Impairment of Dopamine Metabolism in the Brain of Patients with Dementia Assessed using 18F-fluorodopa and PET

IV. 7. Impairment of Dopamine Metabolism in the Brain of Patients with Dementia Assessed using ^{18}F-fluorodopa and PET

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Introduction

The dopaminergic system forms one of major neuronal networks of the central nervous system. It is involved in regulating movement through the extrapyramidal pathways. A part of the system is linked to the neocortex and limbic brain [1],and is presumably related to cognitive function as well as psychotic disorders. It is reasonable to assume, therefore, that the dopaminergic system plays considerable roles, in the manifestation of symptoms associated with dementia. This hypothesis is supported by the fact that a proportion of patients with dementia of the Alzheimer type especially who may suffer a more rapid intellectual decline showed the extrapyramidal signs such as rigidity, tremor, and bradykinesia[2,3]. Positron emission tomography (PET) permits assessment of cerebral metabolism in vivo at various stage of dementia. Recently, measurements of blood flow, glucose consumption, and other physiological parameters have been increasingly employed to evaluate cerebral metabolism. Moreover the dopamine metabolism in the cerebrum can he assessed using ^{18}F-fluorodopa as a labeled agent mostly in movement disorder patients [4,5] . The purpose of the present study was to elucidate disturbances in the dopaminergic function in the brain of demented patients.

Methods

Fluorine-18 was produced at the Cyclotron RI Center, Tohoku University and ^{18}F-FDOPA was synthesized according to the method described by Adam et al.[6]. Following an intravenous bolus injection of FDOPA (2.5-8.3 mCi, specific activity hetween 167-686 mCi/umol) into the subjects, positron tomography was carried out parallel to the orbito-meatal (OM) line by using PT931 (CTI Inc,USA) with 7 mm axial and transaxial resolution. The scanning time was every 5 minutes until 60 min after injection. The emission data was corrected for tissue attenuation hy using transmission data collected by using ^{68}Ge/Ga cylinder source. PET data analysis was carried out by the following: Tissue concentration

of FDOPA was measured using a ROI program on three contiguous PET slices containing the striatum. In order to reduce statistical noise four final sequential images, taken during 40-60 minutes, were added. The ROIs were defined on this images by setting threshold PET values using a computer program that interactively showed the chosen PET values on the count histogram and their corresponding location. Once the boundary PET values were selected the programs automatically calculated area size and average PET values for different frames. In case of very poor striatal radioisotope accumulation, irregular-ROI-draw routine substituted
the program hy referring MRI images of the striatum. The cortical gray matter such as the frontal, temporal, occipital regions, and the cerebellum were defined in the same way. The influx rate (Ki) of FDOPA into the selected regions was then calculatcd employing the graphical analysis described by Patlak et al.[7,8] using the cerebellum radioactivity concentration as the input function.

Studies were performed on twenty-eight subjects over 50 years old including 10 normal subjects (5 males and 5 females; average age: 62.6+ 9.4),11 patients with Alzheimer's and senile dementia (AD/SDAT) (4 males and 7 females; average age: 65.8+11.1) and 7 patients with vascular dementia (5 males and 2 females; average age: 73.3+7.8). The diagnosis of dementia was based on DSM-III-R [9]. The dementia subtypes were judged mainly on the clinical profiles of symptoms, referring the Ischemic Score [10] and CT/MRI findings. The severity of the dementia was evaluated using the mini-mental scale (MMS). CT and MRI were performed in all the subjects. The striatum was morphologically normal in AD/SDAT subjects. One vascular dementia had a small lacuna in one side of the striatum and other two subjects had lacunae in the white matter. Neurological examination revealed no focal abnormality except one AD/SDAT case who showed mild rigidity in his unilateral extremities. Statistical analysis was employed using the Student's T test and the correlation analysis.

The protocol was approved by the Committee for Clinical Application of Radiopharmaceuticals at Tohoku University. Written and informed consents were obtained from a family member of each patient.

Results

The Ki of FDOPA influx into thc striatum (average of both sides) in normal subjects was 0.0115+0.0018 min^{-1} and did not had any significant age effect (Fig.1). The Ki for patients with AD/SDAT and vascular dementia were 0.0108 ± 0.0036 min^{-1} and 0.0091 ± 0.0020 min^{-1} respectively (Table 1). The rate of FDOPA uptake into the striatum was significantly reduced in patients with vascular dementia compared to the normal control ($p<0.01$ by student t-test). The Ki for other cortical regions showed no significant difference among three groups. The age effects on the striatum Ki of the AD/SDAT and

vascular dementia groups were shown in Fig.2. The change again was not significant. Six from seven vascular dementia patients showed lower Ki values than the average normal level. Although the average Ki values for the AD/SDAT group was very close to the normal values, individual values scattered beyond 95 % confidence limit of the controls. Dementia severity was evaluated using the mini-mental state battery. Linear significant correlations were found between Ki and MMS performance in AD/SDAT patients ($Y=0.000193\ X+0.00583$, $r= 0.780$, $p < 0.01$, Fig.3). Correlation between Ki and MMS performance in vascular patients were weak and not significant.

Discussion

Measurement of cerebral metabolism in vivo is often conducted with the compartment analysis, which requires frequent sampling of the arterial blood with the lapse of time. The concept of compartment assumes that the radioactivity in each compartment is derived from a simple chemical component. It has been proved, however, that FDOPA is readily metabolized into several metabolites such as fluorodopamine, fluoroDOPAC, fluoromethyl DOPA (MeFDOPA), etc [11,12]. It is not valid, therefore, to adopt simple compartments in the brain in the FDOPA model. Difficulty to keep dementia subjects in the same study position did not allow longer PET measurement and consequently the quantitation model had to be simple. Patlak et al. proposed a graphical analysis [7,8] as a method to estimate tracer influx to the irreversihle compartment. Hoshi et al. reported fairly good correlation between values obtained by the graphical analysis and by compartment analysis in normal subjects [13]. They also concluded input function using cerebellum radioactivity resulted better estimation of DOPA decarboxylase activity than using metabolites corrected plasma radioactivity. Postmortem studies revealed that there are age-related reductions in the concentration of DA in the caudate nucleus in the group of patients older than 65 [14]. PET observation of a normal aged population also found a gradual decline in FDOPA uptake with age [15]. Howevever, a recent study cast skepticism on this age-related decline [16]. Our data support the latter observation. We reported stability of blood flow and oxygen metabolism in normal healthy population up to 80 years of age [17]. Little change in FDOPA uptake in normal subjects supports well preserved homeostasis in brain metabolism in normal population. Tyrrell et al. reported no significant changes in FDOPA uptake into the caudate and putamen in Alzheimer type dementia patients with extrapyramidal signs [18]. However, they found a greater variance in Ki values of FDOPA in the patients group than in the normal subjects. Our data agrees with their results that AD group had a larger variance in FDOPA uptake rate (Table 1). Two of their patients had putaminal Ki values that were lower than the 99 % confidence limit of the normal values. Thus it was suggested that some AD/SDAT patients had lower FDOPA uptake compared to the normal subjects. It is noteworthy that mildly demented AD/SDAT

patients had higher FDOPA uptake in our study (Fig. 2). This may explain the larger variance in Ki values and suggests increased dopamine metabolism in early course of the AD/SDAT. Further studies including receptor assays will be required. DA and HVA of human postmortem specimens were reported significantly reduced in AD/SDAT patients (for a review,see Gottfries CG [19]). Thus DA metabolism is surely disturbed in AD/SDAT especially at their final stage. In the case of vascular dementia, the concentration of DA also decreased in the caudate nucleus compared with the brains of age-matched controls[20]. This may related to vulnerability of the striatum to the ischemia.

Neurological examination revealed mild rigidity in unilateral hand in one AD/SDAT patient. The rest of the subjects showed no clinical sign of Parkinsonisms. Thus the level of reduced dopamine synthesis seems not so severe that leads to overt neurological symptoms. In conclusion the present study indicated impaired DA metabolism in both AD/SDAT and vascular dementia in the course of the disease, although the underlining mechanisms may not be the same.

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Table 1. FDOPA influx rate (Ki, min^{-1}) into brain regions of AD/SDAT, vascular dementia and the normal controls assessed using FDOPA and the graphical analysis.

	NORMALS	AD/SDAT	VASCULAR
N	10	11	7
STRIATUM	0.0115[a] ± 0.0018	0.0108 ± 0.0036	0.0091 ± 0.0020
FRONTAL	0.0023 ± 0.0008	0.0029 ± 0.0014	0.0017 ± 0.0005
TEMPORAL	0.0019 ± 0.0014	0.0013 ± 0.0016	0.0022 ± 0.0016
OCCIPITAL	0.0002 ± 0.0012	-0.0004 ± 0.0029	0.0004 ± 0.0015
CERBELLUM	0.0083 ± 0.0090	0.0086 ± 0.0053	0.0070 ± 0.0025

a: $p < 0.05$

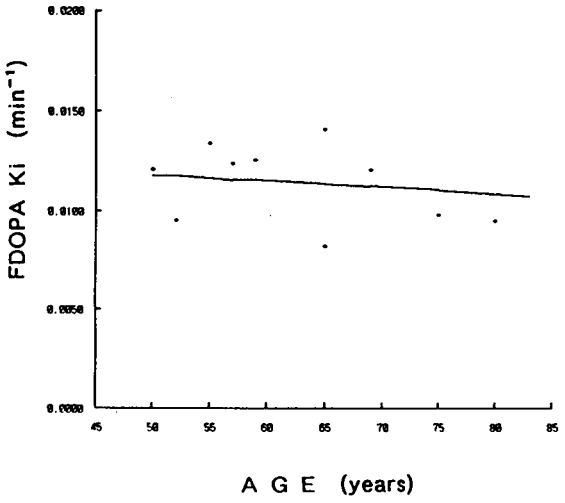

Fig. 1. Lack of age effect on FDOPA influx rate (Ki) of normal subjects. Ki was calculated by graphical method using cerebeller radioactive concentration.

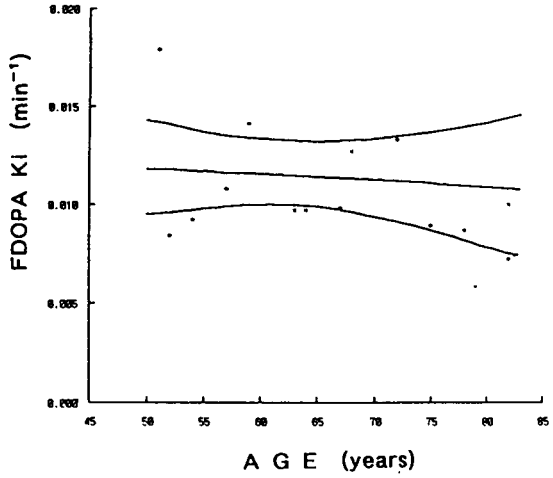

Fig. 2. Age effects on the FDOPA influx rate into the striatum in case of AD/SDAT (•), and in the vascular dementia (x). The regression line and the 95 % confidence limits for normal controls are also shown.

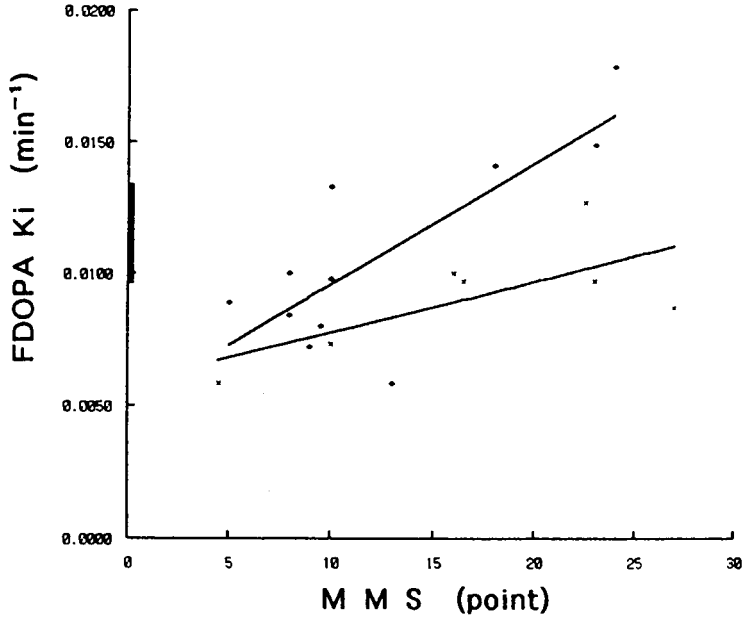

Fig. 3. Correlation of the FDOPA influx rate into the striatum and dementia severity as assessed with the mini-mental state battery (MMS). Data is shown for the AD/SDAT (•) and vascular dementia group (x). The regression line was: Ki = 0.000193×MMS +0.000583 (r=0.780, p<0.01): for AD/SDAT. Correlation in vascular dementia patients was not significant. Range for normal subjects confidence limit) is also shown.