Donepezil Binding to Acetylcholinesterase and Response to Donepezil Therapy in Parkinson's Disease Dementia: [5-11C-methoxy]Donepezil-PET Study

VIII. 4. Donepezil Binding to Acetylcholinesterase and Response to Donepezil Therapy in Parkinson's Disease Dementia: [5-^{11}C-*methoxy*]Donepezil-PET Study

Hiraoka K.[1], Okamura N.[2], Funaki Y.[3], Hayashi A.[4], Tashiro M.[1], Hisanaga K.[5], Fujii T.[4], A Takeda.[6], Yanai K.[2], Iwata R.[3], and Mori E.[4]

[1]*Cyclotron And Radioisotope Center, Tohoku University*
[2]*Department of Pharmacology, Graduate School of Medicine Tohoku University*
[3]*Division of Radiopharmaceutical Chemistry, Cyclotron and Radioisotope Center, Tohoku University,*
[4]*Department of Behavioral Neurology and Cognitive Neuroscience, Graduate School of Medicine Tohoku University*
[5]*Departments of Neurology and Clinical Research, Miyagi National Hospital*
[6]*Department of Neurology, Tohoku University Graduate School of Medicine*

The cholinergic system is one of the most crucial neurotransmitter systems in the brain and is implicated in dementia. The activities of both choline acetyltransferase, which catalyzes acetylcholine synthesis, and acetylcholinesterase (AChE), which degrades brain acetylcholine, are reported to be decreased in the neocortex and hippocampus in Alzheimer's disease (AD) and Parkinson's disease with dementia (PDD), and this decreased activity correlates with the severity of cognitive impairment. Moreover, loss of cholinergic neurons in the nucleus basalis of Meynert has been reported in the brains of AD and PDD patients. On the basis of these pathological findings, reversible AChE inhibitors have been used to potentiate cholinergic neurotransmission, with the aim of improving cognitive function. Currently, several AChE inhibitors are prescribed to patients with dementia. Among them, donepezil hydrochloride has proven effective in ameliorating the cognitive impairment of demented patients.

[5-^{11}C-methoxy]Donepezil ([^{11}C]donepezil) was developed for the in vivo visualization of donepezil binding to AChE and cholinergic imaging using positron emission tomography (PET)[1]. An animal study by Funaki et al.[2] and a pilot study by Okamura et al.[3], which applied [^{11}C]donepezil-PET to AD patients, showed that [^{11}C]donepezil holds promise as a potential agent for imaging AChE in vivo using PET. To exploit the use of [^{11}C]donepezil-PET in clinical research, the kinetic analysis of

[^{11}C]donepezil was established using dynamic 60-min PET scans acquired after intravenous injection of [^{11}C]donepezil in 6 healthy subjects[3].

Subsequently, we applied donepezil-PET imaging to PDD patients. Twelve patients with PDD (9 men, 3 women; mean age ± SD, 69.8 ± 6.4 years) and 13 healthy control subjects matched for age, sex, and education (10 men, 3 women; mean age ± SD, 69.5±6.7 years) were enrolled. The patients met the diagnosis of PD according to the diagnostic criteria of the UK PD Society Brain Bank, based on clinical, laboratory, and radiological findings. To select subjects with dementia, patients with a score of 1 or above on at least one of the sub-items of the Clinical Dementia Rating (CDR) were included in this study. For patients with Parkinson's disease with dementia, daily administration of donepezil was started after [^{11}C]donepezil-PET imaging and continued for 3 months. At baseline and after 3 months of donepezil therapy, cognitive function was evaluated. The Ethics Committee of Tohoku University School of Medicine approved the study protocol, and written informed consent was obtained from all healthy subjects and from patients or their family members.

Radiosynthesis of the [^{11}C]donepezil and the PET procedures used are described elsewhere[1,3]. The acquired PET and metabolite-corrected blood data were analyzed using the software PMOD (PMOD Technologies) and parametric 3D maps of total distribution volume (tDV) in the brain were generated using the classical Logan plot. Images were analyzed using SPM8 (Wellcome Department of Cognitive Neurology) and ImageJ 1.42q (National Institutes of Health, Bethesda, MD).

The tDVs of the total cerebral cortices were estimated using a semi-automatic method. Axial 3D magnetic resonance images were obtained for anatomical reference, which were segmented into gray and white matter using the prior probability templates of SPM8. The total cerebral cortices in the probability maps of the gray matter were extracted by tracing with a manually driven mouse cursor on ImageJ and then co-registered with the tDV images. The co-registered images were used as a mask of the cerebral cortices, and were projected onto the tDV images of each subject to extract the cerebral cortices. Finally, the mean tDV value of the cerebral cortices was calculated. A two-tailed t-test was used for group comparison with statistical significance set at $p < 0.05$.

A between-group comparison examining the difference in tDV values at voxel level was performed using analysis of covariance (ANCOVA) with the software SPM8, with sex, age, and education as covariates in an explorative analysis covering the whole brain without

any a-priori hypothesis. Statistical significance was set at $p < 0.005$ without correction for multiple comparisons, and cluster extent threshold was 100 voxels.

The mean tDVs of the cerebral cortices in the PDD group were significantly lower, showing a mean decrease rate of 22.7%, than those of the control group (PDD, 7.9±2.2; NC, 10.2± 2.7).   In the SPM analysis, the PDD group exhibited a widespread tDV reduction as compared with the control group (Fig. 1).   The mean total distribution volume of the patients with PDD was significantly correlated with improvement of visuoperceptual function after 3 months of donepezil therapy (Table 1).

The use of [^{11}C]donepezil-PET in the present clinical study of PDD revealed that AChE in the cerebral cortices was decreased.   Among previous studies of cholinergic PET imaging utilizing radiolabeled acetylcholine analogues, such as [^{11}C]PMP, Hilker et al[4]. and Bohnen et al[5]. found a 20.0-29.7% and a 10.7-12.9% reduction in cortical acetylcholinesterase activity in Parkinson's disease with and without dementia, respectively, compared with normal subjects.   The reduction rate of the mean tDV value of the cerebral cortices in the PDD group in the present study was similar to that of cortical acetylcholinesterase activity reported in these previous studies.   Voxel-by-voxel analysis using SPM8 revealed a global reduction in acetylcholinesterase density in the brains of PDD patients, similar to the results of previous studies.   The results also suggested that donepezil therapy is more effective in patients with less decrease in acetylcholinesterase, which indicates relative preservation of the cholinergic system.

References

1) Funaki Y., Kato M., Iwata R., et al., J. Pharmacol. Sci. **91** (2003) 105.
2) Okamura N., Funaki Y., Tashiro M., Kato M., Ishikawa Y., Maruyama M., Ishikawa H., Meguro K., Iwata R., Yanai K., Br. J. Clin. Pharmacol. **65** (2008) 472.
3) Neuroimage **46** (2009) 616.
4) Hilker R., Thomas A., Klein J., Weisenbach S., Kalbe E., Burghaus L., Jacobs A.H., Herholz K., Heiss W.D., Neurology **65** (2005)1716.
5) Bohnen N., Kaufer D., Ivanco L., Lopresti B., Koeppe R., Davis J., Mathis C.A., Moore R.Y., DeKosky S.T., Arch. Neurol.**60** (2003)1745.

Table 1. Correlation matrix contrasting mean distribution volume of the cerebral cortices against the change in the cognitive tests after 3-month donepezil therapy.

	change			
		digit span		
	MMSE		fluency	TMT-A
		(WAIS-R)		
correlation coefficient	-0.207	-0.036	0.165	0.116
P	0.593	0.928	0.672	0.827

	change			
	recall task	recognition	visuoperceptual	
				NPI
	(ADAS)	TASK (ADAS)	test	
correlation coefficient	-0.406	0.207	0.837	-0.091
P	0.278	0.594	0.005	0.817

MMSE=MIni-MentalState Fxamination; WAIS-R=Wechsler Adalt Intelligence Scale-Revised; TMT-A=Trail-Making Tesst-A: ADAS=Alzhheimer's Disease Assessment Scale;NPI= Neuropsychiatric Inventory
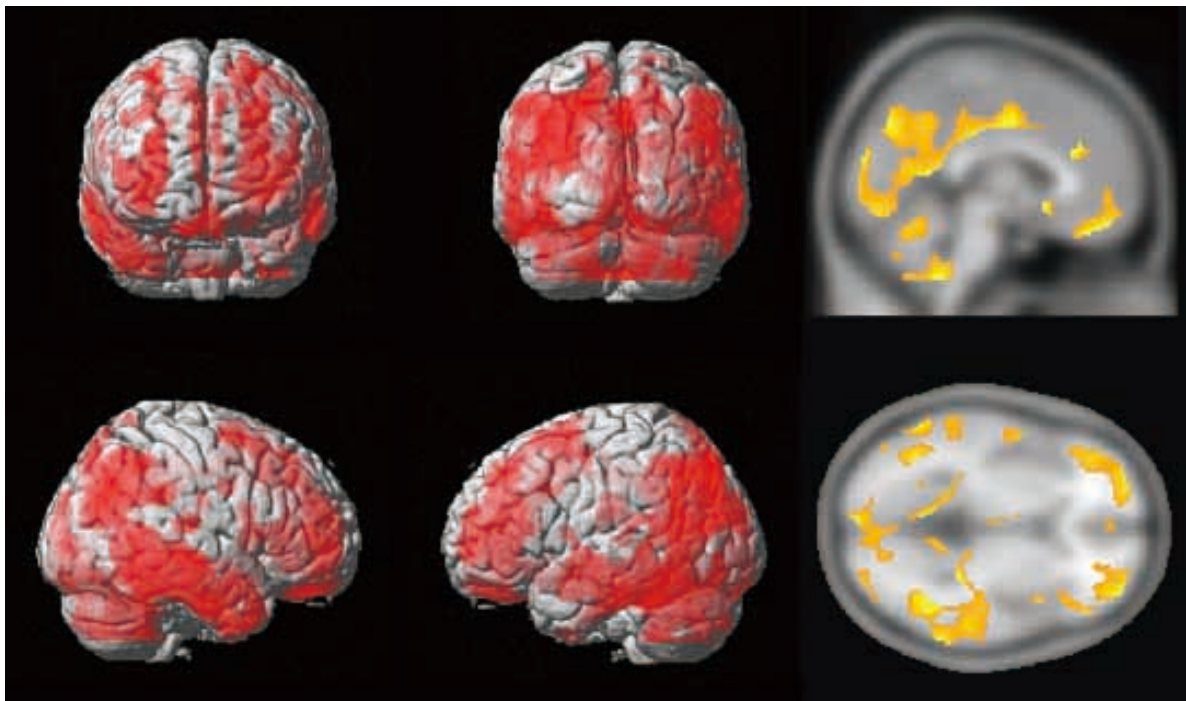

Figure 1. Statistical parametric maps of a significant decrease in [^{11}C]donepezil distribution volume in the PDD group as compared with the normal control group ($p_{uncorrected} < 0.005$).