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III. 4 ^{11}C-Labeling of Indolealkylamine Alkaloids and the Comparative Study of Their Biodistributions

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Introduction

In the indolealkylamine alkaloids, there are a series of hallucinogenic compounds such as N,N-dimethyltryptamine (DMT), N-methyltryptamine (NMT), bufotenine, O-methylbufotenine (OMB), psilocin, psilocybin[1] etc. The structures of these hallucinogenic indolealkylamines are similar to that of serotonine, which plays an important role in the central nervous transfer system. So, these compounds are known to have an affinity for the serotonine$_1$ receptors.[2] In these respects, they are interesting compounds for the study of serotonine action mechanism in brain. For the application of serotonine$_1$ receptor mapping in brain, we tried the ^{11}C-labeling of DMT, NMT, bufotenine, OMB[3] and N,N,N-trimethyltryptamine iodide (TMT) by the reaction of indolealkylamines with $^{11}CH_3I$. In this paper, we also report the comparative study of their biodistributions in rats for the fundamental study of hallucinogenic action mechanism.

Materials and Methods

Tryptamine (1a) and 5-methoxytryptamine (1C) were purchased from Tokyo Kasei Kogyo Co., Ltd. Nω-Methyltryptamine (N-methyltryptamine (NMT)) (5a), N,N-dimethyl-5-methoxytryptamine (5-methoxy-N,N-dimethyltryptamine (5-MDMT) or O-methylbufotenine (OMB)) (3c) and 5-hydroxy-Nω-methyltryptamine oxalate (5-hydroxy-N-methyltryptamine oxalate (5-HNMT oxalate)) were purchased from Aldrich Chem. Co., Inc. The starting materials except above-mentioned were synthesized by the scheme as shown in Chart 1.

i) Syntheses of the starting materials and $^{11}CH_3I$

Synthesis of N,N,N-trimethyltryptamine iodide (TMT) (2a) : 2a was synthesized by the reaction of 1a with excess CH_3I. Yield : 24 %. m.p. ; 233°C (decomp.). MS m/e : 188 (M^+-CH_3I).

Synthesis of N,N-dimethyltryptamine (DMT) (3a) [4] : 3a was obtained by demethylation of 2a with 1M $LiEt_3BH$-THF solution. Yield : 53 %. m.p. : 57-59°C. MS m/e : 188 (M^+).

Preparation of 5-hydroxy-N-methyltryptamine (5-HNMT) (5b) : 5b was prepared by passing 5-HNMT oxalate through a column of ion exchange resin (AG-3, weak base type). 6 mg of 5b was obtained from 100 mg of 5-HNMT oxalate.

Synthesis of 5-methoxy-N-methyltryptamine (5-MNMT) (5c) : (Method A) [5] 5c was synthesized by the reaction of 3c with 2,2,2-trichloroethyl chloroformate,

followed by the reductive cleavage with acetic acid and zinc powder. Yield : 43 % (from 3c). m.p. : 90-93 °C. MS m/e : 204 (M^+).

(Method B) N-Benzyloxycarbonyl-5-methoxytryptamine (4c) was, at first, synthesized by the reaction of 1c with benzylchloroformate. 4c was converted to 5c by the reduction with $LiAlH_4$. Yield : 17 % (from 1c). m.p. : 88-91 °C.

Synthesis of $^{11}CH_3I$ [6] : $^{11}CH_3I$ was synthesized from $^{11}CO_2$ according to the following reaction scheme.

$$^{11}CO_2 \xrightarrow[-20°C]{LiAlH_4 \,/\, THF} \xrightarrow[70°C]{\text{THF evapo.}} \xrightarrow[-20°C]{H_2O} {}^{11}CH_3OH \xrightarrow[100°C]{HI} {}^{11}CH_3I$$

The total time required for the $^{11}CH_3I$ synthesis from $^{11}CO_2$ was within 25 min.

ii) ^{11}C-Labeling

The general synthetic scheme of ^{11}C-indolealkylamines is shown in Chart 2.

^{11}C-N,N-Dimethyltryptamine (^{11}C-DMT) : $^{11}CH_3I$ was purged into the solution of 5a (6 mg, 34 µmol) dissolved in acetone (1 ml) at -78 °C (dry ice-acetone). The reaction mixture was stirred at room temperature for 5 min. After removal of the solvent, the residue was dissolved in small amount of $CHCl_3$ for chromatographic separation of ^{11}C-DMT. The chromatographic separation was performed on a short silica-gel column (SEP-PAK, silica (WATERS LTD.)), eluted with $CHCl_3$/EtOH/50% Me_2NH aq. sol. = 9 ml/1 ml/ 30 µl. ^{11}C-DMT was eluted with 10-20 ml of the solvent. From the collected fractions, the solvent was evaporated in vacuo. To the residue, saline was added, followed by pH adjustment with 0.1N HCl. The neutral solution was sterilized by a membrane filtration (0.22 µm). 10-20 mCi of ^{11}C-DMT was obtained from 50-100 mCi of $^{11}CH_3I$.

^{11}C-N-Methyltryptamine (^{11}C-NMT) : $^{11}CH_3I$ was purged into the solution of 1a (6 mg, 38 µmol) dissolved in acetone (1 ml) at -78 °C. The reaction mixture was stirred at room temperature for 5 min. The solvent was evaporated to dryness. The following preparation for injection was same as that of ^{11}C-DMT. 500 µCi of ^{11}C-NMT was obtained from 45 mCi of $^{11}CH_3I$.

^{11}C-5-Hydroxy-N,N-dimethyltryptamine (^{11}C-bufotenine) : 5b (6 mg, 32 µmol) was used as the starting material. As the reaction solvent, MeOH (1 ml) was used instead of acetone. The reaction with $^{11}CH_3I$ was run at 40 °C for 10 min. Other synthetic conditions of ^{11}C-bufotenine were same as those of ^{11}C-NMT. 2 mCi of ^{11}C-bufotenine was obtained from 44 mCi of $^{11}CH_3I$.

^{11}C-5-Methoxy-N,N-dimethyltryptamine (^{11}C-O-methylbufotenine (^{11}C-OMB)) [3] : $^{11}CH_3I$ was purged into the solution of 5c (6 mg, 29 µmol) dissolved in acetone (1 ml) at -78 °C. The reaction mixture was heated at 40 °C for 10 min with stirring. After removal of the solvent, the residue was dissolved in small amount of water. The chromatographic separation was performed on a short reversed phase column (SEP-PAK, C-18 (WATERS LTD.)). After eluting the reversed phase column with water (10 ml), the solvent was exchanged for EtOH. ^{11}C-OMB was eluted with EtOH. From the collected fractions, the solvent was evaporated to dryness. The following preparation for injection was same as that of ^{11}C-DMT. 1.5 mCi of ^{11}C-OMB was obtained from 28 mCi of $^{11}CH_3I$.

^{11}C-N,N,N-Trimethyltryptamine iodide (^{11}C-TMT) : $^{11}CH_3I$ was purged into the solution of 3a (6 mg, 32 µmol) dissolved in acetone (1 ml) at -78 °C. The reaction mixture was stirred at room temperature for 5 min. After removal of the solvent, the residue was dissolved in small amount of water. The chromatographic separation was performed on a short reversed phase column (SEP-PAK, C-18 (WATERS LTD.)). ^{11}C-TMT was eluted with first 10 ml of water. The solvent was evaporated in vacuo. The following preparation for injection was same as that of ^{11}C-DMT. 12 mCi of ^{11}C-TMT was obtained from 76 mCi of $^{11}CH_3I$.

Radiochemical yield and radiochemical purity : The radiochemical yields are shown in Table 1. The radiochemical purities were analyzed by HPLC and TLC. The analytical conditions and the radiochemical purities of ^{11}C-labeled compounds are shown in Table 2.

iii) Animal experiments

Normal wistar rats (150-180 g) were used for biodistribution studies. ^{11}C-DMT, ^{11}C-NMT, ^{11}C-bufotenine, ^{11}C-OMB and ^{11}C-TMT were injected into rats through the tail lateral vein. The animals were killed by neck dislocation at 5, 10, 30 and 60 min after injection. The organs were removed, blotted, weighed and counted in an automated NaI well counter. The uptake is expressed as the differential absorption ratio (DAR). (DAR = [(the observed tissue activity) × (the body weight)] / [(the injected activity) × (the tissue weight)])

Results and Discussion

In the preparation of non-commercial starting materials, both method A (N-demethylation)[5] and method B (N-monomethylation) are useful because amine or N,N-dimethylamine compounds are relatively easily available.

^{11}C-Labeling conditions of indolealkylamines and their radiochemical yields are summarized in Table 1. The radiochemical yield of ^{11}C-tertiary amine from secondary (^{11}C-DMT synthesis) or ^{11}C-quaternary ammonium salt from tertiary (^{11}C-TMT synthesis) was higher than that of ^{11}C-secondary amine from primary (^{11}C-NMT synthesis) because of the reactivities of respective starting materials with $^{11}CH_3I$. But the radiochemical yield of ^{11}C-bufotenine was low. ^{11}C-OMB has been synthesized by the use of $H^{11}CHO$ [3] but the ^{11}C-labeling of OMB with $^{11}CH_3I$ is more simple and more convenient.

The separation of these ^{11}C-labeled compounds were performed by a short silica-gel or reversed phase (C-18) column but this separation was not enough to remove starting materials.(percentage of contained starting materials : 2-10%) In the receptor mapping study, the further purification is needed because of the hallucinogenic activity of starting materials themselves. These ^{11}C-labeled compounds are able to be purified furthermore by HPLC separation. For example, ^{11}C-DMT is well-separated by the following HPLC conditions ; column : Radialpak silica (WATERS LTD.), eluent : $CHCl_3$/MeOH/50% Me_2NH = 99/1/0.02,flow rate : 2 ml/min, detection : UV-254nm) Now, we have developed the ^{11}C-labeling of psilocin and psilocybin.

The biodistributions of ^{11}C-DMT, ^{11}C-NMT, ^{11}C-bufotenine, ^{11}C-OMB and ^{11}C-TMT are shown in Fig. 1 - Fig. 5. ^{11}C-DMT, ^{11}C-NMT and ^{11}C-OMB were cleared fast from blood but ^{11}C-bufotenine was relatively slow. In the case of ^{11}C-TMT, the gradually increasing blood uptake has been seemed to be owing to the metabolic products of ^{11}C-TMT. These five ^{11}C-labeled compounds were accumulated in liver, lung and small intestine, in which the reactivities of amineoxidase or tryptophan dioxygenase are relatively high. In kidney, the uptakes of four ^{11}C-labeled compounds except ^{11}C-TMT were high but ^{11}C-TMT was excreted. This difference may be owing to the quaternary salt structure of ^{11}C-TMT.

The brain uptakes of ^{11}C-labeled compounds at 30 min are summarized in Table 3. Among these compounds, only TMT has no hallucinogenic action. ^{11}C-DMT and ^{11}C-OMB were relatively highly accumulated in brain and their accumulations were retained. The brain uptakes of ^{11}C-NMT and ^{11}C-bufotenine were low but that of ^{11}C-bufotenine was increasing with time. ^{11}C-TMT was poorly uptaken in brain owing to the blood-brain barrier. These results show that ^{11}C-DMT and ^{11}C-OMB are suitable for the study in brain. But, the radiochemical yield of ^{11}C-OMB was lower than that of ^{11}C-DMT.

^{11}C-DMT may be a most suitable radiopharmaceutical among these ^{11}C-labeled compounds for the study of serotonine action mechanism in brain.

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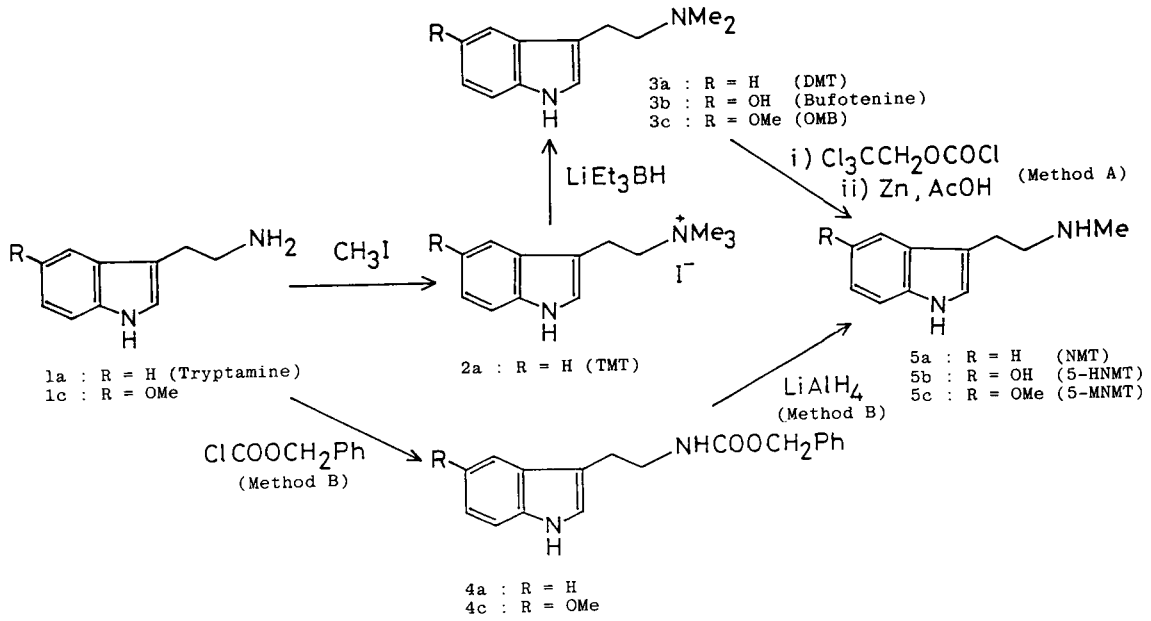

Chart 1. Syntheses of N-methyl- or N,N-dimethyl-indolealkylamines

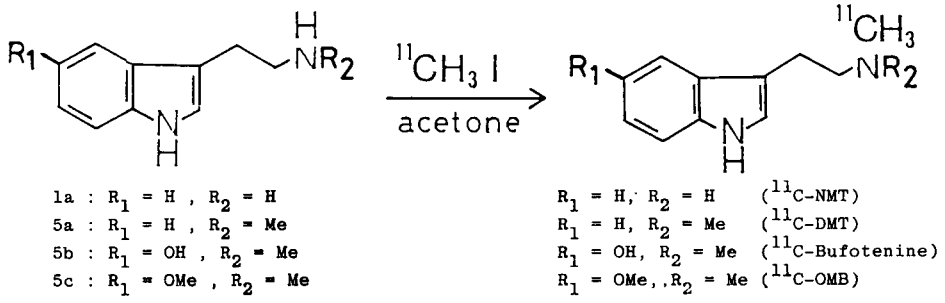

Chart 2. General ^{11}C-labeling scheme of indoleakylamines

Table 1. ^{11}C-Labeling conditions of indolealkylamines and their radiochemical yields

compound	solvent	time (stirring) (min.)	reaction temperature (°C)	radiochemical yield (%)	time required for the synthesis [b] (min.)
^{11}C-DMT	acetone	5	r.t. [a]	50	35
^{11}C-NMT	acetone	5	r.t.	2	20
^{11}C-bufotenine	MeOH	10	40	9	20
^{11}C-OMB	acetone	10	40	18	30
^{11}C-TMT	acetone	5	r.t.	31	25

a) r.t. : room temperature b) from the end of $^{11}CH_3I$ trapping

Table 2. Analytical conditions of ^{11}C-indolealkylamines and their radiochemical purities

compound	HPLC[a]			TLC[b]		radiochemical purity (%)
	column[c]	eluent[d]	retention time (min.)	developing solvent[e]	R_f value	
^{11}C-DMT	P	I	3.9	A B	0.44 0.34	99
^{11}C-NMT	P	I	15.4	A B	0.58 0.28	95
^{11}C-bufotenine	B	II	2.8	A B	0.41 0.46	98
^{11}C-OMB	B	II	5.5	A B	0.41 0.55	92
^{11}C-TMT	B	II	2.0	A B	0.43 0	99

a) flow rate : 2 ml / min.

b) plate : silica-gel (DC-Alufolien Kieselgel 60 F_{254} (Merck))

c) P : μ-Porasil, B : μ-Bondapak C-18

d) I : $CHCl_3$ / EtOH / 50% Me_2NH aq. sol. = 9 / 1 / 0.03
II : MeOH / H_2O = 25 / 75, pH = 3.19 AcOH - AcONa buffer

e) A : n-BuOH / AcOH / H_2O = 12 / 3 / 5 , B : iso-PrOH / 10% NH_4OH / H_2O = 20 / 1 / 2

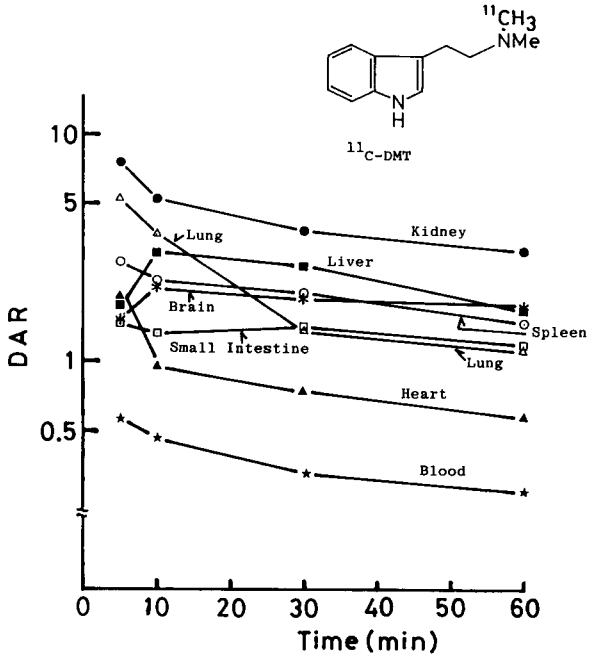

Fig. 1. Tissue distribution of ^{11}C-DMT in normal wistar rats. (n=3)

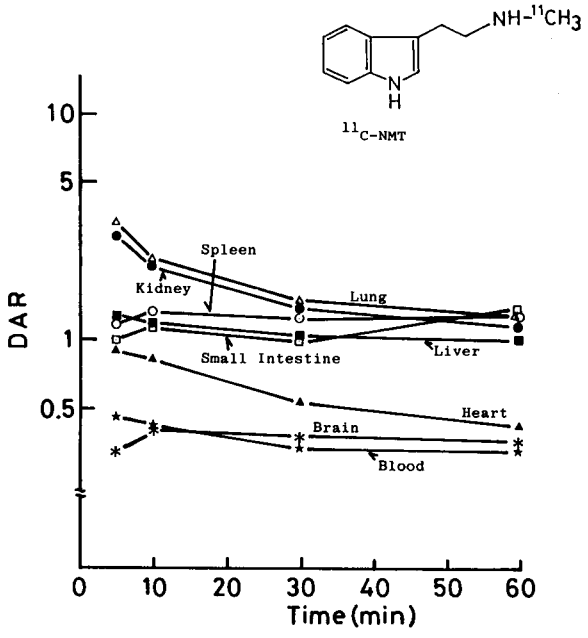

Fig. 2. Tissue distribution of ^{11}C-NMT in normal wistar rats. (n=3)

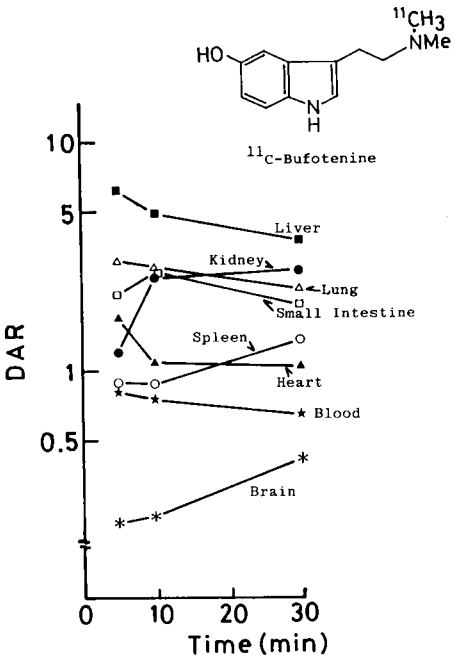

Fig. 3. Tissue distribution of ^{11}C-bufotenine in normal wistar rats. (n=3)

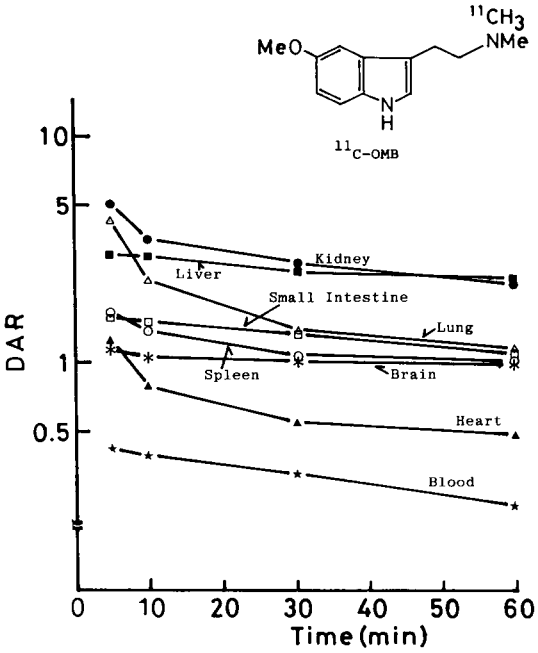

Fig. 4. Tissue distribution of ^{11}C-OMB in normal wistar rats. (n=3)

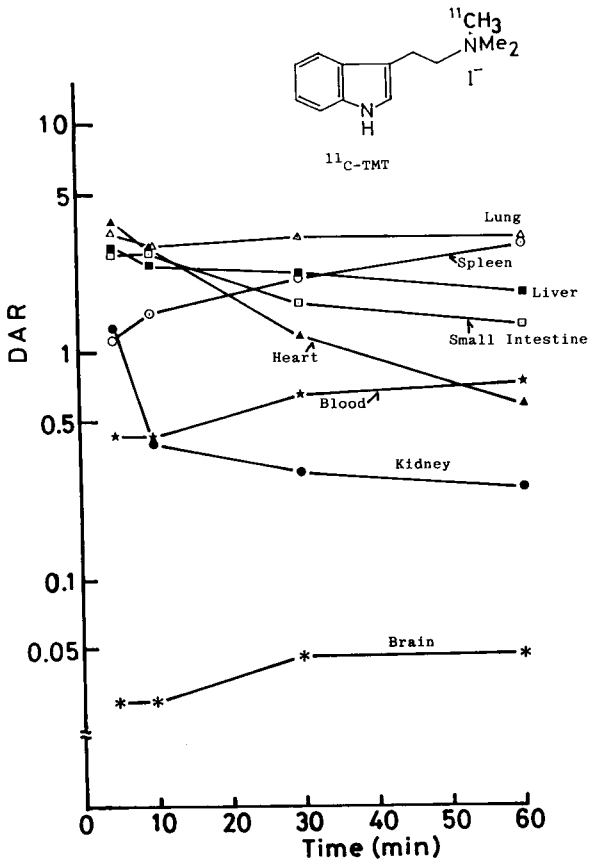

Fig. 5. Tissue distribution of ^{11}C-TMT in normal wistar rats. (n=3)

Table 3. Brain values and brain-, liver-, kidney-, spleen-, small intestine-, lung-, heart-to-blood ratios at 30 min.

compounds	Brain (DAR)	Ratios to blood						
		Brain	Liver	Kidney	Spleen	Small Intestine	Lung	Heart
^{11}C-DMT	1.85	6.0	8.3	12.0	6.3	4.5	4.4	2.3
^{11}C-NMT	0.38	1.1	3.2	4.3	3.8	3.1	4.5	1.6
^{11}C-Bufotenine	0.42	0.6	6.0	4.4	2.1	3.2	3.5	1.6
^{11}C-OMB	1.05	3.2	7.7	8.8	3.2	4.3	4.3	1.7
^{11}C-TMT	0.05	0.07	3.5	0.5	3.3	2.4	4.9	1.8