

Alterations in Brain Distribution of [11C]Methamphetamine in Methamphetamine Sensitized Dog

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Introduction

The repeated administration of methamphetamine (MAP) to experimental animals produces progressive and enduring augmentation of hyper locomotion and stereotyped behavior^{1,2}). This phenomenon is termed behavioral sensitization or reverse tolerance. Since these sensitized animals have been considered a model of MAP psychosis similar to paranoid schizophrenia³), knowledge of the neuronal mechanisms underlying sensitization may provide information on the neurochemical basis of MAP psychosis. We previously reported the significant increase in [¹¹C]MAP radioactivities in the striatum and hypothalamus of MAP sensitized mice⁴) and [¹⁴C]MAP radioactivities in the striatum and the limbic forebrain area of the MAP sensitized rats⁵). Furthermore, *in vivo* measurement of these alterations in brain kinetics of MAP using positron emission tomography (PET) is of interest for elucidating biochemical mechanisms of behavioral sensitization.

In this report, we newly produced a MAP sensitized dog by repeated MAP treatment and showed the alteration in brain distribution of [¹¹C]MAP in a MAP sensitized dog using PET.

Materials and Methods

CHEMICALS AND SYNTHESIS OF [¹¹C]MAP

Anhydrous *N,N*-dimethyl formamide (DMF) was purchased from Amersham Japan Co. Ltd. Other chemicals used were of reagent grade purchased from Wako Pure Chemical Co. Ltd, Osaka, Japan.

[¹¹C]MAP was synthesized as our previous report⁶).

ANIMAL AND DRUG SCHEDULE

A 7-year-old male beagle dog weighing 12.5 kg was used for this study. In the sensitization study, the dog was given daily injection of MAP hydrochloride for 14 days [s.c.

injection (1 mg/kg) for the first 7 days and s.c. injection (1.5 mg/kg) for 7 days] and was then free from MAP for 7 successive days. The locomotion and behavior of the model animal was monitored by video-camera and the change was clarified. This protocol was approved by the Tohoku University animal care committee.

PET STUDY

The dog was initially anesthetized with ketamine (10 mg/kg, s.c.) and maintained under pentobarbital (25 mg/kg, i.v.) anesthesia. Catheters were inserted in the arterial vein for arterial blood sampling and in the venous vein of the fore leg for administration of [¹¹C]MAP. Vital signs (blood pressure, pulse rate, blood pH, O₂ tension, CO₂ tension), monitored and recorded throughout the PET study, were kept within a physiological range. After an intravenous injection of [¹¹C]MAP (6.7-11.3 mCi) into the animal, dynamic scan was carried out parallel to the orbitomeatal (OM) line using PET scanner (PT931, CIT Inc, Noxville USA at the Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan) for 90 min. The following regions of interest were selected: parietal cortex, occipital cortex, temporal cortex, frontal cortex, cerebellum. Tissue concentration of [¹¹C]MAP was measured using a ROI program.

DOG PLASMA METABOLITE ANALYSIS

Arterial blood samples were collected in heparinized tubes at 5, 10, 20, 40 and 50 min after injection of [¹¹C]MAP and centrifuged (3000 rpm×3 min). Plasma samples (0.5 ml) were added to 1 ml of methanol and the mixture sonicated and centrifuged (15,000 rpm×45 sec). The supernatant with the addition of unlabeled MAP was injected into analytical HPLC system. The [¹¹C]MAP fraction were collected and counted in an automated NaI counter. The percentage of [¹¹C]MAP activity in plasma activity was calculated.

Results

BEHAVIORAL SENSITIZATION

In dog, an acute injection of MAP (1mg/kg) initially induced the rotational locomoter activity and stereotyped behavior (looking at the ceiling). The repeated administration of MAP produced an increase in the incidence of the stereotyped behavior and a concomitant decrease in that of the locomoter activity. Furthermore, we observed the decreased latency to the onset of stereotyped behavior following injection of MAP. At 7 days after the second PET study, we tried a challenge test of MAP. A challenge dose of MAP (1 mg/kg) reproduced the hyperlocomotion and stereotyped behavior. The behavioral changes produced by repeated administration of MAP are summarized in Figure 1.

PET STUDY

Figure 2 shows PET images of [¹¹C]MAP of the normal and the sensitized dog brains at 10-20 min after administration. The accumulation of [¹¹C]MAP was more clearly visible in the sensitization model than that in the normal condition. Figure 3 shows the time course of tissue distribution of [¹¹C]MAP in the normal and the sensitized dog brains. [¹¹C]MAP rapidly reached the brain and the maximal uptake was observed at 5-15 min after injection. No significant differences of distribution were noted in the five regions. The maximal level of accumulation of [¹¹C]MAP in the sensitized dog brain was 1.4 times higher than that in the control dog brain.

DOG PLASMA METABOLITE ANALYSIS

We analyzed the metabolites of [¹¹C]MAP in the plasma (Figure 4). The clearance of [¹¹C]MAP from the plasma was rapid. At 10 min after the injection, approximately 40% of the total [¹¹C] activity was in the form of [¹¹C]MAP. No difference was found in metabolism of MAP between the MAP sensitized dog and the control dog.

Discussion

In most studies of behavioral sensitization, rats or mice were used as model animals. But it is necessary for PET study to use more large animals. So, we newly produced a MAP sensitized dog by repeated MAP treatment, and confirmed the enduring behavioral sensitization by the challenge test after the second PET study. Wallach and Gershon reported sensitization to amphetamine in dog⁷⁾, but they only mentioned a decreased latency to onset of the stereotyped behavior in their paper. We observed the behavioral change produced by repeated administration of MAP in detail and clarified the sensitizing effects of MAP on the dog behavior (Figure 1).

[¹¹C]MAP was distributed uniformly in the five regions of dog brain (Figure 3). Sakai *et al.* reported that the major metabolite of MAP in blood after i.v. administration was *p*-hydroxyl-MAP in rat, but the phenolic metabolites were not detected in brain because these were unable to pass through the blood-brain barrier⁸⁾. Only MAP and amphetamine were detected in brain. Consequently, we think the activity of each region reflects the distribution of MAP. This result about uniform distribution is similar to a PET study in monkey⁹⁾. The clearance of [¹¹C]MAP in dog brain, however, is a little faster than that of monkey. They reported 50% of radioactivity remained as [¹¹C]MAP at 60 min after the injection in arterial monkey plasma. In the other hand, approximately 20% of arterial plasma radioactivity was in the form of [¹¹C]MAP at 50 min after the injection in dog (Figure 4). This species difference of MAP metabolism may cause the difference of biological half-life of MAP between dog and monkey brain.

We visualized a significant increase of [¹¹C]MAP in whole brain of MAP sensitized dog (Figure 2). This significant increase of [¹¹C]MAP uptake into the sensitized dog brain

can't be due to the decreased metabolism of MAP in the sensitized dog (Figure 4). Similar results about increased uptake have been obtained using mice and rats in our previous studies^{4,5}). These findings of a lasting increase in [¹¹C]MAP radioactivity in the brain of sensitized animals indicate that subchronic MAP administration causes some functional change in uptake site of MAP.

MAP sensitized animals are widely used as experimental models of stimulant-induced psychosis. The present study suggests that this alteration of [¹¹C]MAP kinetics can be utilized as a marker of MAP abuse in man.

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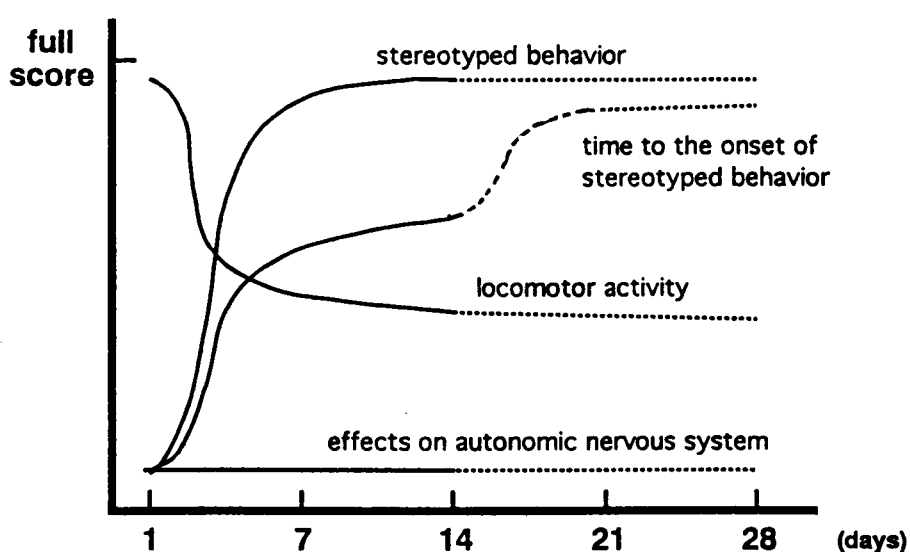


Fig. 1 The effects of repeated MAP administration on the dog behavior.

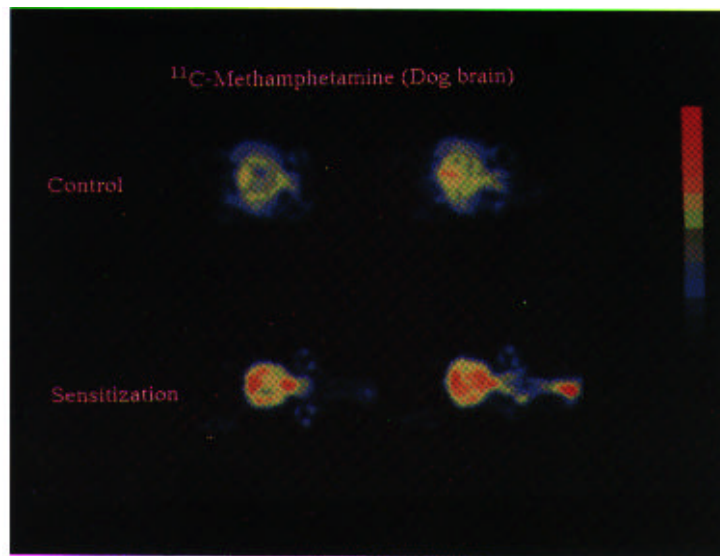


Fig. 2 [^{11}C]MAP PET images in control and sensitized dog brain at 10-20 min after the injection.

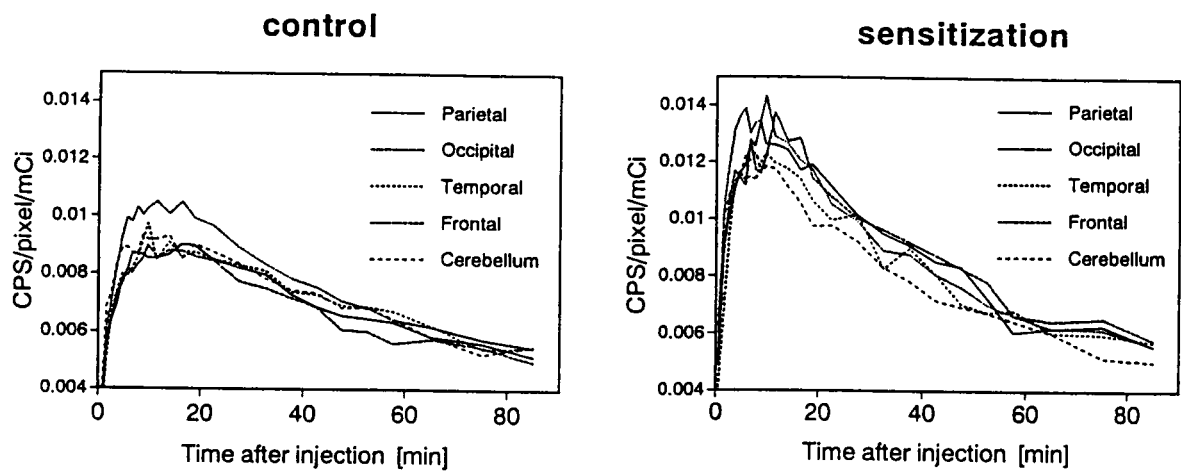


Fig. 3 Time course of tissue distribution of [^{11}C]MAP in control and sensitized dog brain.

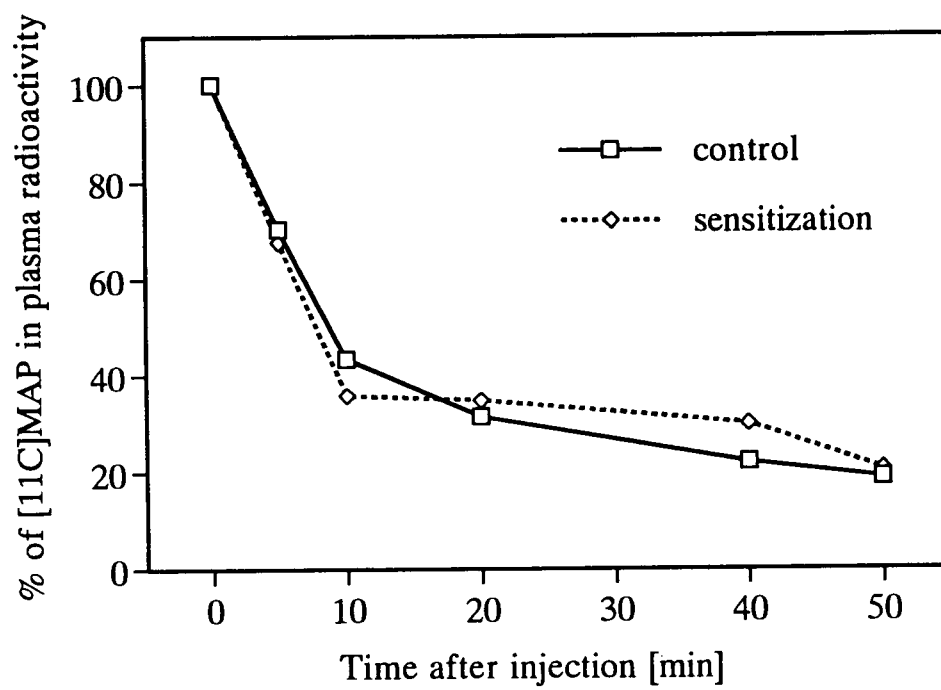


Fig. 4 HPLC analysis of $[^{11}\text{C}]\text{MAP}$ in plasma. The percent of $[^{11}\text{C}]\text{MAP}$ activity in plasma activity is indicated.