Effects of Haloperidol and Cocaine on Pharmacokinetics of [11C]Methamphetamine in Methamphetamine Sensitized Dog

III. 1. Effects of Haloperidol and Cocaine on Pharmacokinetics of [^{11}C]Methamphetamine in Methamphetamine Sensitized Dog

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Introduction

The subchronic administration of methamphetamine (MAP) or amphetamine (AMP) to experimental animals produces progressive and enduring augmentation of hyper locomotion and stereotyped behavior[1,2]. The precise neurochemical mechanism underlying this phenomenon, referred to as behavioral sensitization or reverse tolerance, is not completely understood. Although various mechanisms have been proposed to explain the expression of MAP or AMP-induced behavioral sensitization, little attention has been paid to the pharmacokinetic change. We have previously studied the pharmacokinetic change of MAP in the brain following repeated MAP administration and reported the significant increase in [^{11}C]MAP uptake in the MAP-sensitized mouse brain[3] and [^{14}C]MAP uptake in the MAP-sensitized rat brain[4]. In addition, we reported that the maximum accumulation level of [^{11}C]MAP in the MAP-sensitized dog brain was 1.4 times higher than that in the control[5]. These observations raise the possibility that increased brain MAP levels mediate the development of MAP-induced behavioral sensitization.

In the present study, to investigate the relation between the MAP-induced behavioral sensitization and the pharmacokinetics of MAP, we examined the pretreatment effects of haloperidol and cocaine on brain distribution of [^{11}C]MAP in MAP sensitized dog.

Materials and Methods

SYNTHESIS OF [^{11}C]MAP

The synthesis of [^{11}C]MAP was carried out by modifying the on-line [^{11}C]methylation method[6] as previously report[5]. The mass spectra, HPLC and TLC of this material were identical to authentic material. The specific activity was about 48.1 GBq/μmol at the time of supply. The radiochemical purity of [^{11}C]MAP was determined to be more than 99 %.

POSITRON EMISSION TOMOGRAPHY (PET) STUDY IN A DOG

The MAP-sensitized dog, used in our previous study[5], was initially anesthetized with ketamine (10 mg/kg, s.c.) and maintained under pentobarbital (25 mg/kg, i.v.) anesthesia. Catheters were inserted into the arterial vein for arterial blood sampling and into the venous vein of the foreleg for administration of [^{11}C]MAP. Vital signs (blood pressure, pulse rate, blood pH, pO2, pCO2 and body temperature), monitored and recorded throughout the PET study, were kept within a physiological range. In the haloperidol pretreatment study, haloperidol (1 mg/kg) was intramuscularly administrated at 60 min before injection of [^{11}C]MAP. In the cocaine pretreatment study, cocaine hydrochloride (5 mg/kg) was intravenously administrated three times at 15 min before and 15 and 45 min after injection of [^{11}C]MAP. After an intravenous injection of [^{11}C]MAP (248-418 MBq) into the animal, dynamic scan was carried out parallel to the orbitomeatal (OM) line using PET scanner (PT931, CIT Inc, Noxvile USA at the Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan) for 90 min. The following regions of interest were selected according to our previous report[7] : parietal cortex, occipital cortex, temporal cortex, frontal cortex and cerebellum. Tissue concentration of [^{11}C]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 the injection of [^{11}C]MAP and centrifuged (3000 rpm × 3 min). Plasma samples (0.5 ml) were added to 1 ml of methanol, and the mixture was sonicated and centrifuged (15,000 rpm × 45 sec). The supernatant with the addition of unlabeled MAP was injected into the analytical HPLC system. The [^{11}C]MAP fraction were collected and counted by an automated NaI counter. The percentage of [^{11}C]MAP activity in plasma activity was calculated.

QUANTITATION OF HALOPERIDOL AND COCAINE IN DOG PLASMA

Plasma concentration of haloperidol was determined using a MARKIT-M® Haloperidol Kit (Dainippon Pharmaceutical Co. Ltd, Osaka, Japan).

Plasma concentration of cocaine was determined by modifying the solid-phase extraction and the GC/MS quantitation method previously described by Abuseda *et al.*[8].

Results

PET STUDY IN A DOG

Fig. 1 shows the effects of haloperidol and cocaine pretreatment on the time course of regional distribution of [^{11}C]MAP in a sensitized dog. [^{11}C]MAP showed a widespread distribution throughout the brain. Under the sensitized condition, the maximal level of

accumulation of [^{11}C]MAP was 1.4 times higher than that in the control (Fig. 1A). This phenomenon is prevented by pretreatment of haloperidol (Fig. 1B) and cocaine (Fig. 1C). We found very little difference of the regional distribution of [^{11}C]MAP between the three PET studies, but [^{11}C]MAP clearance from the brain in the two pretreatment studies was a little slower than that in the non-pretreatment study.

DOG PLASMA METABOLITE ANALYSIS

The results of metabolite analysis in the three PET studies are depicted in Fig. 2. At 50 min after the injection, only 20% of MAP was in the unmetabolic form. In the comparison of each PET study, slight but not significant differences were found in metabolism of MAP.

PLASMA CONCENTRATION OF HALOPERIDOL AND COCAINE

The haloperidol plasma level profile during the haloperidol pretreatment PET study is shown in Fig 3A. Blood clearance of haloperidol was linear during the PET study, ranging from 60 to 150 min after the intramuscular administration, and the biological half-life was approximately 180 min. The haloperidol plasma concentration during PET study ranged from 37 to 50 ng/ml.

The cocaine plasma level profile during the cocaine pretreatment PET study is shown in Fig. 3B. Although the blood clearance of cocaine was rapid, the minimal cocaine plasma level remained at 400 ng/ml.

Discussion

In order to investigate the pharmacokinetic change of [^{11}C]MAP in MAP sensitized animals using PET, we created a MAP sensitized dog by repeated MAP administration[5]. In the present PET study using this sensitized dog model, we performed a challenge test applying MAP 7 days before each PET study. The challenge injection of MAP (1 mg/kg) after a 90 days withdrawal period reproduced the hyperlocomotion and stereotyped behavior. This result suggests that the MAP induced behavioral sensitization may last for a long period of abstinence after subchronic MAP administration.

We measured plasma concentration of haloperidol and cocaine to evaluate their pretreatment effects during the PET study. As reviewed by Dahl[9], therapeutic plasma haloperidol concentrations in the range of 5-20 ng/ml have been reported by some investigators, but others have found no such relationship. A generally valid therapeutic plasma concentration range for haloperidol has not yet been defined. However, we considered that the haloperidol plasma level in this study was sufficient for antidopaminergic activity in the brain. In a pharmacokinetic study of cocaine in humans[10], the terminal plasma half-life after intravenous administration of cocaine was relatively short ranging from 31 to 63 min. Since we also found that the clearance of cocaine from the brain was rapid[11], cocaine

was injected three times at 30 min intervals. In this PET study, cocaine plasma concentrations declined exponentially after intravenous injection, but the minimal cocaine plasma level was 400 ng/ml, which was also sufficient to induce a pharmacological effect.

One factor that changes the pharmacokinetics of MAP is the alteration in the metabolism of MAP. Metabolite analysis revealed that the pretreatment of haloperidol and cocaine do not influence the rate of MAP metabolism. This result leads to the conclusion that the pharmacokinetic changes were not due to the changes in the rate of MAP metabolism.

In behavioral studies, dopamine antagonists prevent the development of behavioral sensitization induced by repeated MAP administration[12]. This evidence indicates that stimulation of dopamine receptor by MAP-released dopamine may be necessary for the induction of behavioral sensitization. The present study demonstrated that pretreatment of haloperidol prevents the elevation of brain MAP levels following repeated MAP administration. This observation raises the possibility that dopamine antagonists also influence the pharmacokinetics of MAP and prevent the development of behavioral sensitization.

MAP increases synaptic dopamine primarily by stimulating presynaptic release rather than by blocking the dopamine reuptake, as is the case with cocaine. The molecular mechanism of dopamine efflux of MAP has been attributed to an exchange-diffusion process via the dopamine transporter[13]. Since cocaine binds to dopamine transporter and inhibits the uptake processes for MAP, the result of cocaine pretreatment study apparently suggests that repeated MAP administration causes an increased MAP uptake into the dopaminergic nerve terminal via dopamine transporter. However, cocaine prevented the enhancement of the MAP level in the whole brain, indicating the mechanism of this phenomenon occurs the blood and brain compartments. Although we can not explain this mechanism, it is interesting that cocaine produced a cross-behavioral sensitization with MAP and affected the pharmacokinetics of MAP in MAP-sensitized animal.

While it is unlikely that the elevation of MAP level at the dopamine nerve terminal alone can account for behavioral sensitization, it is possible that the enhanced MAP level may affect its development or expression. Further studies on the pharmacokinetic change of MAP in MAP sensitized animals are presently in progress using rhesus monkeys.

Acknowledgment

We are grateful to the PET staffs of the Cyclotron and Radioisotope Center, Tohoku University, for their cooperation. A part of this research was supported by a scientific research fund from the Ministry of welfare of the Japanese Government.

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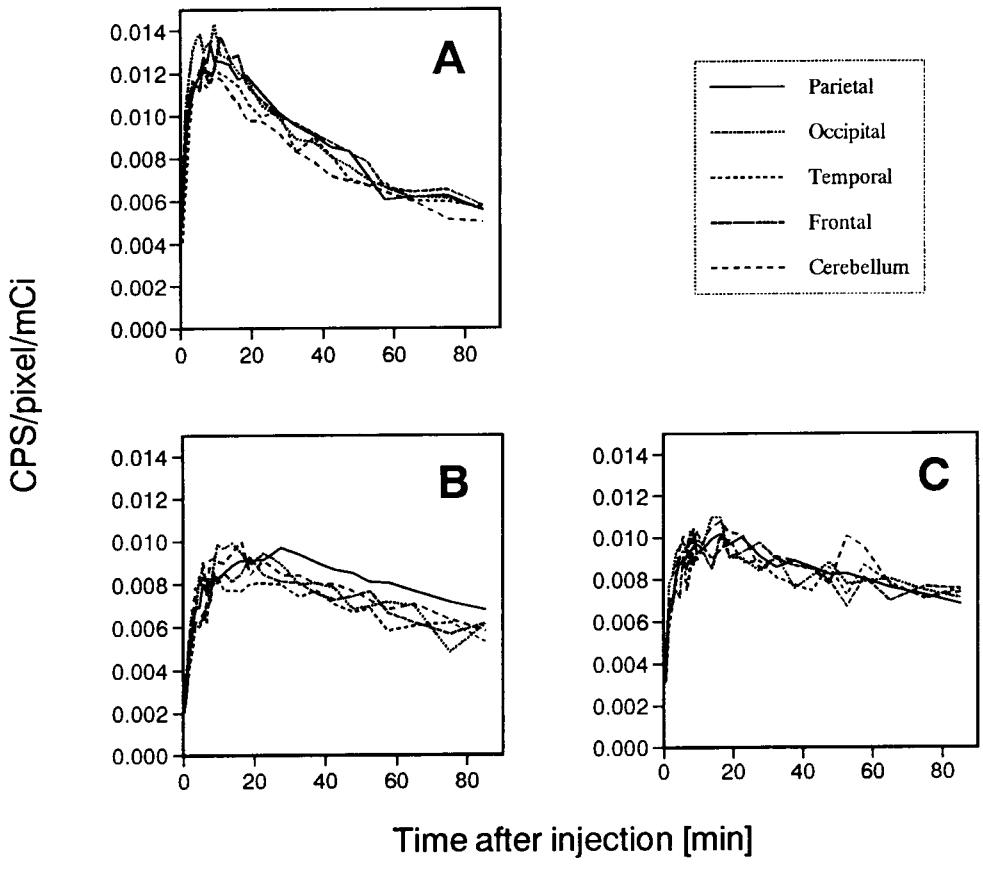

Fig. 1 Time courses of regional distribution of [^{11}C]methamphetamine in a sensitized dog brain. (A) non pretreatment (B) haloperidol pretreatment (C) cocaine pretreatment.

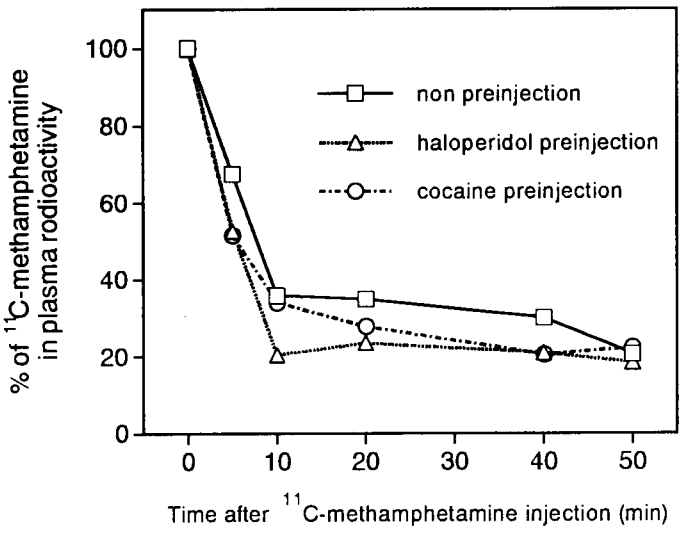

Fig. 2 HPLC analysis of ^{11}C activity in MAP-sensitized dog plasma. The percent of [^{11}C]MAP activity in plasma activity is indicated.

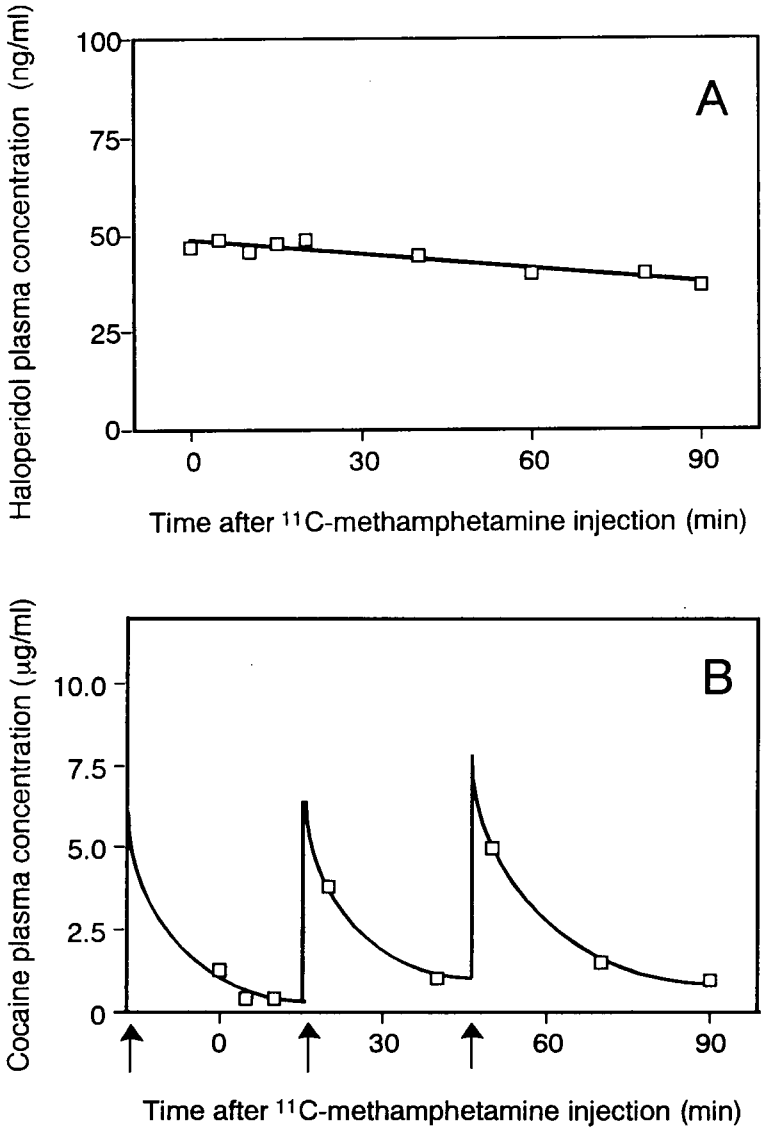

Fig. 3 Plasma concentration of haloperidol (A) and cocaine (B) in MAP-sensitized dog.