III. 5 ¹¹C-Labeled Dimethyltryptamine: A New Radiopharmaceutical for the Brain Imaging

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Introduction

Indolealkylamines such as N,N-dimethyltryptamine(DMT), 5-methoxy-N,N-dimethyltryptamine, and bufotenine are known to have hallucinogenic properties and are found in the serum or the urine both of normal subjects and psychotic patients.¹,²) Indolealkylamines are more specific for 5-hydroxytryptamine binding sites(serotonin₁ receptors) than for serotonin₂ receptors.³) ¹¹C-labeled indolealkylamines are expected as potential serotonin₁ receptor mapping radiopharmaceuticals.⁴) Of these ¹¹C-labeled indolealkylamines we examined ¹¹C-DMT as a new tracer for the brain imaging.

Materials and Methods

Synthesis of ¹¹C-DMT was developed by T. Takahashi et al.⁵) In regional distribution study male wistar rats weighing 190-200 g were sacrificed at 20 min after the injection of ¹¹C-DMT(1-2 mCi) through jugular veins. The brains were frozen in crushed dry ice and about 300 µm coronal sections were cut by a knife on dry ice. Specific regions were removed with a hollow needle(inner diameter 1.2 mm) at -15°C and radioactivites were measured by a NaI well scintillation counter(punch sampling procedure). Autoradiography was applied to a rat injected with approximately 10 mCi of ¹¹C-DMT. The brain was removed at 20 min after the injection and frozen in crushed dry ice. The 30 µm sections of the brain were exposed to a Kodak NMC-1 X-ray film at room temperature for 3 h. Drug treatment was as follows: 10 mg/Kg of DMT, 10 mg/Kg of N-methyltryptamine(NMT), 50 mg/Kg of 5-hydroxy-L-tryptophan(5-HTP)(50 mg/Kg of MK-486 pretreated 30 min before) were administrated into a jugular vein simultaneously with ¹¹C-DMT under light ether anesthesia. Reserpine was administrated intraperitoneally in a dose of 5 mg/Kg at 6 h before ¹¹C-DMT injection. 75 mg/Kg of pargyline was injected intraperitoneally at 2 h before ¹¹C-DMT injection. Subcellular distributions were performed as described by Whittaker and Barker.⁶) In dynamic positron emission transaxial tomographic (PETT) study an adult dog weighing 12 Kg was anesthetized with pentobarbital and continuous sequential scans were performed on the single level of OM+0 from 2 min to 42 min after 11.9 mCi of ¹¹C-DMT was injected.
Results and Discussion

Figure 1 illustrates the tissue distribution of $^{11}$C-DMT in rats. There was a high accumulation in the brain. The accumulation in the brain was increased rapidly in a few minutes and reached a maximum level at 10 min. Regional distribution in the rat brain at 20 min after the injection by the autoradiography and the punch sampling procedure are shown in Figure 2. $^{11}$C-DMT accumulated higher in the cerebral cortex, caudate putamen, and amygdaloid nuclei. On the contrary, the uptake in the cerebellum or medulla oblongata was the lowest in the brain. The accumulation pattern of $^{11}$C-DMT in the rat brain was clearly different from those of $^{18}$F-2-fluoro-2-deoxyglucose and $^{11}$C-methionine (Data were not published.) and appeared to reflect the characteristics of $^{11}$C-DMT itself. Figure 3 shows the relationship between the cerebral cortex concentration of $^{11}$C-DMT and serum concentration at 20 min after the injection. The linear correlation was observed in lower serum concentration and the brain concentration showed a tendency to be saturated in higher serum concentration (more than 5 nmol/ml). Table 1 and Figure 4 show the effects of DMT, NMT, pargyline, reserpine, and 5-HTP on the regional distribution of $^{11}$C-DMT in the rat brain in vivo. The accumulation of $^{11}$C-DMT in the brain was decreased in a high dose of DMT (10 mg/Kg), and the decrease in the radioactivity was the greatest in the cerebral cortex. The simultaneous injection of NMT (10 mg/Kg) also decreased the accumulation of $^{11}$C-DMT. The decrease in $^{11}$C-DMT accumulation was greater in DMT-treated rats than NMT-treated rats. Pargyline, monoamine oxidase inhibitor, diminished the brain concentration of $^{11}$C-DMT probably due to lowering the serum concentration. Reserpine also decreased the accumulation in the brain and this effect was different in each region. The decrease of concentration in the cerebral cortex was greater than those in the thalamus, hypothalamus, and amygdala. 5-HTP had no effect on the regional accumulation. These results indicate that $^{11}$C-DMT has its own compartment of distribution in the rat brain. It was reported that the total number of serotonin$_1$ receptors in the brain was 16 pmol/gram of tissue, wet weight. Therefore this compartment is larger than that of serotonin$_1$ receptors. The subcellular distribution of $^{11}$C-DMT in the rat brain at various loading doses and effects of reserpine and pargyline on the distribution are shown in Figure 5. Reserpine inhibits the re-uptake of neurotransmitters such as serotonin and dopamine in synaptic vesicles. Reserpine had no influences on the subcellular distribution and it is expected that $^{11}$C-DMT does not accumulate in the synaptic vesicles of nerve endings in vivo. The compartment of $^{11}$C-DMT may not include the synaptic vesicles and it is markedly different from the pool of serotonin. The radioactivity in the nuclear(N), crude mitochondrial(CM), and microsomal(MIC) fractions were increased with decreasing loading dose of DMT. Pargyline increased the proportion of activity in the three particles(N+CM+MIC). More than 75% of radioactivity was recovered in those fractions(N+CM+MIC) in pargyline-pretreated rats injected with about 1 umol/Kg of DMT. The effect of pargyline was thought to be caused by the inhibition of metabolism of $^{11}$C-DMT in vivo. As 21%, 62%, and 17% of specific 5-hydroxytryptamine binding(serotonin$_1$...
receptors) is localized in the nuclear, crude mitochondrial, and microsomal fraction, respectively\(^3\), the greater part of \(^{11}\text{C}\)-DMT was considered to bind to the postsynaptic receptors in pargyline-treated rats. In summary, \(^{11}\text{C}\)-DMT is expected to have two distinct pools of distribution. Pool\(_1\) is significantly related to serotonin\(_1\) receptors and \(^{11}\text{C}\)-DMT accumulates in the pool\(_1\) when loading dose of DMT is very low. Pool\(_2\), which was mentioned above precisely, is greater than the pool\(_1\) and may be associated with the compartment of other amines. Figure 6 shows the PETT image and anatomical transaxial section of the same plane in the dog brain. \(^{11}\text{C}\)-DMT was accumulated highly in the brain and the plasma radioactivity in arterial blood was decreased rapidly as shown in Figure 7. In this experiment injected dose of DMT was 1.34 umol(112 pmol/Kg) and the calculated concentration of \(^{11}\text{C}\)-DMT was 90-110 pmol/ml brain tissue volume. If the total mass of DMT injected per body weight is low, it would be feasible to image the distribution of serotonin\(_1\) receptors in vivo with PETT. In the dynamic PETT study of human or dog the loading dose of DMT would be estimated at approximately 1-100 nmol/Kg and most of \(^{11}\text{C}\)-DMT accumulated in the brain would bind to the postsynaptic serotonin\(_1\) receptors. It is also concluded that the brain images of \(^{11}\text{C}\)-DMT represent the pool\(_2\) mentioned above in a high loading dose of DMT.

Acknowledgment

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References

Table 1. The effects of DMT, NMT, pargyline, reserpine, and 5-HTP on the regional accumulation of $^{11}$C-DMT in the brain. * means drugs were administrated simultaneously with $^{11}$C-DMT injection. All data are expressed as the percentages of the accumulation of $^{11}$C-DMT for 20 min in control rats.

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Fig. 1. Tissue distribution of $^{11}$C-DMT in rats. Each point represents the mean of 3 rats. Kidney(Kid)=○ — — ○, Brain=★ — — ★, Liver(Li)=□ — − □, Spleen(Spl.)=▲ — — ▲, Intestine(Int.)=△ — — △, Lung(Lu.)=● — — ●, Heart=● — — ●, Blood=○ — — ○.

Data are expressed as DAR. DAR was defined as follows:

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\frac{\text{observed activity (cpm)/weight of tissue (g)}}{\text{total injected activity (cpm)/total weight of animal (g)}}
\]
Fig. 2. Regional distribution of $^{11}$C-DMT in the rat brain: Autoradiography and punch sampling procedure. Details were described in Materials and Methods. Data are expressed as % administered dose/g in the punch sampling procedure. Each point represents the mean of 4 determinations.
Fig. 3. The relationship between cerebral cortex and serum concentration of $^{11}$C-DMT. The concentration was calculated with % dose/g and loading dose.
Fig. 4. Schematic frontal sections of the rat brain. The left half identifies the structures. The circles on the right half indicate the location of tissue samples; the number is the 'punch number' identified in Table 1. Abbreviations are: CC, corporis callosi; cp, nucleus caudatus putamen; CA, commissura anterior; FMP, fasciculus medialis prosencephali; HI, hippocampus; VL, ventriculus lateralis; tv, nucleus ventralis thalami; a, nucleus amygaloideus; hp, nucleus posterior hypothalami; FOR, formatio reticularis; SN, substantia nigra; SGC, substantia grisea centralis; PCS, pedunculus cerebellaris superior.
Fig. 5. The effects of pretreatment with pargyline and reserpine on the subcellular distributions of $^{14}$C-DMT. N=nuclear fraction. CM=crude mitochondrial fraction. MIC=microsomal fraction. N+CM+MIC represents the sediments at 100,000×G. Pargyline-treated rats=△△△△, Reserpine-treated rats=★★★★, Control rats=○○○○.
Fig. 6. The PETT image and anatomical transaxial section of the same plain in the dog brain.

Fig. 7. Time-activity curve of ROI in the dog brain. Plasma radioactivity curve was superimposed on this figure. The regions measured in this experiment (brain(1), brain(2), and brain(3)) are shown in the PETT image above.