Decreased Binding of[11C]Donepezil as Shown by PET Correlated with the Clinical Effect of Donepezil Administration in Alzheimer's Disease:The Osaki-Tajiri Project

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Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly, characterized by degeneration of basal forebrain cholinergic neurons innervating the cortex, amygdale, and hippocampus[1,2]. Reduced choline acetyltransferase (ChAT) activity, one of the markers of cholinergic deficits in AD, is correlated with severity of senile plaques[3]. ChAT activity is also associated with profound cognitive impairments, such as loss of memory, learning and attention in AD[3,4]. Relationship between cholinergic deficits and cognitive function is now directly shown by neuroimaging studies using positron emission tomography (PET)[5,6].

Several compounds such as (S)-[^{11}C]methyl nicotine (^{11}C-nicotine)[7], N-[^{11}C]methyl-4-piperidyl acetate (^{11}C-MP4A)[8], N-[^{11}C]methyl-piperidin-4-yl propionate(PMP) (^{11}C-PMP)[9], [5-^{11}C-methoxy]donepezil (^{11}C-donepezil)[10] were developed as PET ligands for visualizing the central cholinergic activity, and applied in clinical studies on AD. ^{11}C-Nicotine is only an indicator of nicotinic receptors. Because ^{11}C-MP4A and ^{11}C-PMP are substrate of acetylcholine esterase (AChE) and rapidly converted to the hydrolyzed product especially in regions of high AChE activity, their concentrations strongly depend on flow. On the other hand, ^{11}C-donepezil can be an indicator of total cholinergic terminals, and is a relatively stable radiotracer. The metabolite of ^{11}C-donepezil counted for only 5% of the total radioactivity present in the brain at 60 min after injection of ^{11}C-donepezil[11]. Our previous study using this ligand[10] showed that AD patients exhibited reduction of donepezil binding in the brain even in the

early stage, and that longitudinal evaluation by ^{11}C-donepezil enabled determination of AChE binding occupancy of oral administered donepezil.

There is abundant evidence that the basal forebrain cholinergic system plays a major role in cognitive function, especially in the domain of attention. Cholinergic fibers from the nucleus basalis of Meynert (nbM) to the cerebral cortex are associated with visual attention while fibers to the hippocampi are involved in working memory[12]. Stimulation of cholinergic pathways by nicotine enhances cognition, especially attention both in healthy adults[13] and AD patients[14]. A previous study on AD treated with donepezil showed that visual selective attention tasks could be sensitive markers to detect treatment response[15]. Kadir et al. revealed that ^{11}C-nicotine binding in the right frontal lobe and bilateral parietal lobe significantly associated with attention in AD patients[6]. Bohnen et al. showed that temporal AChE activity measured by ^{11}C-PMP was significantly correlated with attention in AD[16]. While agreement of these PET studies reported AChE activity was correlated with attention, there remains a controversy in the brain regions. We investigated relationship between regional ^{11}C-donepezil binding and cognitive functions including attention in mild to moderate AD patients. We here present a representative case with PET data of ^{11}C-donepezil that was responded by donepezil treatment.

Methods

Subjects : Subjects in this study were AD Patients who diagnosed by NINCDS-ADRDA criteria[17]. The patients who already were administered donepezil were excluded at initial visit the Osaki-Tajiri clinic.

PET : After bolus injection of 134～378 MBq of [^{11}C]donepezil, a dynamic 3D scan was performed for 60 min. Arterialized venous blood samples were obtained from a medial cubital vein for assessing blood RI activity.

Analyses: Regions of interest (ROIs) were drawn on striatum, thalamus, frontal, temporal, parietal, occipital, anterior and posterior cingulate, and hippocampus. The ratio of the concentration in tissue to that in plasma at equilibrium was calculated as distribution volume (DV) by Logan's graphical analysis. We also used average value of regional DVs as a representing value of donepezil binding in whole brain.

Clinical effects: In this study, we used Mini-Mental State Examination (MMSE) as global cognitive function[18], Clinical Global Impression scale (CGI) (3 grades evaluation: 0 pint ~2 point) as clinician's impression, Digit Symbol (DigSm) from WAIS-R as psychomotor speed[19], Trail Making Test A (TMTA) as executive function, the subcategories of Cognitive Abilities Screening Instruments (CASI) as cognitive domains[20,21].

Procedures: The subjects received first PET and above the neuropsychological tests before orally, then the subjects orally took donepezil (5 mg/day) for 6 months. After that, they examine the second PET and the same neuropsychological tests as the 6 months ago.

Results

The result was shown in Table 1 and Table 2. The DV which shows binding the donepezil in the brain decreased 200.1 from the first PET to the second PET. The DV were declined the range from 122.2 to 245.8 between the first PET and the second PET in each ROIs (Table 1). There was no change in MMSE score (Table 2). The neuropsychological tests were improved 2 point in DigSm, 5 second in TMTA, and 2 point in Abstraction and Judgement. Some tests decline the scores, 2 point in Remote Memory, 2 point in Manipulation and Concentration, 1 point in List-generating fluency. The impression of medical doctor improved 1point in CGI.

Comment

In this study, TMTA and DigSm were improved, so it supports the results of Kadir et al[6]. Kadir et al. used the nicotin-tracer, however, we used the donepezil-tracer. Although one subject case report, we directly indicated the effect of donepezil, especially about attention.

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Table 1. Distribution volume on first PET and second PET.

	First PET	Second PET
Striatum	17.5	12.1
Thalamus	16.5	9.8
Frontal lobe	14.0	8.7
Temporal lobe	14.2	9.7
Parietal lobe	14.7	8.8
Occipital lobe	14.1	7.9
Anterior cingulate	13.6	8.3
Posterior cingulate	14.2	9.4
Hippocampus	13.0	9.7
Average of DV	14.7	9.3

Table 2. Neuropsychological tests score on the first PET and second PET.

	First PET	Second PET
MMSE	15	15
DigSm	23	25
TMTA (sec)	150	145
CASI		
C1 remote memory	10	8
C2 recent memory	4	5
C3 attention	2	6
C4 manipulation and concentration	6	4
C5 orientation	13	13
C6 visual construction	10	10
C7 abstraction and fluency	3	5
C8 list-generating fluency	4	3
C9 language abilities	9	9

MMSE = Mini Mental State Examination
TMTA = Trail making test A
CASI = Cognitive abilities Screening Insturument
C1~ C9 = Cognitive domains of CASI