VIII. 8. Imaging Quantification of Dopamine D₂ Function Using Positron Emission Tomography: a Methodological Approach

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Background

PET with certain radioligands, is a sophisticated imaging technique that measures the in vivo receptor function in the brain. Dopamine D₂ neuroreceptor is synthesized from an amino acid, tyrosine in the presynaptic terminal, and stored in a vesicle. This neurotransmitter is released after depolarization in certain tasks. Dopamine (DA) function is the characteristic of synthesis, storage, release, reuptake and interactions with receptors. The radioligand ¹¹C-YM-09251-2 (Nemonapride) has been used as a tracer in this investigation. However, the distribution and kinetics of receptor-ligand interaction in the in vivo brain are quantified by certain kinetic assumptions. Dopamine is correlated with human behavior and personality¹,²). Any discrete locations of D₂ receptors in the brain can cause neurological disorders such as schizophrenia, Parkinson’s disease etc.

Assay of post-synaptic dopamine D₂ function is evaluated by measuring kinetic rate constants. We adopted the conventional three tissue compartment model method (predicted as 2TCM) and the Lammerstma’s reference tissue model method (RTM) (3) to evaluate D₂ function. ¹¹C-Nemonapride (YM)-PET was applied to the normal volunteers and Parkinson’s patients to assess post-synaptic dopamine D₂ function from the ligand-receptor association. Our purpose was to assess the integrity of 2TCM and RTM methods for the tracer, nemonapride by measuring the binding potential (BP) and tracer delivery (R₀) of cortical gray matters relative to reference region (occipital cortex).

Materials & methods

Two groups of human volunteers were assigned to this investigation. 7 male normal subjects, aged 47.4 ± 25.7 y (mean ± S.D.), were studied as resting control. They had no previous history of dementia. In another, 5 Parkinson’s patients (male/female; 2/3), aged 58
± 10.2 y (mean ± S.D.), were assigned to the disease group. The study protocol was approved by the Human Ethics Review Committee of Tohoku University. The volunteers were requested abstaining from eating and/or drinking for at least 3 hours before experiment. They were free from mental anxieties and tensions. The radioligand, $^{11}$C-YM 09151-2 (Nemonapride) with radioactivity dose of 251 ± 150 MBq (mean±S.D.) and 267 ± 57 MBq (mean ± S.D.) were administered to each group subjects, respectively. A dynamic 3D PET scan consisting transmission followed by emission scan, was started to cover the whole brain 5 min after the injection of radiotracer using the scanners, SET-2400W; Shimadzu Co. Japan and/or PT931-04 ECAT CTI, Knoxville, U.S.A. The transmission scan for tissue attenuation correction lasted 10 min for 1 scan, whether the emission scan continued 90 min performing 23 scans (i.e., 1 min/6 scan, 3 min/8 scan, 5 min/6 scan, and 10 min/3 scan). Arterial blood samplings were taken after tracer injection for 23 times (1 ml/18 times, and 3 ml/5 times for plasma metabolites) until dynamic emission scan was finished. The plasma radioactivity was measured, and the plasma metabolite for $^{11}$C-Nemonapride (YM) tracer was measured by the high performance liquid chromatography analysis (HPLC).

In the control group, ROIs were drawn manually on the target structures including corpus striatum, frontal and temporal cortices and occipital cortex as reference region (Fig. 1). The ROIs data of the occipital cortex was used for the reference region in the reference tissue model (RTM) analysis. The kinetic parameters ($K_1$, $k_2$, $k_3$, and $k_4$) of target structures, and the tracer delivery ($R_0$) in the target region relative to the occipital region, were assessed by kinetic least square minimization analysis in the 2TCM and RTM methods. Binding potential (BP) of receptor-radioligand interactions, were also evaluated by applying conventional 2TCM and RTM methods. The tracer uptake ratio between target and reference regions was calculated.

On the other hand, the statistical parametric mapping analysis (SPM-99), was applied on $R_0$ images to test the significance in the difference of BPs between normal subjects and Parkinson’s patients. The SPM analysis was performed to define the parameters of anatomical normalization.

**Results**

In the control group, BP and $R_0$ values of striatum, and cortical regions (frontal and temporal) were calculated by 2 different methods. For the striatum, the calculated BP, measured by the RTM method, were significantly less than by the 2TCM, and the relative tracer delivery ($R_0$) was almost same for both methods. The BP values of frontal and
temporal cortices were lower than those of the striatum (Fig. 2). In another, BP in the striatum was almost similar between normal volunteers and Parkinson’s patients, whether it was reduced in the cortices of the patients’ group (Fig. 2). The average tracer delivery of the normal volunteers and Parkinson’s patients were almost similar (Fig. 2). The volume rendered brain images, developed by the statistical parametric mapping analysis (SPM-99), suggested the significantly reduced BP in the cortices of the Parkinson’s disease patients (Fig. 3).

Discussions & conclusion

Cortical imaging was the choice to explore the feasibility of RTM method. Our investigation showed the robust cortical BP changes rather than subcortical structures in the parametric images of Parkinson’s brain data. RTM method may be appropriate to assess the ligand-receptor interaction of cortices. It can be argued the rapid clearance of nemonapride from the reference region to the receptor rich cortices. Previous investigators found this criteria for another tracer where cerebellum was used as a reference region (4). We compared different data analysis strategies of post-synaptic dopamine D₂ receptor function of living human brain from the ligand-receptor interactions. We also adopted two different kinetic analytical approaches as to determine its integrity. $^{11}$C-Nemonapride was used to assess the post-synaptic DA function. 2 tissue compartment model (2TCM) and reference tissue model (RTM) methods were applied on the normal volunteers and Parkinson’s patients data to evaluate post-synaptic D₂ function. Reference tissue model (RTM) may be applied for our ligand, $^{11}$C-Nemonapride. RTM is attractive for $^{11}$C-Nomenapride kinetic analysis, because both binding potential and tracer-delivery are evaluated by pixel-basis. It is argued that RTM method is more reliable than 2TCM for the tracer, $^{11}$C-Nemonapride (YM). The cortical changes of BP measured by RTM method, may be a target for future analysis of neurodegenerative diseases such as Parkinson’s and schizophrenia. To assess DA function without taking any input function, would have the advent for RTM method. It is to be said that further investigations are needed to evaluate the feasibility and integrity of this imaging analysis using $^{11}$C-Nemonapride (YM).

References


![Image](image1)

Figure 1. Procedure of ROIs analysis on the target (striatum, frontal and temporal cortices) and reference regions (occipital cortices).

![Image](image2)

Figure 2. Kinetic images of BP and R₀ showing the binding potential and tracer delivery of dopamine D₂. The images are shown from the normal volunteers and Parkinson’s patients.
Figure 3. Volume rendered images analyzed by the statistical parametric mapping (SPM-99) showing the $D_2$ binding potential of $^{11}$C-nemonapride (YM) between normal volunteers and Parkinson’s patients. The $D_2$ binding potential reduction in the Parkinson’s patients are visualized.