various psychoactive drugs, such as antidepressants (Ridout and Hindmarch, 2001; Ridout *et al.*, 2003a; Warrington, 1991), anxiolytics (Hindmarch *et al.*, 1977; van Laar *et al.*, 2001), analgesics (Sabatowski *et al.*, 2003; Vainio *et al.*, 1995), and antihistamines (Gengo and Gabos, 1987; Ridout *et al.*, 2003b; Tashiro *et al.*, 2005; Verster *et al.*, 2003; Weiler *et al.*, 2000) alone or in combination with alcohol (Koelega, 1995; Movig *et al.*, 2004; Ramaekers *et al.*, 2002; Seppala *et al.*, 1979; Weiler *et al.*, 2000). Antihistamines are widely used for treating various allergic disorders such as allergic rhinitis and dermatitis, and sedative antihistamines in particular significantly impair driving performance (Aso and Sakai, 1988; Ramaekers *et al.*, 1992; Ridout *et al.*, 2003b; Tashiro *et al.*, 2005; Theunissen *et al.*, 2004; Verster and Volkerts, 2004; Verster *et al.*, 2003; Weiler *et al.*, 2000).

Sedative antihistamines such as D-chlorpheniramine and diphenhydramine can readily cross the blood-brain barrier (BBB) and block histamine H_1 receptors (H_1Rs) in the histaminergic neuronal system of the brain, resulting in sleepiness, drowsiness, fatigue, and psychomotor disturbances that might result in car injury (Ridout *et al.*, 2003b; Theunissen *et al.*, 2004; Verster and Volkerts, 2004; Yanai and Tashiro, 2007). Neuro-receptor positron emission tomography (PET) studies using [^{11}C]doxepin have demonstrated that these sedative antihistamines occupy more than 50% of brain H_1Rs, which may considerably suppress the psychomotor functions of drivers (Okamura *et al.*, 2000; Tagawa *et al.*, 2001; 2006; Yanai and Tashiro, 2007; Yanai *et al.*, 1995, 1999). A simulated driving performance study by Weiler *et al.* (2000) demonstrated that sedative antihistamines had a greater impact on driving ability than alcohol. Ironically, these potentially dangerous sedative antihistamines are more easily available as over-the-counter drugs than newer less-sedating antihistamines (Tashiro *et al.*, 2005). These facts emphasize the importance of research activities to reveal the neural mechanisms of drug-induced sedation among drivers. In order to promote this line of research, it is of great help to know the functional neuroanatomy of car driving as demonstrated by a recent imaging technique (Calhoun *et al.*, 2002; Horikawa *et al.*, 2005; Jeong *et al.*, 2006; Uchiyama *et al.*, 2003; Walter *et al.*, 2001).

Car driving is such a complex task that various regions of the brain may be actively involved. Studies on imaging the neural correlates of car driving have just started compared with performance studies. Most recent imaging studies on car driving have employed a simulated driving task using functional magnetic resonance imaging (MRI) [fMRI] (Calhoun *et al.*, 2002; Uchiyama *et al.*, 2003; Walter *et al.*, 2001) and PET (Horikawa *et al.*, 2005). Walter *et al.* first examined regional cerebral blood flow (rCBF) responses during simulated car driving. They succeeded in visualizing the brain regions associated with vision, sensorimotor coordination, motor function as well as the cerebellum (Walter *et al.*, 2001). To the best of the authors' knowledge, however, neuroimaging studies using a car-driving task have not yet been carried out to elucidate the mechanism of antihistamine-induced impairment of driving performance, with the exception of a few studies on simple cognitive tasks (Mochizuki *et al.*, 2002; Okamura *et al.*, 2000).

The main purpose of the present study was to examine rCBF responses (ΔrCBF) in healthy volunteers during simulated car driving following the oral administration of D-chlorpheniramine, a typical sedative antihistamine, using PET with [^{15}O]H_2O.

SUBJECTS AND METHODS

Fourteen healthy Japanese male volunteers ranging from 20 to 25 years old (mean age $\pm$ SD: 21.9 $\pm$ 1.8 years old) were recruited to the present study. None of the participating subjects were under any medication nor had any previous history of allergic and neuropsychiatric disorders including sleep disturbances. There were no heavy smokers or habitual coffee drinkers among the subjects. The present protocol was approved by the Ethics Committee of Tohoku University Graduate School of Medicine, and written informed consent was obtained from each subject after thorough explanation of the whole procedure and possible risk of the experiment. Ingestion of caffeine, alcohol-containing drinks, nicotine, grapefruit juice, and any other supplement drinks was not permitted from the night before the testing day until the end of the study. All the subjects except for one enrolled in the present study have a valid driver's license and the mean duration of their driving history was 17.2 $\pm$ 13.0 months. All the subjects were evaluated as right-handed based on the results of Edinburgh inventory (Oldfield, 1971), Chapman test (Chapman and Chapman, 1987), and H. N. Handedness Inventory (Hatta and Kawakami, 1995).

EXPERIMENTAL DESIGN

The purpose of the present study is to examine the rCBF effects of D-chlorpheniramine, whose sedative effects have been repeatedly demonstrated by several groups (Hindmarch and Bhatti, 1987; Mochizuki *et al.*, 2002; Nicholson *et al.*, 1991; Starbuck *et al.*,

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2000; Tagawa *et al.*, 2001). The present study was conducted as a single-blind cross-over study. Each subject was given D-chlorpheniramine repetab (6 mg) or a lactobacteria tablet used as placebo in each study. The D-chlorpheniramine repetab was successfully used in our previous activation studies (Mochizuki *et al.*, 2002; Tagawa *et al.*, 2001) as well as the lactobacteria preparation, giving no statistical difference between pre- and post-administration in previous cognitive studies (Mochizuki *et al.*, 2002; Tagawa *et al.*, 2001, 2002; Tashiro *et al.*, 2002, 2004). The same subjects were studied for each drug at an interval of at least 6 days as a wash-out period. The order of drugs given to each subject was randomly assigned and balanced.

According to a previous report, the peak plasma drug concentration of orally administered D-chlorpheniramine is achieved 2 h post-administration (Peets *et al.*, 1972). Thus, the PET investigation was started approximately 2 h after the oral administration of the D-chlorpheniramine repetab, which was given to maintain its high plasma concentration for 2–3 h similarly as in a previous PET study (Tagawa *et al.*, 2002). In the present study, PET scan was started approximately 2 h post-administration of oral tablets (placebo or antihistamine), and a set of 6 PET scans was taken for approximately 1 h per condition. The whole scanning procedure was completed within 3 h post-administration.

The subjects were placed in the dorsal position on the PET coach with their knee on the knee rest, and they were requested to wear a head mount display (HMD: Glasstron PLM-A35, SONY, Tokyo, Japan) to enable them to watch the projected 'in-car' views of the outer world during driving (Figure 1). The steering wheel and acceleration pedal were attached at a suitable position so that the subjects were able to operate them easily and comfortably. This system lacked a brake pedal and the subjects were able to decrease driving speed by setting their foot away from the acceleration pedal. The intravenous infusion line for $[^{15}O]H_2O$ injection was inserted into a subject's right antecubital vein so as not to interfere with the handling of the steering wheel. For a simulated driving task, a commercial computer software was used (Gekisoh99, Twilight Express Co., Ltd, Tokyo, Japan) that operated on a Windows 95/98 operating system. A 'time trial mode' was employed in the present study to measure the total duration of driving from the 'start' to the 'goal' points, where there were three lanes in each side of the road with oncoming cars on the other side of the road but with no traffic signals and pedestrians. The subjects were requested to drive smoothly as in normal car driving, but also as fast as possible from the start to the goal point, avoiding collision and deadlocks. The in-car views during the simulated driving were all videotaped and were later used for rating each volunteer's driving performance. Further

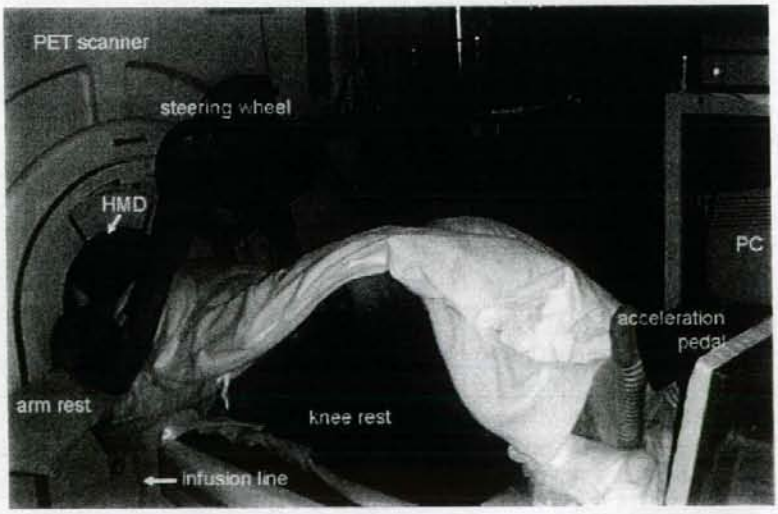

Figure 1. A picture of PET examination during a simulated car-driving task. Each subject wears a HMD monitor for driving. The driving simulator system was attached to a steering wheel and an acceleration pedal. The subject is injected with saline water containing $[^{15}O]H_2O$ via an infusion line inserted into the right antecubital vein

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details regarding this program are already mentioned in our previous report (Horikawa *et al.*, 2005).

PET rCBF images were acquired under the following three conditions: (1) resting condition with the eyes closed, (2) active driving condition where the subjects were requested to drive on their own, and (3) passive driving condition where the subjects were requested to watch the changing in-car view that had been videotaped previously, with their hands and feet fixed on the steering wheel and acceleration pedal, respectively. Two sets of measurements were conducted for each drug condition, where the orders of driving conditions were the resting-active-passive order in the first session and the active-passive-resting order in the second session (Figure 2) in order to eliminate an order effect. However, the order of active and passive driving conditions was fixed since the recorded landscape during active driving was used for the presentation of the following passive driving measurement. A single session took approximately 200 s, where PET scanning commenced shortly after the radioactivity from the head of each subject exceeded 40 counts per second (cps) as measured using the PET system (nearly 30 s after the initiation of $[^{15}O]H_2O$) injection and lasted for 70 s. For the results, driving task continued for 40–90 s following the cessation of PET scanning. In general, all PET examinations were conducted during the daytime ranging within the period between 9:30 and 15:00.

Performance of the subjects was evaluated in terms of the following four criteria: (a) total duration (second) of driving from the start to the goal point, (b) number of collisions to oncoming cars or guardrails, (c) number of lane deviations due to crossing a center line, and (d) number of deadlocks where driving speed becomes lower than 10 km/h. The performance variables in the present study were measured by two raters. These measurements were assessed by a rater and the results of the rating were cross-checked by another rater, producing the same results.

Additionally, subjective sleepiness was also evaluated before drug administration (placebo or D-chlorpheniramine) and just after each PET scanning, using the Stanford Sleepiness Scale (SSS) (Hoddes *et al.*, 1973) (Figure 2).

PET MEASUREMENTS

The rCBF images were obtained at the whole brain level using a PET scanner (SET 2400 W, Shimadzu Co., Ltd, Japan), with an average spatial resolution of 4.5 mm full-width at half-maximum and with a sensitivity of a 20 cm cylindrical phantom of 48.6 kcps/KBq ml in the three-dimensional (3D) mode. PET acquisition was performed for 70 s. Each subject was injected with $[^{15}O]H_2O$ of 157.8 ± 25.6 MBq (4.26 ± 0.69 mCi) on average through the antecubital vein for each scan. PET scans were started shortly after the

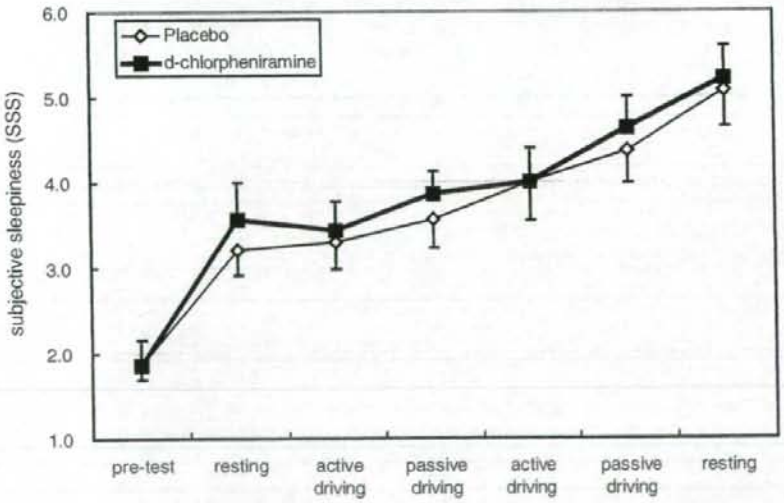

Figure 2. Subjective sleepiness measured using the SSS before oral administration of placebo or D-chlorpheniramine (pre-test) and just after each PET scanning (resting, active driving, and passive driving). There was no significant difference between the placebo and D-chlorpheniramine conditions throughout the whole examination. Error bars indicate the standard error of mean (SEM)

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radioactivity from the head region could be detected and lasted for 70 s.

DATA ANALYSIS

Driving performance data

After the completion of all PET investigations, driving performance was rated for each volunteer. Statistical analysis of the variables for performance and sleepiness was performed to detect significant differences between placebo and D-chlorpheniramine treatments using the non-parametric Wilcoxon *rank sum* test, where $p < 0.05$ was set to be significant, because of the non-normal distribution of the driving performance data.

Brain image analysis

The rCBF images were processed and analyzed using a Statistical Parametric Mapping (SPM) software package (SPM99; Wellcome Department of Cognitive Neurology, London, U.K.) (Friston *et al.*, 1995). Before starting the analysis, intrasubject head movements were corrected (realignment), and then all images were stereotaxially normalized using linear and nonlinear transformations into a stereotaxic coordinate system (normalization to the standard brain space) (Talairach and Tournoux, 1988). The normalized images were then smoothed using a $12 \times 12 \times 12\,mm^3$ Gaussian filter (smoothing). The rCBF values were expressed as ml/dl/min, adjusted using proportional scaling and scaled to a mean of 50 ml/dl/min. A significant change in rCBF was evaluated according to the general linear model at each voxel. To test the hypotheses on specific rCBF changes, the estimates were compared using linear contrasts. The resulting set of voxel values for each contrast constitutes a statistical parametric map of the *t*-statistics.

To identify brain regions that are related to the simulated driving stimulus, rCBF images during active driving were compared with those during the resting and passive driving conditions. The *t*-value of each voxel was transformed into normally distributed *Z*-statistics. For each comparison, each voxel difference with a *Z*-value higher than 2.99, corresponding to $p < 0.001$ (uncorrected), was interpreted as significant. Additionally, each cluster including significant voxel differences and also having at least 10 voxels was interpreted as significant regional rCBF changes.

We further compared rCBF changes during active driving compared to the resting state between the D-chlorpheniramine and placebo conditions. We determined the localization of the peak activation related to the active driving condition as compared with the resting and passive driving conditions. Mean voxel values were calculated among the voxels including the peak and also those exceeding a threshold of $Z > 2.99$. The mean of these voxel values reflected rCBF since all voxel values in the rCBF images were scaled to a mean of 50 ml/dl/min. The rCBF changes (ΔrCBF) were compared between the D-chlorpheniramine and placebo conditions using paired *t*-test. A probability of less than 0.05 was considered to be statistically significant.

RESULTS

Driving performance

All 14 subjects completed the entire investigation. Performance evaluation revealed that the number of lane deviations significantly increased in the D-chlorpheniramine condition compared with the placebo condition (mean value $\pm$ SEM: 2.57 ± 0.60 vs. 6.36 ± 1.80, respectively: $p < 0.01$). All other measurements (duration of driving time and numbers of collisions and deadlocks) demonstrated

Table 1. Driving performance in D-chlorpheniramine and placebo conditions

				Percentile		
Measurement items	Drug	Mean	SEM	25	50	75
Driving duration (s)	Placebo	124.2	2.90	117.1	124.8	133.1
	D-chlorpheniramine	131.1	5.30	110.8	128.0	150.4
Crashes (times)	Placebo	3.68	0.40	2.75	3.75	4.88
	D-chlorpheniramine	5.54	1.10	1.88	4.00	6.25
Deadlocks (times)	Placebo	1.25	0.20	0.50	1.00	1.50
	D-chlorpheniramine	2.36	0.60	0.38	1.00	4.25
Excessive lane shifts[a] (times)	Placebo	2.57	0.60	0.38	1.50	4.63
	D-chlorpheniramine	6.36	1.80	1.38	2.50	10.50

[a] $p < 0.01$.

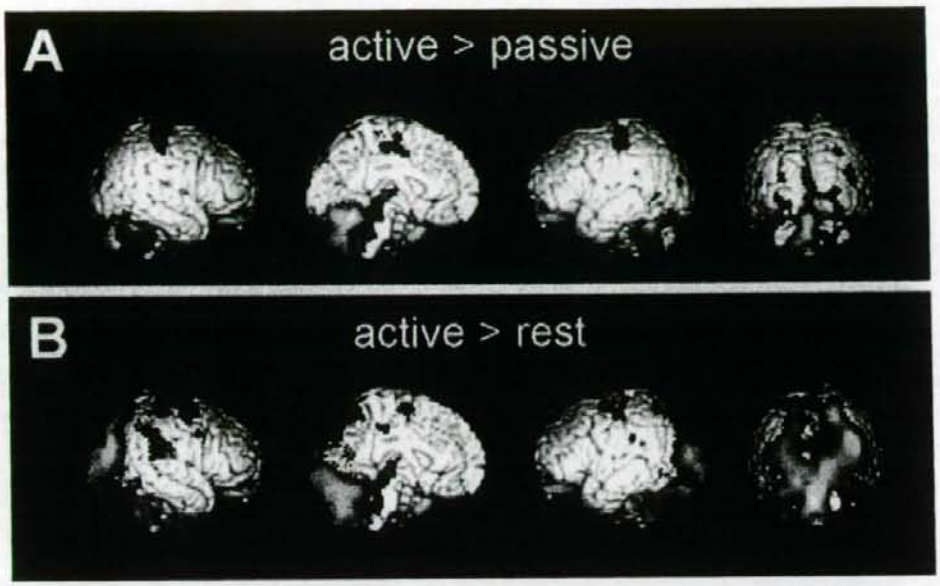

Figure 3. Brain regions significantly activated during the 'active' driving condition compared with the 'passive' driving condition (A). Brain regions significantly activated during the 'active' driving condition compared with the 'resting' condition (B). Statistically significant regions are superimposed onto standard MRI rendered images (statistical threshold: $p < 0.001$ uncorrected; minimum number of voxels, 10)

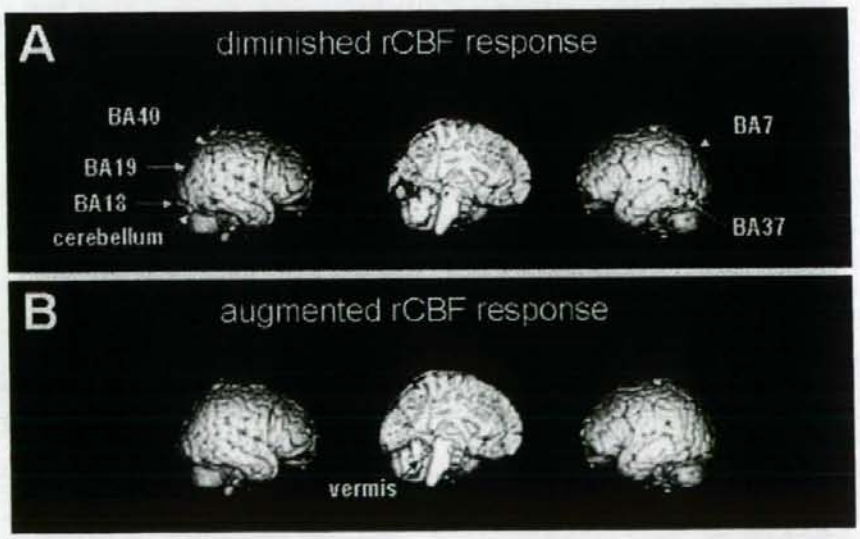

Figure 4. Brain images with augmented rCBF responses (A) and diminished rCBF response (B) following D-chlorpheniramine treatment. Statistically significant regions are superimposed onto standard MRI rendered images (statistical threshold: $p < 0.001$ uncorrected; minimum number of voxels; 10). Abbreviation: BA = Brodmann's area

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Table 2. Regions with diminished and augmented CBF responses in D-chlorpheniramine condition

Area		BA	Coordinate (x,y,z)	Z-score	t-value	Cluster size (voxels)
Diminished CBF response						
Parietal lobe						
Posterior parietal	Lt	7	−24, −80, 48	3.38	3.45	63
Supramarginal gyrus	Rt	40	58, −54, 48	3.08	3.13	22
Temporal lobe						
Inferior temporal	Lt	37	−64, −56, −4	3.14	3.20	18
Parahippocampal gyrus	Rt	35/36	24, −32, −8	3.09	3.15	62
Occipital lobe						
Visual association	Lt	18	−26, −74, −6	3.69	3.79	206
Visual association	Lt	18	−2, −94, 20	3.47	3.55	97
Visual association	Rt	18	18, −90, −12	3.37	3.45	101
Visual association	Rt	19	42, −82, 34	3.62	3.71	151
Cerebellar hemisphere	Rt		38, −84, −20	4.08	4.21	399
Augmented CBF response						
Frontal lobe						
Orbitofrontal	Rt	11	28, 36, −28	3.40	3.47	23
Cerebellar vermis			−10, −46, −22	3.23	3.30	45

D-chlorpheniramine's effects on impaired driving performance but were not significant (Table 1). Subjective sleepiness score was not significantly different between the placebo and D-chlorpheniramine conditions. Sleepiness score increased similarly in both drug conditions (Figure 2), which may have been induced by the present experiment setting in a dark room. Each performance score and the sleepiness scores did not correlate significantly.

Regional brain activity

Regions with increased rCBF during the active driving condition compared with the passive driving condition were detected in the primary sensorimotor [Brodmann's area (BA): BA4], premotor (BA6), cingulate (BA23/31), posterior parietal (BA7), temporal (BA37), and occipital (BA17–19) cortices and in the cerebellar hemisphere, midbrain, globus pallidus, and pulvinar of the thalamus (Figure 3). The regions with increased rCBF during the active driving condition compared with the resting condition covered nearly the same regions mentioned above, but in much wider areas additionally including the right orbitofrontal cortex (BA11) (Figure 3).

Next, the resting CBF images were compared between the D-chlorpheniramine and placebo conditions in order to examine the central effect of D-chlorpheniramine in the resting state. rCBF in the right parietal (BA7 and 40), bilateral temporal (BA21/22) and left occipital cortices (BA17 and 19) as well as in the caudate nucleus and cerebellum following D-chlorpheniramine treatment was higher than that in the same areas following placebo administration. Lower rCBF following D-chlorpheniramine treatment was observed in the bilateral frontal (BA6, 8, 10), right parietal (BA39), bilateral temporal (BA21 and 22), and bilateral insular cortices.

Finally, the regions with altered ΔrCBF ([active driving] − [resting]) compared with the resting condition were compared between the D-chlorpheniramine and placebo conditions. The regions with decreased ΔrCBF following D-chlorpheniramine treatment were detected in the bilateral parietal (BA7/40), temporal (BA36/37), and occipital cortices (BA17 and 19) (Table 2, Figures 4 and 5A–C). The regions with augmented ΔrCBF following D-chlorpheniramine administration were found in the orbitofrontal cortex and cerebellar vermis (Table 2, Figures 4 and 5D). No areas of statistically significant difference were detected by comparison of altered ΔrCBF ([active driving] − [passive driving]) compared with the passive driving condition.

DISCUSSION

Antihistamines are potentially dangerous agents to many drivers and, so far, a large number of studies have been conducted to determine their effects on driving behavior (Aso and Sakai, 1988; Ramaekers *et al.*, 1992; Ridout *et al.*, 2003b; Tashiro *et al.*, 2005; Theunissen *et al.*, 2004; Verster and Volkerts, 2004; Verster *et al.*, 2003; Weiler *et al.*, 2000). Their main therapeutic target in various allergic disorders is H_1Rs in the peripheral blood; however, some components of antihistamines can easily cross the BBB

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and block the H_1Rs of neurons in the brain. The histaminergic neuronal system plays important roles in maintaining arousal and attention, sleep–wake cycle, and learning and memory, and the blockade of H_1Rs may result in sedation characterized by symptoms such as sleepiness, drowsiness, fatigue, and psychomotor disturbances (Brown *et al.*, 2001; Yanai and Tashiro, 2007). In particular, sedative antihistamines such as D-chlorpheniramine and diphenhydramine significantly impair driving performance (Hindmarch, 1976; Qidwai *et al.*, 2002; RedBook, 1998; Ridout *et al.*, 2003b; Verster and Volkerts, 2004; Weiler *et al.*, 2000). The degrees of BBB permeability by antihistamines have been measured using PET and [^{11}C]doxepin in healthy volunteers termed as H_1R occupancy (Holgate *et al.*, 2003; Okamura *et al.*, 2000; Tagawa *et al.*, 2001; Tashiro *et al.*, 2004, 2006; Yanai and Tashiro, 2007; 1999). One of our previous studies demonstrated that a single oral administration of D-chlorpheniramine (2 mg) achieved approximately 49% H_1R occupancy and repetab (6 mg) achieved 53% (Tagawa *et al.*, 2001). Such high H_1R occupancy may considerably suppress psychomotor functions, sometimes manifesting a greater impact on driving ability than alcohol (Weiler *et al.*, 2000). Ironically, sedative antihistamines are more easily available over the counter than newer less-sedating antihistamines, and are still considered among the top-selling OTC drugs for allergic rhinitis (Hindmarch, 1976; Qidwai *et al.*, 2002; RedBook, 1998; Ridout *et al.*, 2003b; Verster and Volkerts, 2004; Weiler *et al.*, 2000). These facts may encourage researchers to exert more effort to elucidate the effects of sedative antihistamines on the neural correlates of car driving.

So far, neural correlates of car driving have been demonstrated using fMRI and PET and the reproducibility of the findings was demonstrated in the present study as well by comparing with the results of other studies (Calhoun *et al.*, 2002; Horikawa *et al.*, 2005; Uchiyama *et al.*, 2003; Walter *et al.*, 2001). Walter *et al.* (2001), who first applied fMRI to the measurement of regional brain activity during simulated driving, demonstrated brain activation in the visual and somatosensory cortices and cerebellum, by comparing active and passive driving conditions created in a simulated environment. Calhoun *et al.* (2002) confirmed the reproducibility of a car-driving study and further divided the car-driving task into several basic components such as visual perception, visual monitoring, vigilance, motor control, motor coordination, and error monitoring and inhibition, using independent component analysis. Uchiyama *et al.* (2003) obtained results similar to those reported by Walter and Calhoun, and additionally demonstrated a correlation between the rCBF response in the anterior cingulate and the driving performance in a driving task to maintain a safe distance from a leading car. In principle, both fMRI and PET with [^{15}O]H_2O measure hemodynamic responses and should produce basically the same results, having been confirmed by applying an identical protocol to identical subjects. Horikawa *et al.* (2005) confirmed the reproducibility of a simulation study scanned using PET and [^{15}O]H_2O. Later, the reliability of using a simulated driving task was partly confirmed by Jeong *et al.* (2006), who applied an actual car-driving task on a road for a PET study using [^{18}F]fluorodeoxyglucose that enabled PET scanning after completion of driving tasks. Their results were nearly the same as those of previous studies using fMRI and simulated driving tasks, demonstrating significant brain activation during active driving in the primary and secondary visual cortices, primary sensorimotor areas, premotor area, parietal association area, cingulate gyrus, thalamus, as well as in the cerebellum. Passive driving showed an almost similar activation pattern, lacking activations in the premotor area, and cingulate and parahippocampal gyri. Thus, the reliability of using a simulated driving system for elucidating neural correlates of car driving was partly confirmed, and it is possible that these simulation studies represent the neural correlates of car driving at least regarding cognitive aspects.

For the evaluation of impaired driving performance due to sedative antihistamines, various measures have been applied such as brake reaction time (Ramaekers and O'Hanlon, 1994; Ramaekers *et al.*, 1992; Verster *et al.*, 2003; Weiler *et al.*, 2000) and vehicle maintenance capability (Aso and Sakai, 1988; Ramaekers and O'Hanlon, 1994; Verster *et al.*, 2003; Weiler *et al.*, 2000) using either an actual or simulated car-driving task. The reaction time is a rather simple task and is mostly associated with basic psychomotor functions of attention, visual cognition, and motor output, mediated mainly by the anterior cingulate gyrus, and occipital and motor cortices, respectively. Vehicle maintenance capability seems to be more complex and can be divided into subcategories such as 'coherence', the ability to maintain a constant distance from a leading car that varied its speed randomly, and 'steering stability', the ability to maintain a constant position in a driving lane (Aso and Sakai, 1988). These tasks may require additional neural functions such as visuo-spatial cognition and visuo-motor coordination, which may require involvement of the temporo-parietal association cortex in addition to the basic

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components of a car-driving task (cingulate, visual, and motor cortices). A previous behavioral study reported that D-chlorpheniramine (6 mg) impaired steering stability (over-steering), where the steering angle was unnecessarily large (Aso and Sakai, 1988). A highway driving test revealed a significant increase in the standard deviation of lateral position (SDLP) following D-chlorpheniramine treatment. Subjective alertness score was also significantly lower following D-chlorpheniramine treatment than that following placebo treatment (Theunissen *et al.*, 2004). According to another study by Weiler *et al.* (2000), steering stability was impaired by both alcohol and diphenhydramine, whereas coherence ability was impaired following only the administration of diphenhydramine. In the present study, impairment of steering stability (number of lane deviations) was demonstrated following D-chlorpheniramine treatment.

As for the non-significant difference in subjective sleepiness scores between the placebo and D-chlorpheniramine conditions, it is important to mention that the PET experiment room was dimly lit during the whole scanning procedure, where spontaneous sleepiness was probably induced. This condition would be relevant to the result showing that the subjective sleepiness scores did not show a significant difference. Such variability would also be attributable to the level of task difficulty. It is suggested that the level of task difficulty in the present study was not very high. However, the effects of D-chlorpheniramine observed in the present study were less pronounced partly because D-chlorpheniramine was given as a sustained release formulation, or repetab, as used in a previous study by Theunissen *et al.* (2004). In addition, this result suggests that subjective sleepiness is not always a reliable measure of sedation.

A comparison of the ΔrCBF between the D-chlorpheniramine and placebo conditions revealed regions with significantly 'diminished' and 'augmented' rCBF responses following D-chlorpheniramine treatment (Figure 4). The regions of diminished rCBF responses were observed in the posterior parietal (BA7 and 40), temporal (BA35 and 37) and occipital regions (BA18 and 19) as well as in the cerebellar hemisphere, which can be linked to functional suppression due to D-chlorpheniramine. Thus, the present results suggest that D-chlorpheniramine suppresses neural activities associated with visuo-spatial cognition and visuo-motor coordination. In general, visual information projected onto the occipital cortex is transferred to the posterior part of the parietal cortex via the dorsal pathway for higher visual processing of motion and visuo-spatial information (Jueptner and Weiller, 1998). Based on these findings, the suppression of rCBF responses in the visual and temporo-parietal association areas following D-chlorpheniramine treatment seems to also be in accordance with the present performance results. In addition, the suppression of the occipital cortex and cerebellum also seems to be reasonable since the cerebellum plays an important role in optimizing motor output based on visual inputs. It is hard to explain the findings in the temporal cortex (BA21/22) that demonstrated both increased and decreased rCBF following D-chlorpheniramine treatment in comparison to that following placebo treatment. Probably, they were caused by a slight difference in the phonetic environment.

To the best of the authors' knowledge, however, there is as yet no imaging study that has elucidated the effects of sedative drugs on the neural correlates of car driving except for a few studies from Calhoun *et al.* (2004, 2005) that applied fMRI to evaluate the brain activity of alcohol-intoxicated drivers. Interestingly, they reported that marked CNS effects due to alcohol were observed only in the orbitofrontal and primary sensorimotor regions but not in the cerebellum, and visual and temporo-parietal regions that seemed to be essential for car driving (Calhoun *et al.*, 2004, 2005). Based on the findings that alcohol impaired steering stability but not coherence ability, it is suggested that alcohol tends to affect motor function more strongly than sedative antihistamines do and that coherence ability tends to be more easily affected by impairment of motor functions. It seems that regional CNS effects during driving are variable and drug- and dose-dependent, stressing the importance of clinical and pharmacological research studies.

The regions with significantly augmented rCBF responses were observed in the orbitofrontal cortex and cerebellar vermis. The cerebellar vermis and orbitofrontal regions seem to be activated possibly as part of the compensatory mechanism to maintain driving performance; however, the specific underlying mechanism remains to be investigated. In addition, subjective sleepiness score was not significantly different between the placebo and D-chlorpheniramine conditions in the present study, suggesting that subjective sleepiness is not necessarily a reliable index of sedation, as demonstrated by other performance studies.

In conclusion, we detected diminished and augmented regional brain responses especially in the occipital and parietal cortices and cerebellar regions following D-chlorpheniramine treatment. These findings suggest that D-chlorpheniramine may suppress

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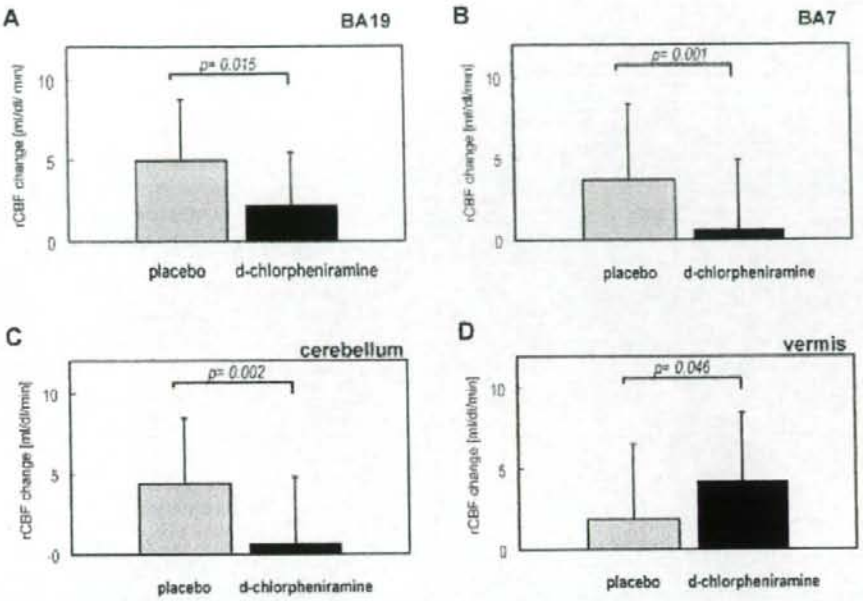

Figure 5. Comparisons of augmented rCBF responses in BA19 (A), BA7 (B) and the cerebellum (C) as well as diminished rCBF response in the cerebellar vermis (D) following D-chlorpheniramine treatment

brain functions particularly those associated with visuo-spatial cognition and visuo-motor coordination, which are essential in car driving. Non-invasive functional neuroimaging is potentially useful not only for elucidating the neural correlates of car driving but also for clarifying the brain mechanism underlying drug-induced impairments of driving performance.

Since the present study is the first attempt to combine simulated driving task and antihistamines, discussion on the limitations of the present study would be useful for replication. The present driving test was relatively short (approximately 150 s) and therefore it is possible that attention processes were not markedly influenced by D-chlorpheniramine as these processes were not affected using this protocol. Probably, the test length could account for the results showing no significant differences in the scores of driving performances and subjective sleepiness. In addition, the order of active and passive driving conditions was fixed partly because of the protocol used in the present study, where the videotaped in-car landscape was used for passive driving. The order effect could be further eliminated if the order of the active and passive driving conditions were balanced, although the present study has already given reasonable results. Since the repetab used in the present study may have slow releasing effects, the sedative effects were less outstanding than those of the immediate release formulation.

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展望 TENBO

アミロイド斑の可視化による アルツハイマー病の早期診断

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1 はじめに

社会の高齢化が懸念されるようになって久しいが，2007年，ついに国内における高齢者人口（65歳以上）の割合は21%を突破し，5人に1人が高齢者，さらに10人に1人が後期高齢者（75歳以上）という本格的な高齢社会が到来した。そして，今後も高齢者人口の割合は増加傾向をたどると見込まれていることから，医療政策上，高齢者に多く見られる認知症性疾患に対する早急かつ実効的な対策が強く求められるようになってきた。特に，認知症の主たる原因疾患とされるアルツハイマー病（AD）については，根本治療薬の開発促進とともに，身体への負担が少なく精度に優れた早期診断法の確立が喫緊の課題となっている。

このような背景にあって，最近ADの革新的な検査手法として，ADの神経病理像であるアミロイド斑（老人斑）を非侵襲的に可視化するアミロイド画像化技術に大きな関心が寄せられている[1,2]。本稿では，最も研究の進んでいるポジトロン断層撮影法（PET）によるアミロイド画像化について，我々の研究成果とともに概要を紹介する。

2 ADの病理とアミロイド画像化

現時点においてAD発症の原因については完全に解明されているわけではないが，脳内アミロイド斑の主要構成成分であるアミロイドβ蛋白質（Aβ）の脳内蓄積が発病の原因と密接に関係していると考えられている。Aβは単体で水溶性のタンパク質であり，正常脳組織では代謝分解や排泄により集積性を示さないが，病的状態ではオリゴマー化を経てβシート構造が規則的に繰り返される不溶性線維構造をとり，アミロイド斑を形成して脳内に蓄積する（**図1**）。

この脳内アミロイド斑の沈着は疾患特異性が

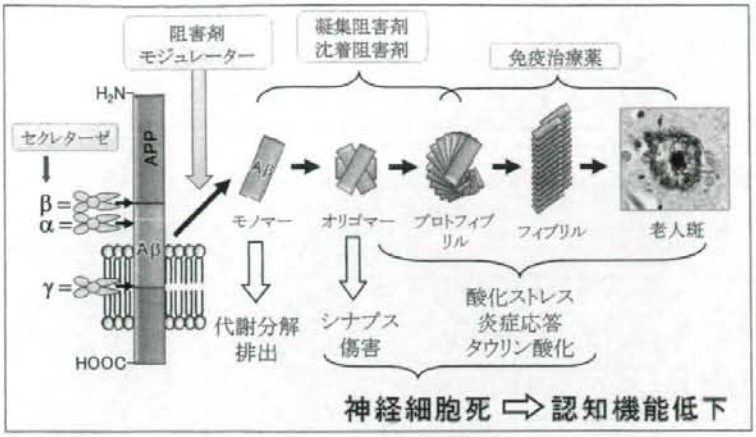

図1　アミロイド斑の形成過程と治療標的

高く，ADの確定診断（死後脳の剖検）を行う際の神経病理学的判定基準の1つとなっているが，Aβの沈着そのものは，臨床的に認知機能の障害が観察され始める10年以上前から出現する病理所見であると考えられている[3]。したがって，この脳内アミロイド斑の蓄積を *in vivo* で定量的に測定（指標化）できれば，認知機能の障害が見られないAD発症前という非常に早期の段階で，将来的にADに移行するリスクが評価できるようになると期待されている。また，Aβの病的蓄積の阻止はADの治療につながるとの考え方から，様々な機序に基づく抗アミロイド療法の開発が進められているが，その治療適合性評価や治療効果判定への応用も期待されている。

このような観点から，近年PETによるアミロイド画像化研究，すなわちアミロイド斑の分子的実体であるAβ凝集体に結合親和性を有するポジトロン標識プローブを用いて，脳内Aβの蓄積を画像化し，非侵襲的な定量評価によってADとの関連性を追求する研究が，急速な勢いで展開されている。

3　アミロイド画像化プローブの開発

一般的な医薬品は，リード化合物の探索，リード化合物の最適化，前臨床評価，臨床試験という開発プロセスを経て市販化され，広く社会で使用されるようになるが，画像化プローブの開発も同様のプロセスをたどる。現在，臨床研究や臨床試験の段階まで開発が進んでいるアミロイド画像化プローブは，主として古くから病理染色や生化学実験などで利用されてきた色素系化合物を原型（リード化合物）として開発されている（**図2**）。

例えば，現在，世界的に最も数多く臨床応用されているプローブのPIB[4]は，ピッツバーグ大学のKlunkらによって，アミロイド斑の染色剤として知られるチオフラビン-Tを改良することで開発された。同様に，ペンシルバニア大学のKungらは，アゾ染料のコンゴレッドと類似骨格を有する蛍光染色剤X-34の部分構造から，SB-13[5]やその誘導体BAY94-9172[6]を開発している。また，カリフォルニア大学ロサンゼルス校のBarrioらが開発したFDDNP[7]は，環境感受性蛍光試薬のPRODANと同じジアルキルアミノナフタレン骨格を有している。各プローブの具体的な結合サイトについて，詳細は不明であるが，少なくともチオフラビン-T，コンゴレッド，FDDNPに対する独立した結合部位の存在が示唆され，様々なリガンド結合モデルが提唱されている[8]。

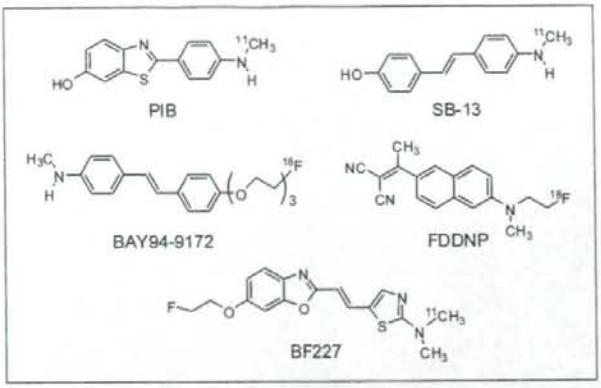

図2　代表的アミロイド画像化プローブ

アミロイド画像化プローブの開発研究は，1990年代中期以降，前記の米国研究グループが世界をリードしてきたが，国内においても1997年から2004年にかけて，(株)BF研究所においてプローブ開発研究が精力的に進められていた。BF研究所では，約2,600個の蛍光色素系化合物ライブラリーからリード化合物の探索を行い，構造最適化を経て独自のプローブ候補BF227を開発した。そして，東北大学においてポジトロン標識体の開発及び有用性評価に関する研究が展開された。

BF227は部分構造にジメチルアミノ基とフロロエチル基を有し，^{11}C（半減期＝20.4分）と^{18}F（半減期＝109.8分）の両核種で標識できるように設計されている。東北大学では，臨床研究への展開を優先目標として，標識技術的に簡便性に優れる^{11}C標識体の合成法を確立し，画像化プローブとしての適性と安全性について評価した。

アミロイド画像化に適したプローブの特性としては，Aβ凝集体に対する高い結合親和性，投与直後の急速な脳内への移行性，そして正常脳組織からの速やかな排泄性が求められる。特に速やかな排泄性は，撮像時間に制限が伴うPETでは，重要なファクターとなる。プローブの脂溶性が高くなった場合，脳内移行性は良くなるものの，正常脳組織に対する非特異的結合性も強くなり，脳外排泄性は悪くなって脳内からの消失は遅延する。すると測定される病変部位と正常部位のシグナル比が小さくなり，得られる画質の劣化や差異の検出能力の低下につながる。したがって，優れた脳内動態性を示す適度な脂溶性を持たせたプローブの設計が重要になる。

BF227については，Aβ凝集体に対して高い結合親和性（Kd：3.6 nM）を示し，AD脳標本を使用した染色実験及びオートラジオグラフィーから，アミロイド斑に対する選択的結合性を有することが確認された。また，正常マウスを用いた実験では，BF227の脳集積率は，投与2分後で7.9%ID/g，60分後ではその1/10以下の0.64%ID/gとなり，PET用脳画像化プローブとして十分な脳移行性を示すと共に，脳外排泄も速やかで，脂溶性薬剤にしばしば見られる大脳白質への非特異的集積は少ないと推定された。これらの結果は，先行したPIBやSB-13の動物実験データと比較しても遜色はなく，BF227の結合特性及び動態特性についてはアミロイド画像化プローブとして実用的なレベルにあると判断された。さらに，BF227の単回投与毒性試験，変異原性試験，被ばく線量推定などの評価により安全性が確認され，臨床研究が開始された。

このように，臨床応用可能なアミロイド画像化プローブの開発は着実な進展を見せているが，それらはPIBやBF227のようにほとんどが^{11}C標識体であり，その半減期の短さから，PET検査の実施効率は低く，それらを利用できるPET施設の数も非常に限定されている。

この問題の解決のためには，より半減期の長い^{18}Fで標識したプローブの開発が必要となる。先に紹介したFDDNPやBAY94-9172のように，これまでにも^{18}F標識プローブは報告されているが，PIBと比較して動態特性的に改良の余地を残しており，更なる開発研究が進めら

れている。東北大学においても BF227 の ^{18}F 標識誘導体 FACT を開発しており，現在，その有用性の評価を進めている。

4 臨床におけるアミロイド画像化研究

AD 患者を対象として PIB-PET を実施した場合，脳白質に若干の非特異的集積性を示すものの，アミロイド斑の好沈着部位である大脳皮質領域に明瞭な放射能の特異的集積を認め，健常高齢者と比較しても容易に弁別可能な画像を与える[9]。この PIB 高集積領域の分布パターンは，剖検によって神経病理学的に検証されていたアミロイド斑の蓄積分布パターンと一致することが明らかになった。また，PIB-PET の後に亡くなった AD 患者の脳病理検査によって，PIB 高集積部位にアミロイド斑の高沈着が確認された[10]。さらに，前頭葉大脳皮質から採取した生検組織中にアミロイド斑が確認された患者群で PIB-PET 検査を行った場合，対象群と比較して，大脳皮質領域で有意に高い PIB の集積が観察された[11]。いずれの報告も臨床研究として被験者数の規模は小さいが，アミロイド斑の沈着と PIB の集積を強く関連づけており，アミロイド画像化のコンセプトの証明（proof of concept）につながる非常に重要な結果である。

アミロイド斑の形成が認知機能障害に先行するという病理学的知見に基づけば，AD 発症直前の段階でもアミロイドの画像化は可能であると考えられる。認知症ほどの認知機能障害は見られないものの，明らかに軽度の認知機能の低下が出現する軽度認知機能障害（MCI）は，AD の発症前段階に相当し，病理学的にはこの段階にある症例では過半数で既に AD と同等の病理像（老人斑，神経原線維変化）を呈することが知られている。このような MCI 患者に対して PIB-PET 検査を実施したところ，その約半数で AD 患者と同程度に大脳皮質領域に PIB の異常集積が認められ，その PIB 陽性被験者の多くはその後の追跡調査で AD に進行したことが確認された[12]。この結果は，MCI の段階で AD の病変を検出していると推察され，AD 発症リスクの高い患者とそうでない患者の鑑別診断に有効である可能性を示唆している。さらに，認知機能的に正常な被験者に対する PIB-PET 検査においても，PIB の異常集積を呈する例が約 10～20% 存在することが報告されている[13,14]。これらの結果は，アミロイド画像化による AD 発症前の早期診断について，実現可能性が高いことを強く示唆している。

筆者らが東北大学で実施している BF227-PET 検査においても，PIB と同様に AD 患者では大脳皮質領域に高い放射能集積性を示した（図 3）[15]。その集積率（SUVR：SUV の対小脳比）は健常者と比較して約 1.2 倍と PIB の場合と比べてやや低い値となり，そのため画像的には病変部のコントラストは若干低くなったが，両群間の集積率の差は統計学的に有意性が認められ，感度・特異度に優れていることが明らかになった。また，AD 患者のほぼ全例，そして MCI 患者の約 60% において，大脳皮質領域で BF227 は高い集積性を示すという結果も得られ，PIB と同様にアミロイド画像化薬剤として

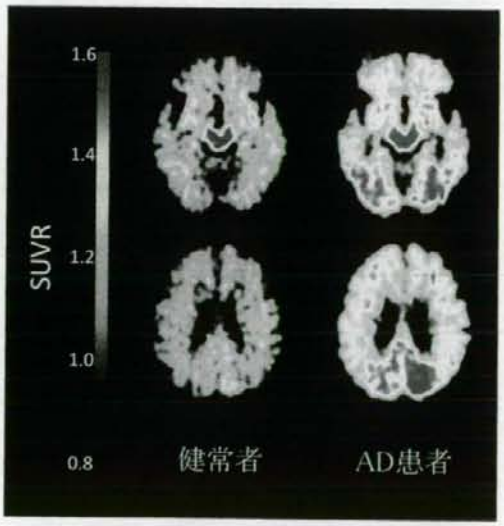

図 3 BF227 の PET 画像

高い有用性が期待されている。

以上のように，アミロイド画像化は，ADの神経病理像の一端（アミロイド斑）を明瞭に描出できるため，一般的な認知機能検査，生化学的検査，核医学検査では把握不可能な脳内病態の検査手法として，利用価値は非常に高いとみられる。ただし，AD以外のレビー小体型認知症[16]やアミロイドアンギオパチー[17]においてもプローブの異常集積性が指摘されていることから，疾患特異性に対しても慎重に検証を進めていく必要がある。

5 おわりに

高齢化が急速に進行する社会にあって，AD患者数の増加を抑制するためには，発症前の段階における予防的介入が有効な対策になると考えられる。その実現のためには，信頼性が高く，一般的な検診手段として広く利用される発症前診断法の開発が必須となるが，アミロイド画像化はその中核的な検査手法として非常に有望である。今後，早期診断法として高い信頼性を確立するためには，AD発症前の被験者を対象とした大規模かつ長期的な追跡調査研究を実施し，有用性に関する確固たるエビデンスの構築を図っていくことが肝要である。

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【アルツハイマー病治療の現状と近未来像】

Current status and future directions in Alzheimer's Disease therapy

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Key words
Alzheimer's Disease,
Cholinesterase inhibitor,
Amyloid β protein,
Disease-modifying drugs

要　約

1．認知症患者においては服薬管理や家族の負担を考え，1日1回投与で，口腔内崩壊錠などの利便性を考慮することが大切である。
2．アルツハイマー病治療の第一選択薬はコリンエステラーゼ阻害薬であるため，アルツハイマー病との診断に辿り着いたら，できるだけ早期の段階でコリンエステラーゼ阻害薬の使用を開始する。BPSDに対しては通常抗精神病薬が使用されてきたが，抗精神病薬の使用は，誤嚥性肺炎や転倒のリスクを上げADLを阻害するため慎重な使用が望まれる。
3．NSAIDなど根本的な作用メカニズムを持つ治療薬（Disease-modifying drugs）が開発され，近未来に導入される可能性がある。

1．塩酸ドネペジルによる治療

高齢者は，体内総水分量の低下による薬物分布容量の低下，腎糸球体濾過率の低下による薬物腎クリアランスの低下さらに肝薬物代謝酵素活性低下による内因性肝薬物クリアランス低下などにより，薬物血中濃度の上昇が起こりやすい。また，血清アルブミン濃度低下による薬物タンパク質結合能の低下や体内脂肪率上昇による脂溶性薬物の体内蓄積により，薬物血中濃度は変化しないにも関わらず，組織内濃度が上昇しやすく，薬物有害事象を生じやすいことが指摘されている[1]。実際我が国における多施設調査では，65歳以上の高齢者への投薬において，一定期間内の全処方の約9％に薬物有害事象が発生したことが報告されている[2]。この比率は意欲低下やうつを有する75歳以上の高齢者で顕著であった。そのため，高齢者薬物治療は，成人量の1/2-1/3量で開始し，緩やかに増量するのが原則である。また，多臓器傷害を反映してどうしても多剤使用（polypharmacy）になりやすいため，治療に優先順位を設ける，漢方処方に目を向ける，或いは針灸治療などの補完代替医療を考えるなどの留意が必要とされる。せん妄の発症にはつねに注意を向け定期的な処方のチェックが要求される。抗認知症薬の投与においてもこの原則は守られるべきで，認知症患者においては服薬管理や家族の負担を考え，1日1回投与で，口腔内崩壊錠などの利便性を考慮することが大切である。

神経伝達物質の研究から，アルツハイマー病脳ではアセチルコリン合成系の活性低下が見られ，病理学的にはマイネルト核でアセチルコリン作動性神経細胞の顕著な脱落がみられる。前脳基底部のマイネルト核から大脳皮質へ投射するアセチルコリン作動性神経系は注意力や知的機能に，また，中隔野から海馬へのアセチルコリン作動性神経系

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は，記憶・学習に深く関与すると考えられており，アセチルコリン系賦活療法がアルツハイマー病治療薬開発の基本ストラテジーとして開発が進められてきた。今日，アルツハイマー病治療の第一選択薬はコリンエステラーゼ阻害薬であるため，アルツハイマー病との診断に辿り着いたら，できるだけ早期の段階でコリンエステラーゼ阻害薬の使用を開始する[3,4]。タクリン，ドネペジル，ガランタミン，リバスチグミンが市場化されたが，本邦ではドネペジル（商品名アリセプト®）のみが承認されている。ドネペジルは1日量3 mgから開始し，2週間の観察期間をおいて5 mgに増量する。症状の具体的な改善点としては，意欲（やる気）のアップがみられることが多く，やらなくなった家事や興味を示さなくなった趣味をまた行うようになった，口数が多くなった，料理をたくさん作るようになったなどの変化がみられることが多い。意欲の向上が，結果として集中力の改善をきたしたものと考えられている。しかし，学習・記憶機能に本質的な改善効果はない。また，短期的には明らかな効果を認めない例も多い。そのような場合でも，長期的な進行抑制効果を期待して投与を続行する場合が多い。

東北大学における2年間の長期的効果を見た成績では，ドネペジルが市場化される以前（2000年以前）はMini-Mental State Examination（MMSE）でアルツハイマー病患者（MMSEで約20点の中等度）では，MMSEは年平均2.8点低下していたが，ドネペジルが市場化されてから（2000以降）の低下は年平均1.2点と有意に緩やかとなった[5]。2年間に渡って認知機能が低下せずに維持された要因として，ベースラインでの認知機能がよいことも重要であった[5]。できるだけ早期段階からのドネペジルの使用が推奨される。

塩酸ドネペジルの有害事象としては，食思不振，嘔吐，下痢，喘息の悪化，徐脈，消化性潰瘍の悪化，頻尿などが知られている。特に，消化性潰瘍との関連においては，非ステロイド系消炎鎮痛剤（NSAID）との併用は特に慎重でなければならない。ドネペジル5 mgで始めてこのような有害事象が出現した場合は，3 mgに戻すか5 mgを隔日に投与してもよい。高度のアルツハイマー病では5 mgで4週間以上観察後に1日量10mgまで増量できる[6]。食思不振，嘔吐などの消化器系の有害事象の発現率は5 mgより多く10mgに増量して1-2週間後に出やすいとされている。ドネペジルは85歳以上の超高齢アルツハイマー病患者にも安全に使用可能である。口腔内崩壊錠も用意されている。レビー小体病でもせん妄の改善や幻視に奏功する場合がある[7]。ガランタミン，リバスチグミン，NMDA受容体阻害薬メマンチンは本邦での承認を目指し治験中である。

2．周辺症状（Behavioral and Psychological Symptoms of Dementia）に対する対応

1996年に国際老年精神医学会は，抑うつ，意欲障害，不安，焦燥，幻覚，妄想，脱抑制，昼夜逆転，徘徊，易怒，介護への抵抗，暴言などの精神症状に対してBehavioral and Psychological Symptoms of Dementia(BPSD)という用語を用いることを提唱した。

認知症において従来研究者が注目してきたのは主として中核症状であるが，実際患者を介護する家族にとって最も深刻な問題となるのはこのBPSDである。BPSDの発症要因については，神経伝達物質異常などの脳内病変，身体疾患の合併やその悪化などの全身的要因と社会心理学的要因が単独あるいは複合して発生するものと考えられている。一方，物盗られ妄想などのように外界の出来事を誤認したことに引き続いて起こる妄想や焦燥などのBPSDは，中核症状の二次的産物と考えた方が理解しやすい。環境から受ける心理ストレスは，患者の混乱や興奮，易怒性，攻撃性などを増悪させるものである。この社会心理学的要因としては，たとえば介護者が介護に慣れておらず患者に非常に厳しく接したりすれば，興奮が生じたり，逆に抑うつ状態を呈することもある。一方，介護者が消耗した状態になれば，患者への対応もうまくできなくなり，BPSDの引き金となる場合もある。このような場合には，これらの環境要因に配慮し，1日に少なくとも1時間は自分の時間を持つなど，家族が介護に余裕を持てる工夫をアドバイスすることがまず大切である。患者の誤りを1つ1つ訂

正したり折檻したりすることで現実の世界に連れ戻そうとしないで，患者のもっている世界を尊重して対応するということである。つまり，介護者から患者への歩み寄りが大切である。

塩酸ドネペジルによって，中核症状だけでなくBPSDも改善することが報告されている[8]。抑うつ，意欲障害，不安，焦燥に対しては抗不安薬や抗うつ薬の投与にて改善することがあるが，過鎮静や脱力，せん妄など副作用に注意する。抗うつ薬としては，低用量の選択的セロトニン再取り込み阻害薬(selective serotonin reuptake inhibitor:SSRI) やセロトニン・ノルアドレナリン再取り込み阻害薬(serotonin and noradrenaline reuptake inhibitor:SNRI)が第一選択薬である。抗コリン作用の強い三環系抗うつ薬の長期・高用量の服用は，せん妄，転倒，尿閉，消化管運動不全（頑固な便秘など）など重篤な薬物有害事象を引き起こす可能性があり使用は控えるべきである。SSRIやSNRIは効果発現までにある程度の時間を要するが，低用量で投与を開始し，副作用に注意しつつ漸増しながら，有効用量まで達してから4～6週間は投与を続けることが重要である。さらに情動不安定性や焦燥，易怒性，攻撃性に対しては，バルプロ酸ナトリウムやカルバマゼピンなどの抗てんかん薬も有効な場合がある。

認知症の患者は，その認知機能障害を基盤にして，些細な思い違いなどから誤認や妄想に発展することが多い。その妄想は，「誰かが自分のものを盗んでいる」といった物盗られ妄想や配偶者に対する嫉妬妄想，「見捨てられる」「邪険に扱われる」といった被害的な内容が多い。また，幻聴や幻視などの幻覚を呈することもあり，犬や猫などの動物や，赤ちゃん，泥棒などの明瞭な具体的なものから「ボーっと後ろに誰かが立っている」などのように対象があいまいなものまである。興奮や不穏も些細なことをきっかけに生じやすく，介護者への暴言や暴力，介護拒否などにつながっている。特に幻覚，妄想そして焦燥，攻撃性，興奮，不穏に対しては対症療法的に低用量の抗精神病薬を用いることも少なくない。従来はハロペリドールを中心とした低用量の定型抗精神病薬が使用されてきたが，近年では錐体外路症状などの副作用が比較的少ない非定型抗精神病薬(第2世代抗精神病薬：second generation antipsychotics)が使用されるようになった。現在わが国における非定型抗精神病薬には，リスペリドンやペロスピロンのようなセロトニン・ドーパミン拮抗薬(serotonin-dopamine antagonist)とオランザピンやクエチアピンのような多受容体作用物質(multi-acting receptor targeted agents)があり，それぞれの薬剤が有効であるとの報告がなされている。いずれも高齢者であることを考慮して，通常成人量の1／3～1／2程度から開始し，錐体外路症状の出現，嚥下機能，身体の不安定感や転倒傾向などを見ながら増減を計る。

しかし，2005年4月に米国食品医薬品局(FDA)は認知症高齢者の行動障害に対して非定型抗精神病薬を投与したエビデンスレベルが高い研究をメタ解析し，投与群では心不全，肺炎や脳血管イベントなどの発生により，プラセボを投与した群に比べて死亡率が1.6～1.7倍高かった[9]というコメントを警告として発表し，この死亡率の上昇と保険適用未承認であることの2点を各メーカーの添付文書に明示するように要請した。わが国でも同様の対応がとられたものの，実際の臨床現場では大きな困惑と混乱を招いている。抗精神病薬の使用にあたっては以上の知見を踏まえて副作用や死亡率，保険適用外であることについて触れ，患者や介護者のQOLの観点から検討し，十分なインフォームド・コンセントのうえで使用することを考慮すべきである。

3．根本的な作用メカニズムを持つ治療薬（Disease-modifying drugs）開発の現状

米国のKooらは，ある種の非ステロイド系抗炎症薬がγ-セクレターゼ活性を阻害することなく，APPからAβの産生過程においてAβ42の産生を抑えるという事実を報告して世界の注目を引いた[10]。今日までにこのような抗炎症薬によるアルツハイマー病臨床治験は世界で7件行われたが，6件がNegative studyであった。

Myriad Pharmaceuticals社のFlurbiprofenの第2相臨床試験は，カナダと英国の31施設において，軽

症から中期のアルツハイマー病患者207名を対象に400mgと800mgの2本立てで行われた。その結果，軽症アルツハイマー病患者において800mg投与群で改善が確認され，米国において第3相試験が実施されている最中である。Flurbiprofenはドネペジルのような症状緩和薬と異なり，γ-セクレターゼ調節薬として根本治療薬の範疇に属する新しいクラスの薬物として注目される。Neurochem社は同じく根本治療薬の範疇に属するアミロイド凝集阻害薬としてのTramiprosateを開発したが，欧米で相次いで第3相試験が打ち切られ，今日に至っている。

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<細　胞ニュース>

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