Journal of Radioanalytical and Nuclear Chemistry, Vol. 240, No. 2 (1999) 535–540

N-[^{11}C]methyl-3,4-methylenedioxyamphetamine (Ecstasy) and 2-methyl-N-[^{11}C]methyl-4,5-methylenedioxyamphetamine: Synthesis and biodistribution studies

M. Patt,[1] D. Gündisch,[2] U. Wüllner,[3] A. Blocher, K.-A. Kovar,[2] H.-J. Machulla[1]*

[1] *Section Radiopharmacy, PET-Center*
[2] *Institute of Pharmacy*
[3] *Department of Neurology*
Eberhardt-Karls-University Tübingen, Germany

(Received May 7, 1998)

In order to evaluate the neurobiological mechanism causing the psychogenic effects of methylenedioxy-derivatives of amphetamine, the carbon-11 labeled analogues of 3,4-methylenedioxymethamphetamine (MDMA), **2** and 2,N-dimethyl-4,5-methylenedioxyamphetamine (MADAM-6) **4** were prepared for application in in-vivo PET studies by methylation of 3,4-methylenedioxyamphetamine (MDA) **1** and 2-methyl-4,5-methylenedioxyamphetamine **3** with [^{11}C]CH_3I. The radiochemical yield was determined in dependence on time, temperature and amount of precursor. The best conditions for a fast labeling reaction with carbon-11 on a preparative scale were found to be a reaction time of 10 min using 1 mg of the corresponding dimethyl-precursors **1** or **3**, thus obtaining radiochemical yields of 60% (based on produced [^{11}C]CH_3I). Biodistribution studies were performed in rats, a high brain to blood ratio of 7.5 was observed for [^{11}C]MDMA in contrast to a ratio of 3.7 for [^{11}C]MADAM-6.

Introduction

The phenethylamine MDMA (3,4-methylenedioxy-methamphetamine, "Ecstasy", "Adam") **2** (Fig. 1) is chemically related to amphetamines and psychedelics like mescaline and methylenedioxyamphetamine (MDA) **1**. MDMA was reported to possess antidepressant and anxiolytic properties and to evoke a well-controllable emotional experience with relaxation, peaceful feelings, increased empathy, and a drop in fear responses, mostly without distortion of sensory perception and thought and without marked stimulation. Together with MDE (3,4-methylenedioxyethamphetamine) and MBDB (N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine) it might constitute a new psychoactive substance class: the entactogens. The first preparation and description of MDMA was a German patent issued to the company E. Merck (1914). In 1984, MDMA began to gain popularity as a new recreational drug. Public controverse discussions about illegal abuse, usefulness for insight-oriented psychotherapy, and possible neurotoxicity in humans played an important role for the assignment to Schedule I status by the Drug Enforcement Agency in 1985.

The most prominent neurochemical effect of MDMA is the ability to induce serotonin release. MDMA has a high affinity at reuptake sites of central catecholaminergic, dopaminergic, and serotonergic neurons.

The structure of the amphetamine derivative MADAM-6 (2,N-dimethyl-4,5-methylenedioxyamphetamine) **4** was designed to be that of MDMA, the most popular representative of the entactogens. Reported anecdotally MADAM-6 seems to lack any psychogenic activity. Only one methyl group attached at what should be a reasonably indifferent position can so effectively change the action of a compound. Such a strong activity change from a small structural change indicates the methyl group to be at an important position, such as a target of a critical fit in some receptor site or metabolism. However, the reason for the missing psychoactivity of MADAM-6 is still unknown. In order to investigate the pharmacological properties and binding characteristics of both MDMA and MADAM-6, a labeling procedure with the short-lived positron emitter, carbon-11, was established.

Recently, the labeling of MDMA and biodistribution studies in mice have been reported.[1] In that study the work-up of the reaction mixture after the labeling step consists of a single HPLC-purification. However, from our experience gained during the labeling studies of both N-[^{11}C]methyl-2,5-dimethoxy-4-bromo-amphetamine[2] and N-[^{11}C]methyl-2,5-dimethoxy-4-methylamphetamine[3] we know that the corresponding demethyl-compound can not be fully separated from the ^{11}C-labeled product under the applied HPLC conditions, i.e., if the ^{11}C-labeled product is eluted after the demethyl-precursor. Since MDA and MDMA are expected to have at least similar binding characteristics[4,5] a contamination of the [^{11}C]MDMA injection solution with the precursor MDA might interfere with receptor binding and biodistribution in vivo. Therefore, for the biodistribution studies in rats a second HPLC separation was performed thus reducing the amount of the demethyl-precursors by at least a factor of 10. For imaging purposes with both positron emission tomography (PET) and autoradiography, the rat model is better suited than the mouse due to the higher anatomical resolution. Therefore, biodistribution of MDMA are reinvestigated in rats and the results are compared to those obtained for MADAM-6.

* E-mail: machulla@uni-tuebingen.ge

0236–5731/99/USD 17.00

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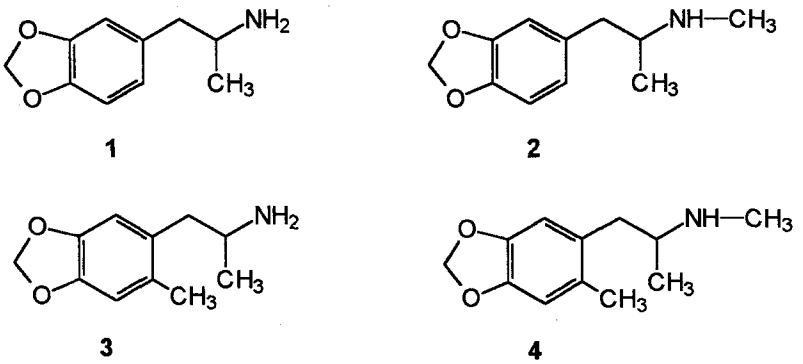

Fig. 1. Structures of MDMA **2** and MADAM-6 **4**

Experimental

The starting material for the labeling of MDMA and the reference compound, 3,4-methylenedioxyamphetamine (MDA) **1** and 3,4-methylenedioxymethamphetamine (MDMA) **2**, respectively, were prepared according to a literature procedure.[6] 2,N-Dimethyl-4,5-methylenedioxyamphetamine **4** was prepared as described by SHULGIN et al.[7] Except for the melting point, no analytical data was available, therefore all compounds were characterised by ^{1}H- and ^{13}C-NMR and EI-MS. The ^{1}H-NMR spectra of **1** and **2** were recorded on a Bruker AC 80 (80 MHz), the ^{13}C-NMR spectra were recorded on a Bruker WM 400 (400 MHz) spectrometer and are not decoupled, the ^{1}H- and ^{13}C-NMR spectra of **3** and **4** were recorded on a Bruker AC 250 (250 MHz) spectrometer. TMS was used as internal standard in all measurements. The electron impact mass spectra of **1** and **2** were obtained using a Hewlett Packard mass spectrometer MSD 5970 (quadrupole) at 70 eV and a source temperature of 220 °C, whereas a TSQ 70, Finnigan MAT with a direct inlet and a source temperature of 200 °C was used for **3** and **4**.

3,4-Methylenedioxyamphetamine, MDA 1

MDA was obtained as the hydrochloride in a yield of 88%. The melting point was 201 °C. EI-MS m/z 179 (5%), 136 (100%), 105 (5%), 77 (30%), ^{1}H-NMR ($CDCl_3$/TMS) δ 6.7 (d,1H,ArH), 6.6 (dd,2H,ArH), 5.8 (s,2H,OCH_2O), 3.0 (m,1H,CH), 2.5 (dd,2H,CH_2), 1.8 (s,2H,NH_2), 1.1 (d,3H,CH_3), ^{13}C-NMR ($CDCl_3$/TMS) δ 146.8 (s, C-3), 145.1 (s, C-4), 132.7 (s, C-1), 121.3 (d, C-6), 108.7 (d, C-2), 107.3 (d, C-5), 100.0 (t, methylenedioxy-carbon), 47.7 (d, tertiary carbon), 45.4 (t, benzylic carbon), 22.5 (q, CH<u>C</u>H_3).

3,4-Methylenedioxymethamphetamine, MDMA 2

MDMA was prepared as the hydrochloride in a yield of 85%, the melting point was 152 °C. For characterising the compound ^{1}H-, ^{13}C-NMR and EI-MS were applied. EI-MS m/z 193 (2%), 177 (2%), 135 (20%), 77 (10%), 58 (100%), ^{1}H-NMR ($CDCl_3$/TMS) δ 6.7 (d,1H,ArH), 6.7 (dd,2H,ArH), 5.9 (s,2H,OCH_2O), 2.8 (m,1H,CH), 2.6 (dd,2H,CH_2), 2.4 (s,3H,NHC<u>H</u>$_3$), 1.5 (bs,1H,NH), 1.1 (d,3H,CHC<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$/TMS) δ 146.9 (s, C-3), 145.2 (s, C-4), 132.4 (s, C-1), 121.3 (d, C-6), 108.7 (d, C-2), 107.3 (d, C-5), 100.0 (t, methylenedioxy-carbon), 55.6 (d, tertiary carbon), 42.2 (t, benzylic carbon), 33.0 (q, $NHCH_3$), 18.7 (q, CH<u>C</u>H_3).

2-Methyl-4,5-methylenedioxyamphetamine 3

To a suspension of 1.48 g (39 mmol) $LiAlH_4$ in 37 ml anhydrous THF a solution of 2.8 g (13.7 mmol) 1-(2-methyl-4,5-methylenedioxyphenyl)-2-nitropropene[7] in 25 ml anhydrous THF were added under vigorous stirring. The mixture was refluxed for 22 hours and excess $LiAlH_4$ was destroyed by the addition of 15 ml H_2O and 50 ml isopropanol (IPA). The remaining emulsion was purified by filtration; the filtrate was washed with 20 ml IPA and concentrated by a rotational evaporator, yielding the crude product as a yellowish oil. By subsequent vacuum destillation 0.93 g of product (13%) were obtained as a colourless oil, bp 79–81 °C (0.02 mbar). For characterising the compound ^{1}H-, ^{13}C-NMR and EI-MS were applied. EI-MS m/z 194 (15%), 177 (18%), 162 (5%), 150 (90%), 135 (10%), 119 (2%), 91 (10%), 77 (5%), 65 (8%), 51 (5%), 44 (100%), ^{1}H-NMR ($CDCl_3$/TMS) δ 6.6 (s,2H,ArH), 5.9 (s,2H,OCH_2O), 3.1 (m,1H,CH), 2.5 (m,2H,CH_2), 2.3 (s,3H,ArC<u>H</u>$_3$), 1.2 (bs,2H,NH_2), 1.1 (d,3H,CHC<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$/TMS) δ 145.7 and 145.4 (C-4 and C-5), 130.8 and 129.2 (C-1 and C-2), 110.4 and 110.0

(C-3 and C-6), 100.6 (methylenedioxy-carbon), 47.6 ($\underline{C}HCH_3$), 43.7 (benzylic carbon), 23.6 ($CH\underline{C}H_3$), 19.5 (aromatic -CH_3).

2,N-dimethyl-4,5-methylenedioxyamphetamine, MADAM-6 **4**

MADAM-6 **4** was prepared as a colourless oil, bp 65 °C (0.03 mbar), according to the procedure described by SHULGIN et al.[7] in 14% yield from 2-methyl-4,5-methylenedioxyphenylaceton.

For characterising the compound ^{1}H-, ^{13}C-NMR and EI-MS were applied. EI-MS m/z 208 (25%), 191 (3%), 177 (10%), 161 (3%), 150 (100%), 135 (10%), 119 (5%), 103 (5%), 96 (12%), 91 (15%), 77 (12%), 65 (20%), 58 (100%), ^{1}H-NMR ($CDCl_3$/TMS) δ 6.6 (s,2H,ArH), 5.9 (s,2H,OCH_2O), 2.7 (m,1H,CH), 2.5 (m,2H,CH_2), 2.5 (s,3H,$NHC\underline{H}_3$), 2.4 (s,3H,$ArC\underline{H}_3$), 1.5 (bs,1H,NH), 1.1 (d,3H,$CHC\underline{H}_3$); ^{13}C-NMR ($CDCl_3$/TMS) δ 145.7 and 145.5 (2s, C-4 and C-5), 130.6 and 129.3 (2s, C-1 and C-2), 110.4 and 110.0 (2s, C-3 and C-6), 100.6 (s, methylenedioxy-carbon), 55.6 (s,$NHCH_3$), 40.6 (s, benzylic carbon), 34.1 (s, $\underline{C}HCH_3$), 19.7 (s, $CH\underline{C}H_3$), 19.5 (s, aromatic -CH_3).

Labeling procedure

[^{11}C]CO_2 was produced at the cyclotron of the PET-Center (PETtrace, GE Medical Systems) via the ^{14}N(p,α)^{11}C reaction, trapped on molecular sieve 4Å and converted to [^{11}C]methane in presence of Ni catalyst (Shimalite-Ni reduced 80/100, Shimadzu). [^{11}C]Methane was reacted with elemental iodine at 720 °C, thus giving [^{11}C]CH_3I in 40% radiochemical yield (EOB) based on produced [^{11}C]CO_2 in 12.5 minutes. The activity was trapped in a 10 ml Reactivial, containing 5 ml of CH_3CN. 1 ml portions of the [^{11}C]CH_3I solution were added to a solution of MDA **1** or demethyl-MADAM-6 **3** in CH_3CN, the vial was sealed, and kept heated for different reaction times at temperatures of 80 and 120 and 70, 80 and 120 °C, respectively. After cooling to room temperature an aliquot of the reaction mixture was analysed by HPLC (Econosil 10 µ, 250 mm×4.6 mm, Alltech, MeOH/0.15M NH_4NO_3-buffer at pH 9.9, 987.5/12.5 v/v, flow 2 ml/min). Under these conditions the *k'* values for CH_3I, demethyl-MADAM-6, MDA, MADAM-6 and MDMA were 0.25, 1.88, 2.00, 3.13 and 3.75, respectively. The calculation of the radiochemical yields was based on the time at which the production of [^{11}C]CH_3I was finished.

In preparative runs [^{11}C]CH_3I was trapped in an automated system (Nina, Nuclear Interface, Münster, Germany) in 1 ml DMF at –40 °C containing 1 mg of precursor **1** or **3**. The mixture was heated to 130 °C for 10 minutes, diluted with 0.5 ml HPLC eluent and purified by semipreparative HPLC (Econosil 10 µ, 250 mm×10 mm, Alltech, MeOH/0.15M NH_4NO_3-buffer at pH 9.9, 10/1 v/v, flow 8 ml/min). The peak containing the ^{11}C-labeled product was cut into a reservoir containing 70 ml H_2O. The product was fixed on a solid phase extraction cartridge (SEP PAK C-18 plus, Waters), washed with 10 ml H_2O and eluted with 10 ml MeOH. The specific activity was determined by means of UV-absorbance (280 nm) of the peaks corresponding to MDMA or MADAM-6 (a) in the preparative chromatogram, and (b) in the analysis of an aliquot of the final product solution after a calibration curve had been obtained from injections of the cold standards **2** and **4**. In those productions used in the animal experiments a second HPLC separation was performed under the same conditions after evaporating the HPLC eluent (8–10 ml) and redissolving the product in a smaller volume (1 ml) of eluent.

Animal experiments

Male Sprague Dawley rats (250 g) were anaesthetised with Pentobarbital (50 mg/kg) and injected with 100 µl buffered tracer solution. All rats received the same amount of cold MDMA or MADAM-6, i.e., 0.28 nmol and 0.17 nmol, respectively. In addition, the amount of **1** or **3** was determined to be not more than 0.05 nmol and 0.01 nmol, respectively. The low level of precursor in the injection solution could only be assured by performing a second HPLC separation.

The solution (100 µl) was administered into a femoral vein. After 5, 10 and 30 minutes the rats were sacrificed by heart puncture. Blood, urine and tissue samples from brain, liver, kidneys, spleen, lung, heart, muscle, fat, bone, colon, small intestine were taken, weighed and counted for γ-activity. Data were related to the total radioactivity administered as percentage of injected dose and weight (% ID/g), in cases in which the total organ was taken the data were additionally related to the total organ (% ID/organ).

Results and discussion

For the [^{11}C]methylation reaction of 3,4-methylene-dioxyamphetamine (MDA) and 2-methyl-4,5-methylenedioxyamphetamine the yield of [^{11}C]MDMA and [^{11}C]MADAM-6 was determined in dependence on reaction temperature in CH_3CN (Table 1). In all experiments the reaction time was 8 minutes. At low temperatures (40 °C) reaction kinetics of the methylation reactions of both precursors are quite low, therefore, within 8 minutes only moderate yields of [^{11}C]MDMA and [^{11}C]MADAM-6 are obtained, i.e., 21 and 23%, respectively. By application of higher reaction temperatures the yields could be significantly improved, thus at 110 °C [^{11}C]MDMA and [^{11}C]MADAM-6 were

obtained in a yield of 73% and 70%, respectively. In the case of [^{11}C]MADAM-6 experiments were also run at 125 °C resulting in radiochemical yields of 84%. However, reaction temperatures about 120 °C are difficult to achieve due to a significant increase of pressure inside the reaction vessel. Therefore, in the preparative runs the solvent was changed to DMF because of its higher boiling point. The product yield of [^{11}C]MDMA and [^{11}C]MADAM-6 was determined for reaction times between 2 and 20 minutes in acetonitrile at 80 and 120 °C and at 70, 80 and 120 °C, respectively. The experiments were performed with 3.0 mg of precursor **1** or **3**. At higher temperatures (120 °C) the increase of radiochemical yield with time is considerably faster than at lower temperatures (70 or 80°C), therefore yields of 70 to 80% are obtained already after 10 minutes (Fig. 2).

Table 1. Dependence of radiochemical yield on reaction temperature, reaction conditions: 2 mg precursor, 1 ml CH_3CN, reaction time 8 min, n = 3, ±sd.

Temperature, °C	Radiochemical yield, %	
	[^{11}C]MDMA	[^{11}C]MADAM-6
40	21 ± 4	23 ± 6
70	53 ± 4	39 ± 4
90	67 ± 4	55 ± 5
110	73 ± 4	70 ± 4
125	Not determined	84 ± 6

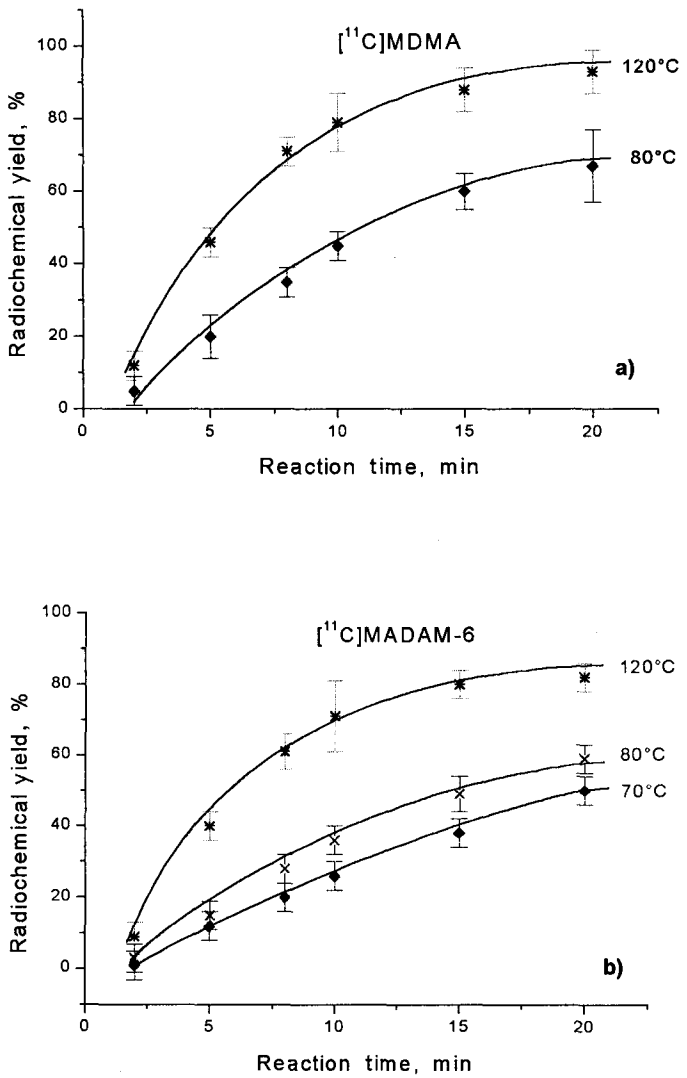

Fig. 2. Dependence of radiochemical yield of (a) [^{11}C]MDMA on reaction time at 80 and 120 °C (reaction conditions: 3 mg **1** (13.9 μmol), 3 ml CH_3CN, $n = 3$) and of (b) [^{11}C]MADAM-6 on reaction time at 70, 80 and 120 °C (reaction conditions: 3 mg **3** (15.5 μmol), 3 ml CH_3CN, $n = 3$)

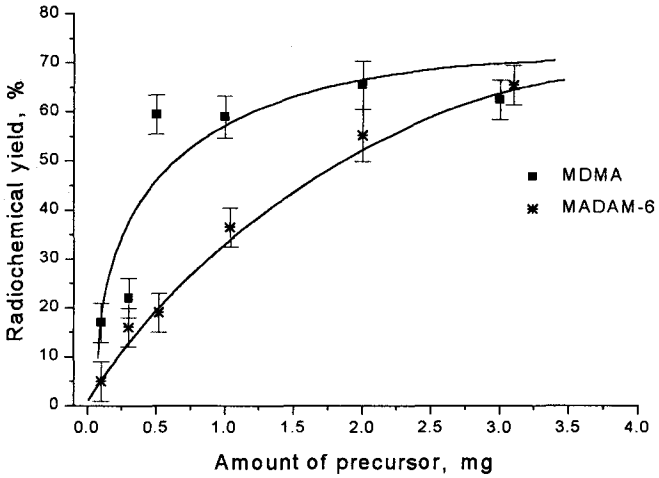

Fig. 3. Dependence of radiochemical yield of [^{11}C]MDMA and [^{11}C]MADAM-6 on amount of precursor (reaction conditions: 90 °C, 8 min, 1 ml CH_3CN, $n = 3$)

Table 2. Biodistribution data for [^{11}C]MDMA and [^{11}C]MADAM-6, values are mean of 3 experiments ±sd, % injected dose per g tissue

	[^{11}C]MDMA			[^{11}C]MADAM-6		
Organ	5 min	10 min	30 min	5 min	10 min	30 min
Brain	0.53 ± 0.03	0.45 ± 0.04	0.28 ± 0.02	0.55 ± 0.01	0.55 ± 0.03	0.45 ± 0.01
Liver	1.06 ± 0.09	1.8 ± 0.5	2.5 ± 0.5	1.5 ± 0.4	1.62 ± 0.09	2.8 ± 0.6
Heart	0.51 ± 0.09	0.22 ± 0.03	0.12 ± 0.01	0.59 ± 0.05	0.41 ± 0.02	0.17 ± 0.01
Kidneys	2.6 ± 0.3	1.0 ± 0.2	0.57 ± 0.07	2.7 ± 0.2	2.5 ± 0.2	1.08 ± 0.04
Spleen	1.4 ± 0.3	0.9 ± 0.2	0.41 ± 0.04	1.7 ± 0.2	1.3 ± 0.2	0.57 ± 0.05
Lung	4.9 ± 1.8	1.6 ± 0.6	0.47 ± 0.06	8.8 ± 4.7	4.2 ± 1.0	1.3 ± 0.5
Muscle	0.17 ± 0.01	0.16 ± 0.01	0.11 ± 0.03	0.20 ± 0.02	0.20 ± 0.03	0.19 ± 0.02
Bone	0.15 ± 0.02	0.08 ± 0.06	0.07 ± 0.01	0.25 ± 0.02	0.20 ± 0.02	0.11 ± 0.02
Colon	0.12 ± 0.02	0.09 ± 0.01	0.05 ± 0.01	0.20 ± 0.03	0.19 ± 0.04	0.09 ± 0.01
Small intestine	0.56 ± 0.09	0.4 ± 0.1	0.4 ± 0.1	0.8 ± 0.3	0.73 ± 0.04	0.9 ± 0.4
Fat	0.08 ± 0.02	0.04 ± 0.01	0.03 ± 0.01	0.11 ± 0.01	0.09 ± 0.02	0.07 ± 0.02
Urine	8.6 ± 2.8	11.1 ± 3.3	28 ± 15	28 ± 17	29 ± 6	69 ± 43
Blood	0.09 ± 0.01	0.06 ± 0.01	0.05 ± 0.01	0.20 ± 0.01	0.15 ± 0.02	0.12 ± 0.01
Brain to blood ratio	5.9 ± 0.7	7.5 ± 1.4	5.6 ± 1.2	2.8 ± 0.2	3.7 ± 0.5	3.8 ± 0.3

Table 3. Biodistribution data for [^{11}C]MDMA and [^{11}C]MADAM-6, values are mean of 3 experiments ±sd, % injected dose per organ

	[^{11}C]MDMA			[^{11}C]MADAM-6		
Organ	5 min	10 min	30 min	5 min	10 min	30 min
Brain	1.03 ± 0.07	0.83 ± 0.09	0.54 ± 0.04	0.97 ± 0.03	1.03 ± 0.05	0.80 ± 0.03
Liver	9.5 ± 1.9	15.2 ± 3.3	22.1 ± 5.2	11.5 ± 1.4	13.2 ± 0.6	21.0 ± 3.0
Heart	0.45 ± 0.08	0.18 ± 0.03	0.10 ± 0.01	0.5 ± 0.1	0.32 ± 0.02	0.13 ± 0.02
Kidneys	6.0 ± 0.9	2.1 ± 0.4	1.3 ± 0.1	4.7 ± 0.4	4.4 ± 0.2	2.0 ± 0.2
Spleen	1.0 ± 0.2	0.6 ± 0.1	0.26 ± 0.01	0.9 ± 0.1	0.9 ± 0.3	0.34 ± 0.03

The dependence of the radiochemical yield on the amount of precursor was determined in a range between 0.1 and 3.0 mg of starting material i.e., MDA **1** and 2-methyl-4,5-methylenedioxyamphetamine **3** at a reaction time of 8 minutes and 90 °C in acetonitrile. As shown in Fig. 3 the yield increases with the amount of precursor. In the case of MADAM-6 yields up to 65% are obtained with 3 mg of precursor while for similar yields of [^{11}C]MDMA higher amounts of precursor are necessary.

With regard to the half-life of carbon-11, the best results in the preparation of [^{11}C]MDMA and [^{11}C]MADAM-6 are obtained using 1 mg of precursor **1** or **3** within a reaction time of 10 minutes at a temperature of 110 °C in CH_3CN or 130 °C in DMF. The reaction mixture was purified twice by semipreparative HPLC. [^{11}C]MDMA and [^{11}C]MADAM-6 are obtained in a small peak volume which is easily evaporated and redissolved in isotonic phosphate buffer for injection. At end of synthesis (overall synthesis time 40 minutes) the specific activity was determined to be in the range of 74±19 GBq/μmol (2000±500 Ci/mmol) in 3 experiments.

After intravenous administration of [^{11}C]MDMA and [^{11}C]MADAM-6 to rats the tracer activity was determined in blood, urine and various organs after 5, 10 and 30 minutes (Table 2). After injection both tracers were rapidly extracted from the blood pool resulting in a blood activity of 0.09% iD/g ([^{11}C]MDMA) and 0.20% iD/g ([^{11}C]MADAM-6) at 5 minutes. In kidneys 2.6% iD/g ([^{11}C]MDMA) and 2.7% iD/g ([^{11}C]MADAM-6) was observed at 5 minutes. Interestingly, in lungs MDMA and MADAM-6 activity accumulated up to 4.9% iD/g and 8.8% iD/g at 5 minutes and 1.6% iD/g and 4.2% iD/g at 10 minutes. In heart the amount of the tracers were 0.51% iD/g and 0.59% iD/g at 5 minutes post injection and decreased to 0.22% iD/g (MDMA) and 0.41% iD/g (MADAM-6) at 10 minutes, respectively. Both [^{11}C]MDMA and [^{11}C]MADAM-6 exhibit a brain uptake of about 1% with the maximum at 5 and 10 minutes post injection (Table 3), respectively. The highest brain to blood ratio (7.5) is found for MDMA at 10-minute post injection, while the brain to blood ratio for MADAM-6 increases from 2.8 at 5-minute to 3.8 at 30-minute p.i.. In liver, the uptake continued to increase from 1.06% iD/g at 5 minutes to 2.5% iD/g at 30 minutes for MDMA and from 1.5% iD/g at 5 minutes to 2.8% iD/g at 30 minutes for MADAM-6, the total activity was 9.5% iD/organ growing to 22.1% iD/organ for MDMA and 11.5% iD/organ to 21.0% iD/organ for MADAM-6.

In summary, both tracers were rapidly extracted out of the blood pool resulting in a very low blood background. While a considerable amount of tracer activity was excreted through kidney and urine during the period of the study, up to 22% (MDMA) and 21% (MADAM-6) accumulated in liver thus indicating two different metabolic pathways of major importance.

These results are in good correlation with the values reported for biodistribution of MDMA in mice. In the study by SHIUE et al.[1] distribution of tracer was determined at 5-, 30- and 60-minute post injection. In heart and spleen almost identical values (expressed as% iD/organ) and very similar time courses are seen in rats and mice. The reported initial brain uptake in mice is almost twice as high as in the rat (1.9% iD/organ compared to 1.0% iD/organ at 5 min) but the shape of time-activity curve is very similar. In the rat liver a continuing activity accumulation was observed while in mice there was a maximum value of 18.6% iD/organ at 30 minutes decreasing to 11.3% iD/organ at 60 minutes. In kidneys the same time course of activity was observed for both species with somewhat higher values in mice (8.3% iD/organ compared to 6.0% iD/organ), indicating maybe a higher hepatic excretion in the rat and a higher renal excretion in mice.

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