Effects of Sedative Antihistamines on the Regional Cerebral Blood Flow During Simulated Car Driving

VIII. 4. Effects of Sedative Antihistamines on the Regional Cerebral Blood Flow During Simulated Car Driving

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Introduction

Histamine H_1 receptor antagonists (antihistamines) are widely used for treatment of allergic disorders and are well-known for central nervous system (CNS) side effects such as drowsiness, sleepiness and impaired psychomotor performance[1)]. Car driving is closely connected with our everyday life. There are so many reports about the effects of antihistamines on car driving performance but its mechanism has not been demonstrated yet. Recently, some functional MRI (fMRI) studies have been published on brain activities during simulated car driving[2,3,4)]. Walter and colleagues revealed that the regional cerebral blood flow (rCBF) increased in the sensorimotor cortex and the cerebellum, by comparing active and passive driving conditions. Calhoun and colleagues demonstrated that car driving was able to be divided into several basic componentsand that fMRI was useful to investigate the neural correlates of car driving. However, there was no functional neuroimaging study on the drug-induced sedation during car driving. So we investigated the rCBF changes during simulated car driving after oral administration of d-chlorpheniramine, a sedative antihistamine, by positron emission tomography (PET) with $H_2{}^{15}O$.

Materials and Methods

Subjects

Fourteen healthy male volunteers, ranging 20-25 years old (mean +/- SD: 21.9 +/- 1.8), participated in the present study. All subjects were evaluated as right-handed based on the Edinburgh inventory and Chapman test. Mean driving history of all the subjects

was 17 months. Written informed consent was obtained from each subject and the study was performed in compliance with the relevant laws and institutional guidelines.

Study design

The present study was conducted as a single-blind crossover study. The subject was given one of a d-chlorpheniramine 6 mg repetab (Polaramin) or a placebo in each study. According to the previous report, it was estimated that the peak plasma drug concentration of orally-administered d-chlorpheniramine was achieved at 2 hours post-administration. Then, the PET investigation started approximately 2 hours after oral administration of d-chlorpheniramine 6 mg and so did it for placebo.

PET scans were performed for the following three conditions: 1) resting condition with the eyes closed, 2) active driving condition where the subjects had to drive by their own, using a steering wheel and accelerating pedal, and 3) passive driving condition where the subjects were requested to watch the changing landscape that had been videotaped, with the both hands fixed on the handle and with the right leg kept on the accelerating pedal.

Driving simulation

Commercially available software (Gekisoh 99, Twilight Express Co., Tokyo, Japan) was used for simulated driving task. The subjects were positioned in a PET scanner, wearing a head mount display (HMD: Glasstron PLM-A35, SONY, Tokyo, Japan) in a comfortable manner. They were able to operate the steering wheel and press the accelerating pedal quickly while watching landscape of driving course projected onto the HMD.

PET measurements and data analysis

The rCBF images were obtained using a 3D-acquisition PET scanner (SET 2400W, Shimadzu Co. Ltd., Japan), with an average spatial resolution of 4.5 mm the full-width half-maximum and with a sensitivity of a 20 cm cylindrical phantom of 48.6 k.c.p.s. $KBq^{-1}ml^{-1}$. PET acquisition was performed for the duration of 70 sec. The subject was injected with $H_2{}^{15}O$ of 157.8 ± 25.6 MBq (5.8 ± 0.9mCi) through the antecubital vein for each scan.

The rCBF images obtained were realigned, normalized and smoothed by Statistical Parametric Mapping (SPM) software (SPM99; Welcome Department of Cognitive Neurology, London, U.K.). T-Statistics were computed for each voxel for the

comparisons: 1) active driving condition or passive driving condition scan minus resting condition scan after oral administration of placebo or d-chlorpheniramine, 2) after oral d-chlorpheniramine minus placebo in condition of active driving scan. For each comparison, each voxel difference with Z-value higher than 3.01, corresponding to $p < 0.001$ (uncorrected), was considered as significant changes in rCBF.

Results

After oral administration of placebo, the significant increase of rCBF was found in the sensorimotor (Brodman Area: BA 4), premotor (BA6), parietal (BA 7, 40), temporal (BA 37), occipital (BA17-19) cortices and in the cerebellum, midbrain, pulvinar, globus pallidus medialis and cingulated gyrus during active driving compared with the resting condition (Fig. 1). And the regions of increased CBF during active driving in comparison to the passive driving condition were nearly the same. Compared to placebo, d-chlorpheniramine produced significant increase of rCBF in the cerebellar vermis and decrease of parietal (BA 7), temporal (BA 37), occipital (BA 19) cortices and cerebellum hemisphere during active driving.

Discussion

Car driving is closely connected with our everyday life and needs integration of various brain functions such as attention to other vehicles and walkers, circumstantial judgment, motor programming and output, working memory, etc. It is well-known that antihistamines, especially first generation antihistamines, have sedative side effects. These side effects are dangerous especially during operating a machine or driving a car. The sedative antihistamines are available more easily as over-the-counter drugs than newer less sedating antihistamines. There are various methods to evaluate driving performance after administrating sedative drugs such as subjective sleepiness, reaction time, EEG changes, vehicle maintenance capability, during both actual and simulated driving.

Walter and colleagues first measured the regional brain activity in healthy volunteers during simulated driving using fMRI[2]. They detected the brain activation mainly in the visual and somatosensory cortices and in the cerebellum by contrasting active and passive driving conditions. It has been demonstrated functional neuroimaging is a very useful tool to elucidate neural correlates of driving. In the present study, the contrast between active and resting conditions and that between active and passive conditions both

demonstrated similar results to the previous fMRI study by Walter and colleagues[2]. Taking all these findings together, it could be concluded that $H_2{}^{15}O$-PET gives basically the same results as those obtained with fMRI.

On the other hand, rCBF responses were reduced after administration of d-chlorpheniramine in the parietal (BA 7), temporal (BA 37), occipital regions, that are considered to be the visuo-spatial pathway. The results might suggest that d-chlorpheniramine tends to suppress mainly visuo-spatial function during simulated driving.

References

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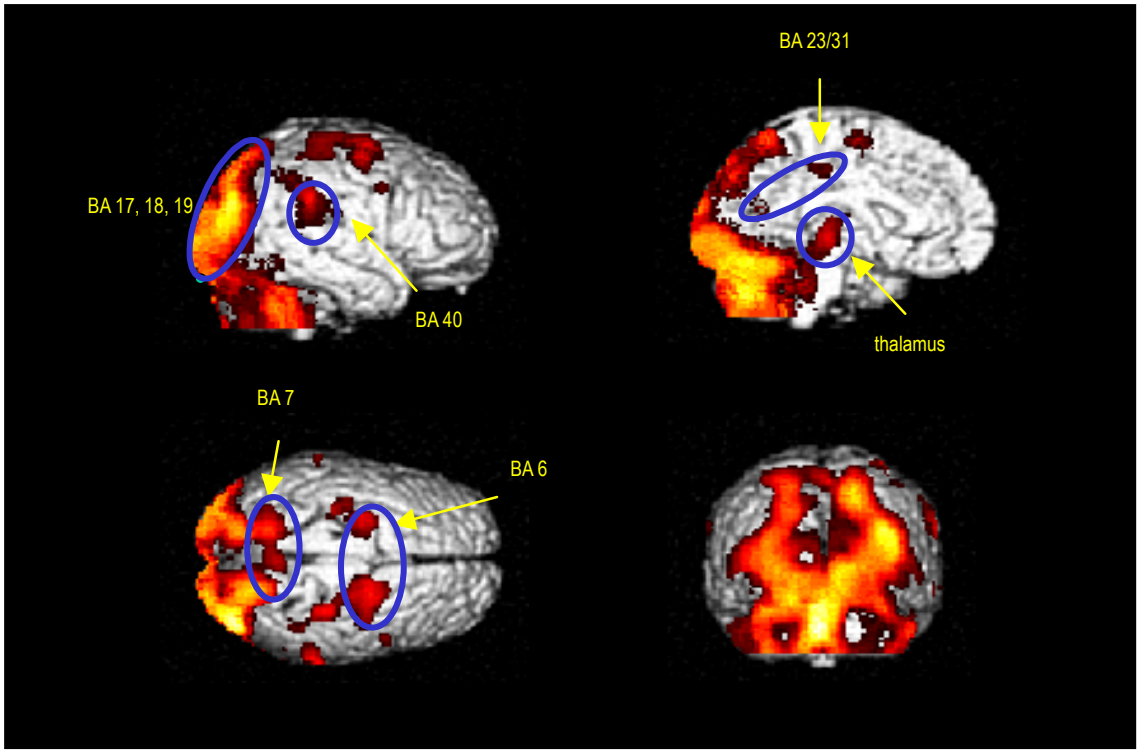

Fig. 1. The significant increase of rCBF during active driving compared with resting condition after oral administration of placebo.