterns during Task1 in BA9, -10, and -44/45 were compared in both hemispheres (Fig. 3). Basically, there was no clear difference in shape of $\Delta\text{oxy-Hb}$ waveforms between drug treatments (Fig. 3). In the all treatment conditions, there was an initial small peak (at 5 s after task onset) and the highest peak (at 60 to 70 s after task onset) in hemodynamic responses. There were some significant differences between hemispheres and between treatment conditions, with the general trend for higher activation following placebo treatment than

following antihistamine treatment (Fig. 3). So, hemodynamic responses during the word fluency task seemed to be suppressed by antihistamine treatment compared with placebo (Fig. 3), as previously demonstrated by Tsujii and colleagues⁵).

FDG-PET results and NIRS results seem to be contradictory based on the “coupling” theory (linear correlation between the regional energy consumption and perfusion), where slight increased consumptions of oxygen and glucose due to regional brain activation are followed by a rapid and considerable surge in oxygen and glucose concentrations due to rapid capillary dilations in the activated brain regions. Thus, in principle, brain activation should be accompanied by a marked increase in oxy-Hb concentration. Antihistamines might possibly suppress the permeability of brain capillaries, dulling the prompt hemodynamic responses. However, such suppression might complicate continuous hemodynamic responses (up to 30 min, as in the present study).

Conclusion

Under sedative condition of administering antihistamine, physiological “coupling” between metabolism and perfusion in the healthy human brain may not be maintained. This uncoupling may be caused by a combination of increased energy demands in the prefrontal regions and suppression of vascular permeability in brain capillaries after antihistamine treatment. Further research is needed to elucidate this mechanism.

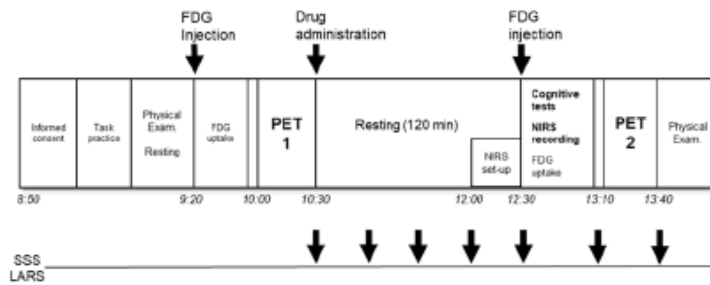
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References

- 1) Haas, H., & Panula, P., *Nat Rev Neurosci*, 4(2) (2003) 121–30.
- 2) Theunissen, E.L., Vermeeren, A., van Oers, A.C., et al., *Clin Exp Allergy*, 34(2) (2004) 250–8.
- 3) Friston, K.J., Frith, C.D., Liddle, P.F., et al., *vol.11, no. 4*, (1991) 690-699.
- 4) Kikuchi, A, Fairuz, B.M.N., Inami, A, et al., *Hum Psychopharmacol Clin Exp*. (2018) e2655.
- 5) Tsujii, T., Yamamoto, E., Ohira, T., Takahashi, T., et al., *Neurosci Res* 67(1), (2010) 80-5.

Time course of whole study



Time course of cognitive test

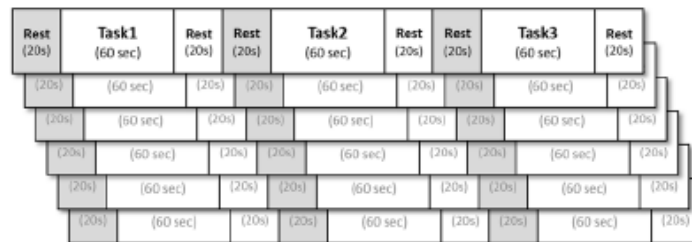


Figure 1. Schematic diagrams of the entire study protocol (top) and of the cognitive test protocol. FDG, [¹⁸F]fluorodeoxyglucose; LARS, line analog rating scale; NIRS, near-infrared spectroscopy; PET, positron emission tomography; SSS, Stanford Sleepiness Scale (Reproduced from Ref.4).

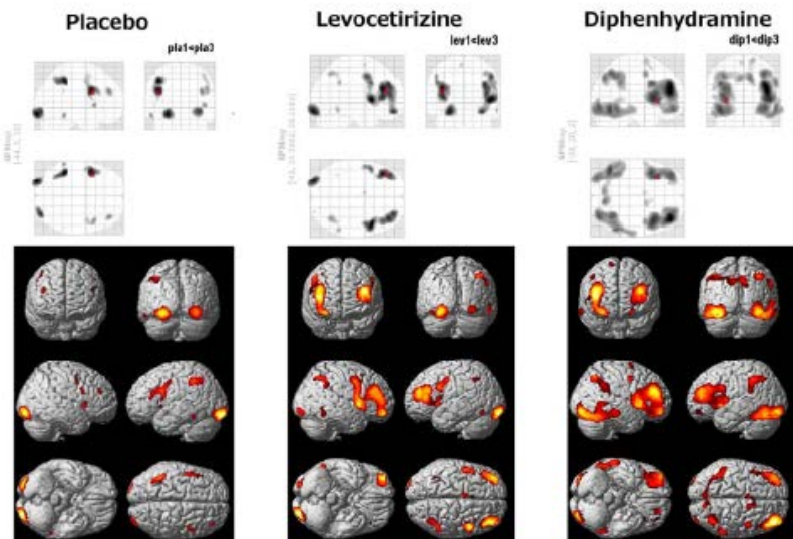


Figure 2. Results of voxel-by-voxel statistical parametric analysis of positron emission tomography [¹⁸F]fluorodeoxyglucose images. Statistically significant voxels are presented in the transparent standard brain space (glass brain, top) and superimposed onto the standard magnetic resonance imaging brain template images (bottom). The metabolic results of a voxel-by-voxel comparison of regional cerebral glucose metabolic images using statistical parametric mapping (SPM8; height threshold, $p < .05$, corresponding to z value >3.1 ; extent threshold 10 voxel minimum, with correction for multiple comparisons). L, left hemisphere; R, right hemisphere (Reproduced from Ref.4)

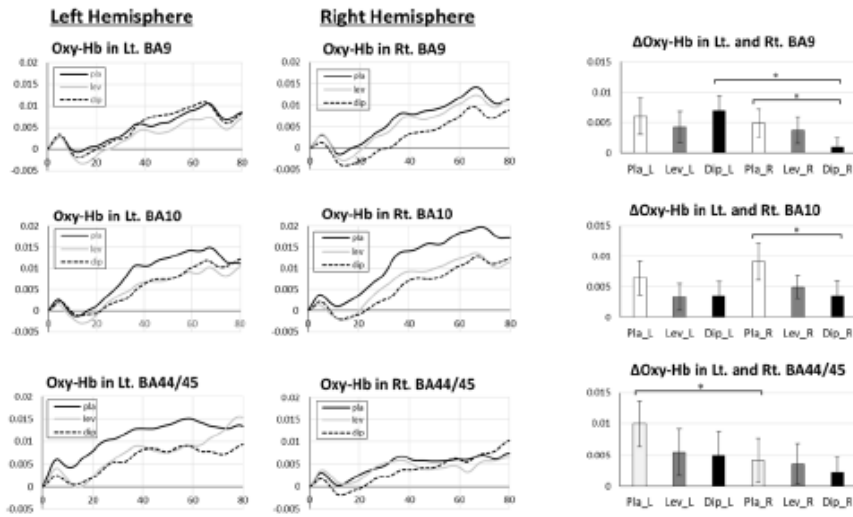


Figure 3. Changes in oxygenated hemoglobin (Δ oxy-Hb) waveforms showing cortical activation patterns during word fluency task (Task1) in BA9, BA10, and BA44/BA45 in the left and right hemispheres measured with near-infrared spectroscopy (left and middle columns). Results of statistical examination regarding the quantitative analysis of activation (right column). * $p < .05$, ** $p < .001$ for the post hoc Wilcoxon signed rank test. BA, Brodmann area; Lt., left; Rt., right; Pla, placebo; Lev, levocetirizine; Dip, diphenhydramine; oxy-Hb, oxygenated haemoglobin (Reproduced from Ref.4).