III. 6 Visualization of Neural Transmission in Dopaminergic Neurons of Dog Brain Using PET

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The brain is an unresting organ that continuously receives signals from perceptive organs, integrates the informations and creates the responses. When the signals to one neuron are converged and then diverged to other neurons, the synaptic transmission among neurons plays main role. The presynaptic terminal liberates a chemical transmitter substance in response to a depolarization. This chemical depolarizes postsynaptic cell at an excitatory synapse and tends to maintain the membrane potential of the postsynaptic cell below the threshold at an inhibitory synapse. Therefore, the neurotransmitter formation at the presynaptic ending and neurotransmitter-receptor binding at the postsynaptic site reflects the capacity of neural transmission.

Using a positron emission tomography, presynaptic neurotransmitter metabolism (Garnett et al., 1983) and postsynaptic neurotransmitter receptor site (Wagner et al., 1983) were studied in human brain. Leenders et al. (1984) tried to visualize pre- and post-synaptic dopaminergic system in the same individual.

In the present study, we visualized the accumulation of 6-[18F]fluoro-L-dopa (FDOPA) which mimics L-dopa metabolism in the synaptic terminal. Further, [11C] YM-09151-2 which has high affinity and specificity to dopamine receptors was utilized to visualize dopamine receptors in the dopaminergic neuron system. The present method provides non-invasive evaluation for the neural transmission at the presynaptic and post synaptic regions in living animals and humans.

Materials and Method
Animal Preparation

Fifteen Kg male Beagle was anesthetized under 3 % halothane, 2 L/min of N2O and 1 L/min of oxygen. After introduction, 0.5 to 1 % of halothane was inhaled to maintain anesthesia during the study. Two canula, one for blood samplings and another for administration of FDOPA and YM-09151-2, were inserted to femoral artery and cubital vein, respectively. Arterial blood pressure was monitored using pressure sensor through arterial line. Body temperature was measured by thermometer in the rectum.
Preparation of [11C]YM-09151-2 and 18FDOPA

YM-09151-2 was labeled with Carbon-11 according to the method described previously (Iwata et al., 1988, Ido et al., 1988). Radioactivity was 5 mCi (25 nmol) at the administration.

1.9 mCi of 18FDOPA (1 mg) was prepared according to the method developed by Firnau et al. (1984).

Scan Procedure

Dog brain was scanned repeatedly with ECAT-II at 5 mm above and below the orbitomeatal line. Data acquisition time was 5 minutes during first 20 minutes after injection, and thereafter 10 minutes until 2 hours after injection. Radioactivities of [11C] YM-09151-2 administrated through cubital vein and accumulated to basal ganglia and other brain structures were then measured.

After the decay of C-11, 18FDOPA was intravenously administrated and the same scan procedure was performed as [11C] YM-09151-2 study.

During the scannings, arterial blood samplings were performed periodically to estimate plasma radioactivities of C-11 in the YM study and F-18 in the FDOPA study. The fraction of C-11 YM and its metabolites in the plasma was determined with liquid chromatogram.

Results

Figure 1 shows tomographic PET images of [11C] YM-09151 (A) and 18FDOPA (B) at 60 minutes after administration at 5 mm below the orbitomeatal line. Clear accumulation and retention of [11C] YM-09151-2 and [18F] FDOPA was visible.

Figure 2 illustrated the radioactivities of C-11 (A) and F-18 (B) in the basal ganglia and arterial plasma against the time after administration. In Figure 2-A, the fraction of [11C] YM-09151-2 was also plotted.

Discussion

Firnau et al. (1987) demonstrated that in the rhesus monkey the retention of fluorine-18 in the cerebral dopaminergic regions (such as striatum) after F-18 FDOPA administration is predominantly due to 6-[18F]fluoro-dopamine which was derived in vivo from 6-[18F]fluoro-L-dopa. Therefore, in the PET study, the ratio of F-18 radioactivity in the striatum to the total amount of FDOPA administrated is the practical index for dopamine synthesis.

In contrast, F-18 radioactivities in non-dopaminergic regions such as occipital cortex were due to methyl-dopa. The clearance rate of F-18 methyl-fluorodopa in the non dopaminergic regions might represent the enzyme activity such as catechol-O-methyltransferase which converts L-dopa to methyl-dopamine.
The ratio of F-18 radioactivity in the striatum to that in the cerebellum or occipital cortex was used for the index of dopamine synthesis. However, FDOPA metabolism in non-dopaminergic regions might be independent of dopaminergic system and different among individuals.

We analyzed metabolites of F-18 FDOPA in the blood (results not included in the present paper). There were several metabolites such as methyl-L-dopa. The fraction of FDOPA in the blood should be correctly determined to evaluate input amount of FDOPA to the brain.

C-11 labeled YM-09151-2 binds dopamine-2 receptor with high affinity and specificity. In non-dopaminergic regions, C-11 radioactivities due to non specific binding to dopamine receptor might be found. In the sequential scannings after administration, C-11 radioactivities in the cortex and cerebellum were rapidly declined. On the other hand, the retention of C-11 radioactivities in the basal ganglia was remarkable indicating the specific binding of the tracer to dopaminergic receptors.

In order to establish the quantitative analysis of neurotransmitter-receptor bindings, further estimation of the fraction of metabolites in the plasma and the fraction of non-specific bindings is needed.

References
Time Activity Curve of YM-09151

Fig. 2(A).

Time Activity Curve of FDOPA

Fig. 2(B).