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journal or publication title	CYRIC annual report
volume	1994
page range	185-190
year	1994
URL	<a href="http://hdl.handle.net/10097/49848">http://hdl.handle.net/10097/49848</a>

## IV. 2. Assessment of Dopamine Neurotransmission in Dementia Using Positron Emission Tomography

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### Introduction

Current leading role of positron emission tomography(PET) may be human receptor mapping. Numerous radioligands have been developed for imaging of neuronal receptors covering dopamine, serotonin, benzodiazepine and so on. The neurotransmission depends on various processes including neurotransmitter synthesis, storage in the presynaptic neurons, neurotransmitter release into synaptic clefts, binding to receptors, and activation of second messenger systems. Reuptake, breakdown, and binding to autoreceptors are also crucial for neurotransmission. Dysfunction of any single or complex of above process inevitably leads to neurological or psychological disorders. Parkinson's disease is a typical example of this type of dysfunction. Selective degeneration of dopaminergic neurons within pars compacta of the substantia nigra is the pathological process of this entity<sup>1)</sup>. 6-[<sup>18</sup>F]fluoro-L-dopa(FDOPA)<sup>2)</sup>, an analogue of L-dopa, is incorporated into dopaminergic nerve endings, converted to fluorodopamine<sup>3)</sup> and stored in synaptic vesicles. Injection of FDOPA and PET measurement is a powerful tool to assess overall function of presynaptic dopaminergic neurotransmission<sup>4)</sup>. Loss of FDOPA incorporation was demonstrated in Parkinson's patients<sup>5)</sup>. Enhanced activity or supersensitivity of D2 receptors in such patients was also shown by PET<sup>6)</sup>.

Alzheimer's dementia is a progressive disease and its definitive diagnosis is only given at autopsy because of lack of clinical diagnostic markers. There had been increasing interests in the neurochemical changes in dementia brain. Deficiencies in several transmitter systems such as acetylcholine (Ach), noradrenaline, dopamine (DA), serotonin, and some neuropeptides were reported<sup>7)</sup>. Therefore in vivo measurement of neurotransmitter function by PET may be a possible clinical tool for dementia diagnosis. We discuss here altered dopaminergic neurotransmission in AD/SDAT and vascular dementia which was revealed by PET measurements.

## Methods

### DOPAMINE METABOLISM MEASUREMENT

$6\text{-}^{18}\text{F}\text{-L-FDOPA}$  was synthesized according to the method described by Adam et al.<sup>8)</sup>. Following an intravenous bolus injection of FDOPA to subjects, positron tomography was carried out by using PT931 (CTI Inc, USA) with 7 mm axial and transaxial resolution<sup>9)</sup>. Emission scans were performed every 5 minutes for 60 min after injection. Tissue FDOPA concentration was measured defining ROIs on three image planes that included the striatum<sup>10)</sup>. The influx rate ( $K_i$ ) of FDOPA into the selected regions was then calculated employing the graphical analysis described by Patlak et al.<sup>11,12)</sup> using concentration of the cerebellum radioactivity as the input function. A linear fitting was carried out using data between 25 and 60 min post FDOPA injection.

### DOPAMINE RECEPTOR MEASUREMENT

Dopamine D2 receptor binding potential was measured by using  $^{11}\text{C}$  labeled benzamide derivative, N-[1-benzyl-2-methyl-pyrrolidinyl]-5-chloro-2-methoxy-4-methylaminobenzamide, NMAB)<sup>13,14)</sup>. A three compartment model was used for brain kinetics of NMAB. The influx of NMAB from capillary to brain parenchyma was expressed as  $K_i$ , a parameter including blood flow and permeability-surface area product for NMAB at BBB. Characteristic of specific bindings of NMAB was represented by  $k_3$ , which is a bimolecular association constant of  $B_{\text{max}}$ (receptor density) times  $k_{\text{on}}$ , and  $k_4$ , a dissociation constant. Nonlinear least square fitting of brain activity to the model estimates from the above parameters yielded estimation of the rate constants. The ratio of  $k_3/k_4$  was used as an index of the D2 receptor function.

### SUBJECTS

Studies were performed on thirty-two subjects over 50 years old including 11 normal subjects (6 males and 5 females; average age:  $63.3 \pm 9.2$ ), 12 patients with Alzheimer's and senile dementia (AD/SDAT) (5 males and 7 females; average age:  $67.0 \pm 11.3$ ) and 9 patients with vascular dementia (5 males and 4 females; average age:  $74.1 \pm 6.9$ ). The diagnosis of dementia was based on DSM-III-R<sup>15)</sup>. The dementia subtypes were judged mainly on the clinical profiles of symptoms, referenced to the Ischemic Score<sup>16)</sup> and CT/MRI findings. The severity of the dementia was evaluated using the mini-mental state battery (MMS).

### Results

The  $K_i$  of FDOPA influx into the striatum and other cortical regions (average of both sides) in normal subjects and two types of dementia were summarized in Figure 1. Two way ANOVA revealed  $K_i$  differed significantly between the striatum and all cortical regions ( $F\text{-value} = 155.3$ ,  $p < 0.01$ ).  $K_i$  to the occipital cortex was negligible ( $0.00006 \pm 0.00207 \text{ min}^{-1}$ ) and significantly smaller than the frontal and temporal cortex ( $p < 0.01$  by the multiple

comparison). The striatal Ki of the normal group was  $0.0116 \pm 0.0017 \text{ min}^{-1}$  and showed no age-related decline ( $\text{Ki} = -0.00003 \cdot \text{Age} \pm 0.01333$ ,  $r = -0.152$ ). The striatal Ki differed significantly among study groups ( $F\text{-value} = 5.03$ ,  $p < 0.01$ , by ANOVA). Vascular dementia group showed reduced striatal Ki ( $0.0081 \pm 0.0026 \text{ min}^{-1}$ ) than normals ( $0.0110 \pm 0.0031 \text{ min}^{-1}$ ,  $p < 0.05$ , by the multiple comparison). The multiple regression analysis revealed Ki could be predicted by age and dementia severity as evaluated with the mini-mental state as  $\text{Ki} = -0.000046 \cdot \text{Age} + 0.000382 \cdot \text{MMS} + 0.008076$  ( $r^2 = 0.590$ ,  $p < 0.01$ ) for AD/SDAT and  $\text{Ki} = -0.000088 \cdot \text{Age} + 0.000226 \cdot \text{MMS} + 0.010483$  ( $r^2 = 0.401$ ,  $p < 0.05$ ) for the vascular dementia. The MMS term in AD/SDAT was most significant with its t-value as 3.168 ( $p < 0.01$ ). The correlation analysis supported dependence of Ki on MMS (Figure 2).

NMAB uptake, assessed by the ratio of the  $k_3/k_4$ , was  $1.18 \pm 0.96$  for normal control,  $2.28 \pm 1.26$  for AD/SDAT, and  $5.74 \pm 2.51$  for vascular dementia. Student t-statistic revealed the vascular group had significantly higher binding potentials than the control ( $p < 0.01$ ). PET images of typical cases were shown in Figure 3.

## Discussion

Dopaminergic neurons has not only crucial to motor regulation but a part of the system is linked to the neocortex and limbic brain<sup>17</sup>). The nucleus accumbens or the ventral striatum connects to the amygdala, ventral pallidum, thalamus, the limbic and premotor cortex and functions as an interface between the limbic and the motor system. It is thought to be related to the temporal control of behavior, reward-related learning and memory function<sup>18</sup>). The dopaminergic projections from  $A_{10}$  of the ventral tegmentum to the nucleus accumbens may play a mediating role for incentive motivation<sup>19</sup>). The striatal ACh neurons receive an input from extrinsic DA neurons of the mesencephalic tegmentum and give output to interneurons containing somatostatin/NPY, neurotensin or GABA. DA controls ACh-mediated transmission in an inhibitory manner through D2 receptors<sup>20</sup>). D2 receptor upregulation induced by a partial meso-diencephalic hemitransection in mice was counteracted by nicotine treatment<sup>21</sup>). These results confirms close interaction between dopaminergic and cholinergic system. It is reasonable to assume, therefore, that the dopaminergic system plays fundamental roles, in the process of higher brain function.

Postmortem studies revealed that there are some age-related reductions in the concentration of DA in the caudate nucleus in the group of patients older than 65<sup>22</sup>). PET observation of a normal aged population also found a gradual decline in FDOPA uptake with age<sup>23</sup>). However, a recent study opposed this age-related decline<sup>24</sup>). Our data support the latter observation. We reported stability of blood flow and oxygen metabolism in the neurologically normal populations up to 80 years of age<sup>25</sup>). Little change in FDOPA uptake in normal subjects supports well preserved homeostasis in brain metabolism in normal population. Disturbed DA metabolism in demented subjects, therefore, is hardly explained by the age-related reductions.

DA and HVA of human postmortem specimens were reported significantly reduced in AD/SDAT patients (for a review, see Gottfries, C. G.)<sup>26</sup>). The aromatic amino acid decarboxylase, an enzyme that catabolize L-dopa to dopamine, was reported to decrease in senile dementia<sup>27</sup>). Thus, DA metabolism must be disturbed in AD/SDAT especially at the 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<sup>28</sup>).

Tyrrell, et al.<sup>28</sup>) reported a greater variance in  $K_i$  values of FDOPA in the patients' group than in normal subjects despite of no significant changes in FDOPA uptake into the caudate and putamen in Alzheimer type dementia patients with extrapyramidal signs. 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 relatively higher FDOPA uptake in our study (Figure 2). This may explain the larger variance in  $K_i$  values and suggests increased dopamine metabolism in early course of the AD/SDAT. There are some reports about reciprocal activities between cortical and subcortical DA neurons. Underactivity of the frontal cortical DA system may result paradoxically, in overactivity of the subcortical DA projection (see review by Robbins TW)<sup>29</sup>). Although precise reason for DA hyperactivity in our early AD/SDAT patients is not known, it may reflect a disturbed neuronal function including the striatal DA system.

Intercorrelation between level of dopamine metabolism and D2 receptor function in our study was not straightforward (Figure 4). Diminished DA synthesis might be partly compensated by upregulation of D2 receptors in vascular dementia subjects. However, D2 receptor function varied rather independently from the level of dopamine metabolism in AD/SDAT subjects. Reduction of dopamine synthesis as well as D2 receptor function seen in a part of AD/SDAT patients which may reflect hypoactivity of DA neurotransmission. The other patients showed hyperactivity of both DA synthesis and D2 receptors. These data support heterogeneity of AD/SDAT<sup>30</sup>) and PET assessment of DA function may predict outcome of neuroleptic treatments for dementia symptoms.

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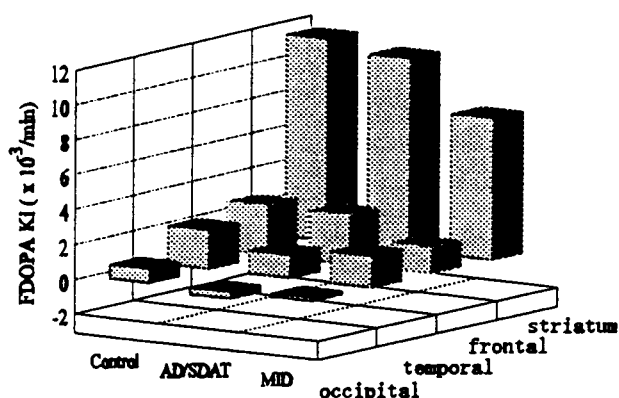


Fig. 1. The mean FDOPA influx rate ( $\text{min}^{-1}$ ) into the brain regions in control, AD/SDT, MID groups. The columns represent the striatum, frontal cortex, temporal cortex, occipital cortex from right to left.

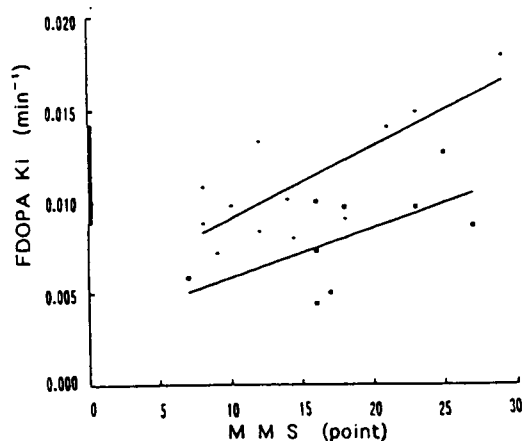


Fig. 2. Correlation of FDOPA Ki into the striatum with dementia severity as assessed by mini-mental state battery (MMS points, abscissa) in MID(□) and AD/SDAT(■). The values are averages of right and left striatum. From Itoh M, et al.<sup>10</sup>

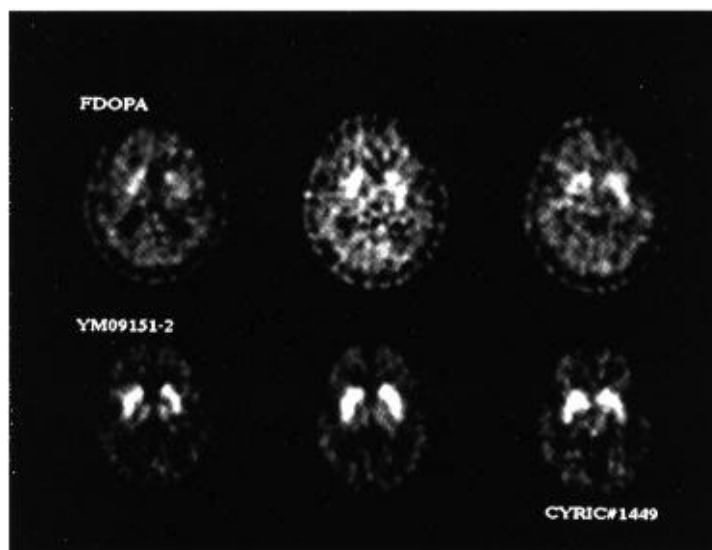


Fig. 3. Uncoupling of FDOPA influx into the striatum (upper row) and dopamine D2 receptor activity (bottom row) in a vascular dementia case.

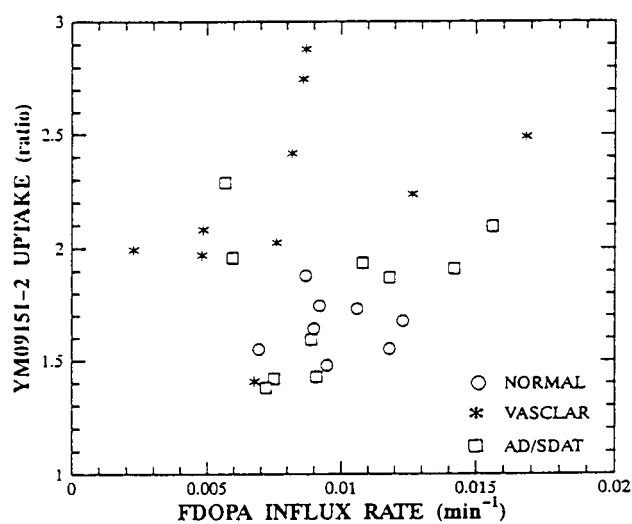


Fig. 4. Scatter diagram comparing FDOPA influx rate (abscissa) into the striatum and dopamine D2 receptor function in dementia. The values for the right and left striatum are separately plotted.