Electrophysiological Study, Biodistribution in Mice, and Preliminary PET Evaluation in a Rhesus Monkey of 1-Amino-3-\([^{18}\text{F}]\)fluoromethyl-5-methyl-adamantane (\([^{18}\text{F}]\)-MEM): A Potential Radioligand for Mapping the NMDA-Receptor Complex

Samuel Samnick, Simon Ametamey, Klaus L. Leenders, Peter Vontobel, Guenter Quack, Chris G. Parsons, Henrik Neu and Pius A. Schubiger

1CENTRE FOR RADIOPHARMACY, PAUL SCHERRER INSTITUTE, VILLIGEN, SWITZERLAND; 2PET PROGRAM, PAUL SCHERRER INSTITUTE, VILLIGEN-PSI, SWITZERLAND; AND 3MERZ & CO. GMBH, FRANKFURT/MAIN, GERMANY

ABSTRACT. The effect of the fluorinated memantine derivative and NMDA receptor antagonist, 1-amino-3-fluoromethyl-5-methyl-adamantane (\([^{18}\text{F}]\)-MEM), at the NMDA receptor ion channel was studied by patch clamp recording. The results showed that \([^{18}\text{F}]\)-MEM is a moderate NMDA receptor channel blocker.

INTRODUCTION

The glutamatergic N-methyl-D-aspartate (NMDA) receptor is a major ionotropic receptor type that mediates excitatory synaptic transmission in the mammalian central nervous system (10, 24, 25). The NMDA receptor when activated controls the opening of an ion-channel, which permits the entry of monovalent and divalent cations (mainly Na\(^+\) and Ca\(^{2+}\)) into target cells. In recent years, increasing attention has focused on the NMDA receptor because of its involvement in various brain physiological and pathophysiological processes. Excessive activation of the receptor, in response to brain injury, can lead to cell death, probably caused by an excess accumulation of intracellular Ca\(^{2+}\) (7). It seems likely that the NMDA receptor contributes importantly to the etiology and progression of many neurological disease states such as ischemia (34), epilepsy (29), traumatic CNS injury, hypoglycemia (7), Alzheimer’s disease (15, 39), and Huntington’s disease (46).

In addition, the NMDA receptor has been shown to be essential for neuronal and behavioral plasticity, and hence has effects on learning and memory (25, 26). NMDA receptor-mediated long-term potentiation in the rat hippocampus is now a main experimental model for investigations on learning and memory at a molecular level (3). Thus, there has been great interest in the development of radioligands for imaging the NMDA receptor complex in the living human brain by noninvasive tomographic techniques like positron emission tomography (PET). Because uncompetitive NMDA antagonists (ion-channel blockers) have proved to be important tools for investigating the basic mechanisms of NMDA receptor function (19), several compounds mainly based on the uncompetitive NMDA antagonists phencyclidine (PCP), (+)-MK-801, and ketamine have been labelled successfully with positron-emitting nuclides for in vivo studies with PET (2, 5, 14, 17, 21, 30, 36).
3-fluoromethyl-5-methyl-adamantane (19F-MEM), a fluorine associated ion-channel. The 18F-labelled analog 18F-MEM was the PCP binding site located within the NMDA receptor-nated memantine derivative 18F-MEM. tracer for in vivo [18F]fluorine. In a previous work (35), we synthesized 1-amino-3-(tert-butyloxy)carbamoyl]-3-(toluenesulfonyloxyl)methyl-5-methyl-adamantane which does not lend itself to facile isotopic labelling with either radionuclides, could provide a radioligand with potential for investigating the NMDA receptor complex by PET. Memantine data suggest that memantine, labelled with a positron-emitting radionuclide, is a fast uncompetitive NMDA antagonist with rapid access to open-state of the channel (27). The starting point for the present work was the finding that the clinically used drug memantine (1-amino-3,5-dimethyladamantane, Fig. 1), with beneficial effects in the treatment of various neurological and psychiatric disorders like Parkinson’s disease and spasticity of cerebral and spinal origin (16, 32, 42), is a fast uncompetitive NMDA antagonist with rapid access to open NMDA receptor channels (22, 28). In addition, its ability to penetrate the blood-brain barrier, its poor metabolism in man, and the suggestion that none of the known metabolites is a potent NMDA antagonist confer on memantine distinct advantages compared to radiotracers for the NMDA receptor complex.

Unfortunately, the evaluation of their potential as tracers for PET has not been encouraging.

The development of radiotracers for the NMDA receptor complex appears relatively more difficult compared to radiotracers for common receptor and transporter proteins, owing to the differences in the nature of the binding sites. Whereas the binding sites of common receptors and transporters are located close to the surface of the membrane, the NMDA receptor channels are buried deeper within the membrane, and their accessibility is thus severely restricted by the amount and duration of agonist that is available to activate the channel. The reason for this is that the ion-channel blockers may bind to the open-state of the channel (27).

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FIG. 1. Structures of memantine and the new [18F]fluorinated memantine derivative 18F-MEM.

Materials and Methods

General

Both 1-[N-(tert-butylxoy)carbamoyl]-3-(toluenesulfonyloxy)methyl-5-methyl-adamantane (1) and 1-amino-3-fluoromethyl-5-methyl-adamantane (18F-MEM) were synthesized as described previously (35). TLC and radio-TLC chromatograms were performed on silica gel plates (SIL G/UV254, Merck) using CH2Cl2:MeOH (7:3) as mobile phase. Visualization of nonradioactive compound (18F-MEM) was achieved by ninhydrin spray. The (+)-MK-801 maleate was purchased from RBI Research Biochemicals International (Rahn AG, Zürich, Switzerland) and memantine hydrochloride was a gift from Merck & Co. (Frankfurt/M, Germany). Unless otherwise noted, all other reagents and solvents were of analytical quality or HPLC grade and were purchased from Merck (Darmstadt, Germany) or from Fluka Chemie (Buchs, Switzerland). The [18F]fluoride for nucleophilic labelling was produced by irradiation of 98% enriched [18O]H2O by the 18O(p,n)18F reaction as described previously (33). PET scans were performed using a PRT-2 Prototype rotating tomograph (Siemens-CTI) with a spatial resolution of 6 mm (40). Two systems were used for the isotopic HPLC separations:

SYSTEM A (SEMIPREPARATIVE). This system consisted of a Waters 510 pump; a Valco 6-port valve with 5 mL loop; a NKAUER UV detector; a Geiger-Müller counter LND 714 with an Eberlein RM-14 instrument; and a Waters µ-Bondapak C-18 column; 300 × 7.8 mm and 0.1% H3PO4: EtOH at 4 mL/min.

SYSTEM B (ANALYTICAL). This system consisted of a Rheodyne injector with 100-µL loop; a Merck-Hitachi L 6200 pump; a NaI scintillation detector (Scintillation Meter type 540, Mini Instruments Ltd. Burnham on Crouch, UK); a Merck-Hitachi L-4000 UV detector (at 215 nm); a Merck-Hitachi D-2500 Chroma integrator; and a Waters µ-Bondapak C-18 column, 300 × 4.6 mm and 0.1% H3PO4; EtOH (88:12) at 2 mL/min.

Radiochemical Synthesis of 1-amino-3-[18F]fluoromethyl-5-methyl-adamantane (18F-MEM)

The 18F-MEM was prepared according to a modified protocol previously described (35). Briefly, aqueous [18F]fluoride, obtained via 18O(p,n)18F reaction as described above, was placed into a 10-ml Reacti-vial® containing 3 mg K2CO3. A solution consisting of 14 mg Kryptofix 2.2.2 in 0.5 mL CH3CN was added and the solvent was removed under a stream of nitrogen in a block heater at 100°C, followed by azotropic evaporation with CH2CN (2×, 1.0 mL). Two milligrams of the precursor 1 were dissolved in 0.5 mL dry DMSO and added to the residue with a syringe. The Reacti-vial was heated at 130°C for 20 min. The reaction mixture was diluted with H2O (5 mL) and passed through a Sep-Pak C-18 Cartridge (Millipore Corp.). The cartridge was washed with H2O (5 mL), and the protected intermediate 18F-BOC-MEM was eluted from the Sep-Pak with ether (10 mL) and collected in a new Reacti-vial. After ether evaporation under a stream of nitrogen, 18F-BOC-MEM was subsequently deprotected by heating with 20% HCl (1 mL) for 10 min at 110°C. The resulting 18F-MEM was isolated by reversed-phase HPLC (system A). Besides HPLC, TLC was used to determine the identity of 18F-MEM (Rf = 0.38). For in vivo investigations, the collected product fraction was buffered with 0.6 M phosphate buffer to give, after sterile filtration, an isotonic and injectable radiopharmaceutical.
**Patch Clamp Studies**

Patch clamp recordings were made from cultured superior collicular and hippocampal neurons obtained from (E20) rat embryos at room temperature (20–22°C) with the aid of an EPC-7 amplifier at a membrane potential of −70 mV as described (28). Patch clamp electrodes were pulled and polished with a horizontal puller (DMZ) and had an internal tip diameter between 1.0 and 1.2 μm and a tip resistance of 4–5 MΩ. Cells were continuously superfused via one of eight channels of a custom-designed fast superfusion system with a common outflow. Test substances then were applied by rapidly switching channels. Complete exchange of the superfused solution was achieved within 10 to 20 msec. The application of the solutions and the synchronized on-line electronic acquisition of data were controlled by the program TIDA for Windows. Only results from stable cells were accepted for inclusion in the final analysis; i.e., following recovery of responses to NMDA by at least 75% of their depression by 19F-MEM.

The contents of the intracellular (electrode) solution were as follows [mM]: CaCl2 [120], TEACl [20], EGTA [10], MgCl2 [1], CaCl2 [0.2], Glucose [10], ATP [2], cAMP [0.25]. The extracellular solution had the following basic composition (mM): NaCl [140], KCl [3], CaCl2 [0.2], Glucose [10], HEPES [10], Sucrose [4.5] and Glycine [0.001]. Neurons were pharmacologically isolated from one another by the inclusion of 0.3 μM tetrodotoxin (TTX) to block voltage-activated sodium currents. Test substances were added to this solution in concentrations detailed in results and pH corrected, when necessary, to 7.35.

**Biodistribution Studies in Mice**

Biodistribution studies were carried out in female ICR mice (25–30 g, obtained from Animal Research Institute of the University of Zurich) according to the regulations for animal research from the Veterinary Health Authorities of the Canton Aargau, Switzerland. After a single intravenous (IV) administration of 1.5–3.0 MBq of 18F-MEM (in 0.1–0.2 mL solution), the animals were held in metabolic cages. The animals (3 mice per time point) were sacrificed 60 min p.i. The tissue radioactivity was calculated from the corresponding %ID/g and feces were collected and monitored for radioactivity. The concentrations were assayed as described above. The whole brain was dissected and the following regions were delineated: striatum, temporal and frontal cortices, cerebellum, and white matter. Three types of experiments were performed: (i) a baseline study, to obtain 18F-MEM pharmacokinetics in the control state; (ii) blockade experiments by IV pretreatment with memantine hydrochloride (0.5, 1.0, and 2.5 mg/kg respectively, 30 min before PET study) and with (+)-MK-801 maleate (0.5 mg/kg, 5 min prior IV injection of 18F-MEM); (iii) a blockade study by IV co-injection of 0.1 mg/kg haloperidol and 18F-MEM. The aim of the blocking studies being to determine the extent of specific binding of 18F-MEM to the NMDA receptor ion-channel and the sigma opiate binding sites. The measured activity values expressed in Bq/mL were normalized to injected activity per gram body weight and plotted versus time. Finally, venous blood samples (1.0 mL) were collected at 5, 15, 30, 60, and 90 min after tracer administration, and aliquots (0.25 mL) of whole blood and plasma were assayed for radioactivity in a cross-calibrated counter and the values decay corrected.

**RESULTS AND DISCUSSION**

**Patch Clamp**

The most important properties of NMDA receptors and of the associated ion-channels (NMDA channels) have been established by means of electrophysiological studies (1). Thus, the direct effect of channel blockers at the NMDA receptor channel has been clearly demonstrated for memantine by patch clamp experiments (4, 28).

19F-MEM, like memantine (28), phencyclidine (PCP), and MK-801 (11), use dependently blocked current responses of cultured neurons to NMDA. The blockade of whole-cell current responses to NMDA was concentration-dependent (Fig. 2A). The calculated IC50 values using the four-parameter logistic equation (28) were 5.96 ± 0.67 μM (peak: max. response; Hill 1.10) and 6.89 ± 1.58 μM (plateau: response after desensitization; Hill 1.16) (Fig. 2B). The IC50 values of other known uncompetitive antagonists such as memantine, PCP, ketamine, and dextromethorphan were 2.92 ± 0.31 μM, 1.04 ± 0.16 μM, 1.56 ± 0.10 μM, and 6.10 ± 3.60 μM, respectively. It has been demonstrated by autoradiographic and biochemical techniques that compounds that bind to PCP binding site within the NMDA receptor channel (e.g., TCP and memantine) bind to two different sites in rat brain (41, 45). It has also been shown that TCP and its congeners have moderate affinity for the σ-opiate receptor (37). Whether 19F-MEM also binds to the σ-opiate or to other PCP-sensitive receptor sites could not be answered directly by patch clamp experiments. However, provisional unpublished data indicate that 19F-MEM does bind to the sigma sites ([3H]-DTG, IC50 = 2.7 μM, Hill 0.8, Panlabs) with similar potency to the MK-801 site ([3H]-MK-801, Ki = 3.1 ± 0.3 μM, Hill 1.1, Merz).

The blockade of whole-cell current responses to NMDA by 19F-MEM was voltage-dependent (Fig. 2C), at +70 mV, strong...
depolarization: no blockade; at −70 mV, concentration-dependent blockade).

**Radiosynthesis**

1-Amino-3-[18F]fluoromethyl-5-methyl-adamantane (18F-MEM) was prepared by the no-carrier added (n.c.a.) nucleophilic radiofluorination of 1-[N-(tert-butyloxy)carbamoyl]-3-(tosuonesulfonyloxy)methyl-5-methyl-adamantane (1) in DMSO using K18F/kryptofix 2.2.2 as fluorination agent (9), followed by the deprotection of the resulting 18F-BOC-MEM intermediate by addition of aqueous HCl (Fig. 3).

Among the alkylsulfonates, the triflate-leaving group has been reported to react rapidly with activated [18F]fluoride (6, 20). Unfortunately, owing to its high instability, 1-[N-(tert-butyloxy) carbamoyl]-3-(trifluoromethylsulfonyloxy)methyl-5-methyl-adamantane, the triflate analog of compound 1, does not appear to be a suitable precursor for the desired radiofluorination. Compound 1 with the tosylate-leaving group is, however, stable; prolonged storage up to 6 months at 4°C did not result in its decomposition. The radiosynthesis via the tosylate pathway method (12, 13) was therefore undertaken. 18F-MEM was obtained in 22 ± 7% (decay-corrected to EOB) radiochemical yield after reversed-phase HPLC (System A) in a total synthesis time of 90 min. Low radiochemical yields of 18F-MEM (<10%) were obtained using K18F/kryptofix 2.2.2 in acetonitrile or tetra-n-

![FIG. 2. Evidence for open NMDA receptor channel blockade by 19F-MEM.](image1)

![FIG. 3. Radiosynthesis of 18F-MEM.](image2)
butylammonium $^{18}$F fluoride (6). Additionally, TLC (Gelman ITLC-SG, CH$_2$Cl$_2$/MeOH 70:30) and analytical HPLC revealed a virtually 99% radiochemical purity.

### Biodistribution Studies in Mice

The distribution of radioactivity in the various tissues of female ICR mice following IV administration of $^{18}$F-MEM is summarized in Table 1. The negligible activity in the bone indicates that no significant in vivo defluorination of the tracer had occurred. The $^{18}$F-MEM showed a relatively fast blood clearance. Significant uptake was initially observed in the lung, kidney, liver, and heart, but decreased gradually with time. The high accumulation of activity in these organs could be explained in part by the high lipophilicity of $^{18}$F-MEM (logP = 2.6) and by the good perfusion of these organs. Also, $^{18}$F-MEM showed high brain uptake (up to 3.6% ID/g at 60 min p.i.), indicative of good blood-brain barrier penetration, with increasing brain/blood ratios up to 9.3, 120 min p.i.

In a regional dissection study, high radioactivity concentrations were observed in the cerebellum, frontal cortex, and hippocampus. Within 120 min, about 15% of the injected activity was found in collected urine, whereas only 0.04% of the injected dose was eliminated by hepatobiliary excretion. Co-injection of $^{18}$F-MEM with (+)-MK-801 (0.10 mg/kg) reduced the initial $^{18}$F-MEM uptake by 32%, 26%, 25%, and 15% 60 min p.i. in the hippocampus, frontal cortex, occipital cortex, and cerebellum, respectively (Fig. 4). In addition, the blockade by MK-801 led to an increase of the renal excretion of radioactivity. More than 20% of the injected activity was found in urine (data not shown).

### TABLE 1. Organ Distribution of $^{18}$F-MEM in ICR Mice and the Corresponding Brain/Blood Ratios

<table>
<thead>
<tr>
<th>% ID/g organ (median, n = 3)</th>
<th>5 min</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
<th>240 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>1.04 ± 0.16</td>
<td>0.84 ± 0.06</td>
<td>0.74 ± 0.16</td>
<td>0.58 ± 0.20</td>
<td>0.11 ± 0.01</td>
<td>0.10 ± 0.02</td>
</tr>
<tr>
<td>Lung</td>
<td>15.10 ± 1.32</td>
<td>12.96 ± 1.30</td>
<td>11.86 ± 1.62</td>
<td>7.38 ± 2.22</td>
<td>1.60 ± 0.41</td>
<td>0.74 ± 0.27</td>
</tr>
<tr>
<td>Kidney</td>
<td>17.58 ± 0.70</td>
<td>13.00 ± 2.67</td>
<td>9.44 ± 2.30</td>
<td>5.10 ± 1.11</td>
<td>2.02 ± 0.63</td>
<td>0.99 ± 0.24</td>
</tr>
<tr>
<td>Heart</td>
<td>6.36 ± 0.92</td>
<td>3.44 ± 0.46</td>
<td>2.42 ± 0.73</td>
<td>1.62 ± 0.21</td>
<td>0.24 ± 0.05</td>
<td>0.22 ± 0.03</td>
</tr>
<tr>
<td>Liver</td>
<td>5.23 ± 0.15</td>
<td>4.53 ± 1.27</td>
<td>5.91 ± 0.60</td>
<td>3.97 ± 0.71</td>
<td>1.07 ± 0.25</td>
<td>0.54 ± 0.13</td>
</tr>
<tr>
<td>Muscle</td>
<td>2.20 ± 0.37</td>
<td>2.00 ± 0.28</td>
<td>1.80 ± 0.37</td>
<td>1.40 ± 0.31</td>
<td>0.30 ± 0.04</td>
<td>0.20 ± 0.04</td>
</tr>
<tr>
<td>Bone</td>
<td>0.92 ± 0.20</td>
<td>0.73 ± 0.31</td>
<td>0.80 ± 0.32</td>
<td>0.60 ± 0.14</td>
<td>0.47 ± 0.06</td>
<td>0.21 ± 0.05</td>
</tr>
<tr>
<td>Bladder/urine</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>13.13 ± 3.8</td>
<td>14.90 ± 2.4</td>
<td>20.60 ± 3.6</td>
</tr>
<tr>
<td>Feces</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>0.08 ± 0.01</td>
<td>0.04 ± 0.01</td>
<td>0.06 ± 0.01</td>
</tr>
<tr>
<td>Brain</td>
<td>2.50 ± 0.13</td>
<td>2.96 ± 0.25</td>
<td>3.76 ± 0.45</td>
<td>3.67 ± 0.21</td>
<td>1.02 ± 0.14</td>
<td>0.58 ± 0.01</td>
</tr>
<tr>
<td>Brain/blood$^a$</td>
<td>2.40 ± 0.30</td>
<td>3.52 ± 0.31</td>
<td>5.10 ± 0.51</td>
<td>6.33 ± 1.35</td>
<td>9.27 ± 0.27</td>
<td>5.80 ± 0.42</td>
</tr>
</tbody>
</table>

n.d., Not determined.
$^a$ % ID/g organ/% ID/g blood.

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FIG. 4. The % ID/g of $^{18}$F-MEM in organ tissues of mice in control and after co-injection with 0.10 mg/kg of (+)-MK-801, 60 min p.i.
FIG. 5. Pharmacokinetics of $^{18}$F-MEM obtained by PET studies in the cerebellum (A, B), striatum (C, D), the frontal cortex (E, F), and the temporal cortex (G, H) in a rhesus monkey under baseline conditions and blockade studies with memantine hydrochloride (left column), (+)-MK-801 maleate, and haloperidol (right column).

$\Delta$ Baseline; □ 1.0mg/kg memantine; ◆ 0.5mg/kg memantine; ● 2.5mg/kg memantine; ★ 0.5mg/kg (+)-MK-801
O 0.1mg/kg haloperidol
**PET Studies**

The radioactivity time curve obtained from the baseline scan shows high brain uptake and low clearance of the radiotracer from the examined brain regions, with a plateau from 35 min p.i. onwards (Fig. 5). The radiotracer cleared rapidly from the blood. The blood uptake 15 min p.i. decreased by 94 ± 2% compared to the activity concentration measured in the collected blood 2 min following the IV injection of 18F-MEM. Drug treatment did not change the value of the plasma uptake counted under baseline conditions. Metabolic studies indicated that more than 97% of radioactivity in monkey plasma was parent compound. The good uptake and retention in the frontal and temporal cortices and in the striatal area are consistent with the reported high concentration of NMDA receptors in these brain areas (23, 31). The hippocampus contains the largest number of PCP binding sites (23, 45). However, owing to the resolution of the PET tomograph, delineation of the hippocampus was not possible. Preinjection with therapeutic doses of memantine (0.50 and 1 mg/kg) 30 min prior to IV administration of 18F-MEM led to a reduction of activity uptake up to 32% from 60 min p.i. onwards in the examined brain regions, including the striatum, frontal and temporal cortices, and the cerebellum (Fig. 5A, C, E, G). In contrast, pretreatment of the monkey with 2.5 mg/kg of memantine caused an increase in the brain uptake of the radiotracer. The reason for this is unclear. However, the inhibition of saturable but not necessarily specific binding sites in the periphery and/or the depolarization of the ion-channels, which occurs at high concentrations of memantine (42), need to be considered as possible factors.

The highest uptake of radioactivity in rhesus monkey brain occurred in the cerebellum. This persistent high-activity concentration observed in the cerebellum is in contrast to the regional radioactivity distribution obtained in the mouse brain as well as the suggested regional distribution of the PCP binding sites (23, 45). Conversely, studies using uncompetitive NMDA radioligands such as [18F]methyl-MK-801 (2) and S-[11C]ketamine (17) have also documented high uptake of radioactivity in the cerebellum of monkeys. To our knowledge no species differences in the concentration of the NMDA receptors in the mammalian brain have been reported.

Biochemical binding studies and autoradiographic analysis using [3H]TCP indicated the presence of two different PCP sites with different affinities in both the human brain and the rat brain (41, 45). It has been suggested that PCP and most compounds that interact with the PCP-sensitive sites within the NMDA receptor complex also cross-react with σ-opiate receptors located mostly in the cerebellum (31, 37, 38, 47). One notable exception is the anticonvulsant (+)-MK-801, which is also the most potent uncompetitive NMDA receptor ligand known to date (8, 43, 44). A blockade study with (+)-MK-801 was therefore undertaken. The binding of 18F-MEM decreased also in all the brain regions in the same range after pretreatment of the monkey with (+)-MK-801 maleate in a pharmacologically active dose (0.5 mg/kg) (18), suggesting competition for the same binding sites (Fig. 5B, D, F, H).

In a preliminary experiment in monkey we examined the extent of specific binding of 18F-MEM to the sigma receptors using haloperidol, a compound with high affinity for the dopamine D2 receptor and the sigma binding sites. We observed a decrease in uptake, which was similar to that observed using (+)-MK-801 as a blocking agent (Fig. 5B, D, F, H). The reduction in the uptake of radioactivity was, however, more pronounced in the cerebellum, a region known to contain high concentration of sigma sites. This suggests that binding was also occurring to the sigma recognition sites.

More detailed studies including blockade experiments and the use of different doses of various NMDA and sigma receptor antagonists are therefore currently ongoing and will be reported elsewhere.

**CONCLUSION**

The new [18F]fluorinated memantine derivative, 1-amino-3-[18F]fluoromethyl-5-methyl-adamantane (18F-MEM), is a moderate NMDA receptor channel blocker as attested by patch clamp recording of whole-cell current responses of hippocampal cells to NMDA using the nonradioactive analog 19F-MEM.

In our study of 18F-MEM pharmacokinetics in mice and in one monkey, relatively high uptake and retention levels of the radiotracer in the brain were observed. Approximately 75% of the total uptake in mouse brain was found in the hippocampus and in the cerebral cortices, regions known to contain the highest densities of the NMDA receptors. The specificity of the 18F-MEM binding in mouse brain was attested by the reduction of the activity concentration after co-injection of 18F-MEM with (+)-MK-801. Binding of 18F-MEM to the PCP site of the NMDA receptor channel was also confirmed by the reduction of radioactivity concentrations in the cortical areas, striatum, and in the cerebellum after pretreatment of the monkey with therapeutic doses of memantine and a pharmacological dose of (+)-MK-801. The binding of 18F-MEM to the sigma recognition site has also been demonstrated in a preliminary experiment.

However, a serious problem with uncompetitive NMDA receptor antagonists such as memantine and (+)-MK-801 remains to be the dose-dependent blockade of the “open-state” of the ion-channel. Because depolarization of the ion-channel, which occurs above certain concentrations of the channel-blocker, may lead to an enhancement of the radiotracer uptake, the choice of an optimal dosage regimen of these drugs is crucial. Moreover, it seems likely that normal brain physiological variations, resulting in alterations in availability of NMDA binding sites, may also influence uptake of tracers like 18F-MEM.

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**References**


