Alterations in Biodistribution of [11C]Cocaine in Cocaine and Methamphetamine sensitization Mice

III. 3. Alterations in Biodistribution of [^{11}C]Cocaine in Cocaine and Methamphetamine sensitization Mice

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Introduction

The repeated administration of cocaine or 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. It is reported that animals pretreated with MAP exhibit behavioral augmentation in response to a challenge of cocaine (cross-sensitization)[3]. Conversely, it is also documented that a challenge of MAP produces the cross-sensitization in animals pretreated with cocaine[4]. Although enhanced synaptic transmission of dopamine (DA) neurons has been implicated in such behavioral sensitization, the precise mechanism of this long-term increase in dopamine releasability remains unknown.

In the present study, we designed two experiments in order to investigate the mechanism of the cross-behavioral sensitization between cocaine and MAP. In the first experiment (Exp. 1), we investigated the alterations in the biodistributions of [^{11}C]cocaine in cocaine-sensitization mice. In the second experiment (Exp. 2), we examined the biodistribution of [^{11}C]cocaine in MAP-sensitization mice.

Materials and Methods

CHEMICALS

d-Methamphetamine hydrochloride and cocaine hydrochloride were kindly supplied by Eishin Co. Ltd., Sendai, Japan. *dℓ*-Amphetamine[5] and Norcocaine[6] were prepared in our laboratory. Other chemicals used were reagent grade purchased from Wako Pure Chemical Co. Ltd., Osaka, Japan.

ANIMALS

In all experiments male ddY mice approximately 7-8 weeks old weighing 30-35 g each were used. These mice were maintained under a 12 hr light-dark cycle and were provided with free access of food and water.

PREPARATION OF [^{11}C]COCAINE

[^{11}C]Cocaine was prepared by the direct methylation of norcocaine using [^{11}C]methyl iodide described previously[7].

ANIMAL EXPERIMENTS

The effect of repeated treatment and termination of nonradioactive cocaine (Exp. 1) or MAP (Exp. 2) on the uptake of [^{11}C]cocaine were investigated. In the sensitization model, the treatment of nonlabeled MAP (2 mg/kg) was continued for 7 days by intraperitoneal (*i.p.*) injection and then the mice were free from MAP for 7 successive days. Cocaine (10 mg/kg) was injected for 14 days and abstained for 7 successive days. In the control, saline was injected for 7 days (for MAP) or 14 days (for cocaine) instead of the administration of nonlabeled drug.

[^{11}C]Cocaine hydrochloride was injected into the tail vein and the mice were decapitated at 1, 5, 10, 15 and 30 min after the injection. The organs (brain, liver, kidney, lung, heart, spleen, stomach, small intestine, muscle) and the eight brain areas (striatum, frontoparietal cortex, posterior cortex, hippocampus, hypothalamus, midbrain, cerebellum, medulla oblongata)[8] were dissected and weighed. The radioactivities of these regions were counted by an automated NaI counter. The distribution of carbon-11 activity was expressed as the differential absorption ratio (DAR).

Results

EXPERIMENT 1

The distribution of [^{11}C]cocaine in various organs of cocaine sensitization mice are shown in Fig. 1. In the saline pretreated control groups, the accumulations of [^{11}C]cocaine were high in the liver and small intestine. The DAR of [^{11}C]cocaine in the liver, kidney and brain of the cocaine sensitization mice was higher than that of the saline-pretreated controls at 10 min after the injection. The clearance of [^{11}C]cocaine activity in these organs was delayed. Fig. 2. shows the regional distribution of [^{11}C]cocaine in the cocaine sensitization mice brain. There were no significant differences of the radioactivity in the regions, but the frontoparietal cortex showed higher values at 5 min after the injection. Compared with the control groups, the peaks of the [^{11}C] cocaine uptake were delayed from 5 to 15 min after the injection in most regions in the sensitization model.

EXPERIMENT 2

No difference was found in organ distribution of [^{11}C]cocaine between the MAP sensitization mice and the control mice at various times after the injection (Fig. 3). There were no differences in the regional distributions of [^{11}C]cocaine between the brain of the MAP sensitization mice and the control mice (Fig. 4).

Discussions

Repeated administrations of cocaine or MAP to animals results in behavioral sensitization. Many studies strongly suggest that such behavioral sensitization is due to an enhanced DA release following a challenge of cocaine or MAP. Kanzaki *et al* . suggest that subchronic MAP treatment changes some functional change in the DA transporting systems that are involved in DA release and uptake on presynaptic DA terminals[9]. We reported previously a significant increase in [^{11}C]MAP radioactivities in the striatum and hypothalamus in MAP pretreated mice[10]. This variation may cause an increase in the uptake of MAP and lead to an increase in the DA release at the synaptic cleft. In the present study, we demonstrate that, in most brain regions of the cocaine-sensitized mice, the peaks of the [^{11}C]cocaine uptake were delayed from 5 to 15 min after *i.v.* injection. The main central action of cocaine on the DA neurons is thought to be the inhibition of the DA uptake. In addition, it has been shown that [^{3}H]cocaine preferentially labels sites on the DA nerve terminals in the striatum and [^{3}H]cocaine binding sites are functionally linked to the DA uptake sites[11,12] . These finding indicate that subchronic cocaine administration causes some functional changes in the cocaine binding site linked to the DA transporting system.

On the other hand, there was no significant differences between the MAP sensitization group and the control group in biodistribution of [^{11}C]cocaine in the present study. It is conceivable that the DA uptake sites might be altered progressively by subchronic MAP administration and critical changes might not occur on the cocaine binding site. Further studies are needed on behavioral sensitization following subchronic administration of either cocaine or MAP.

Acknowledgments

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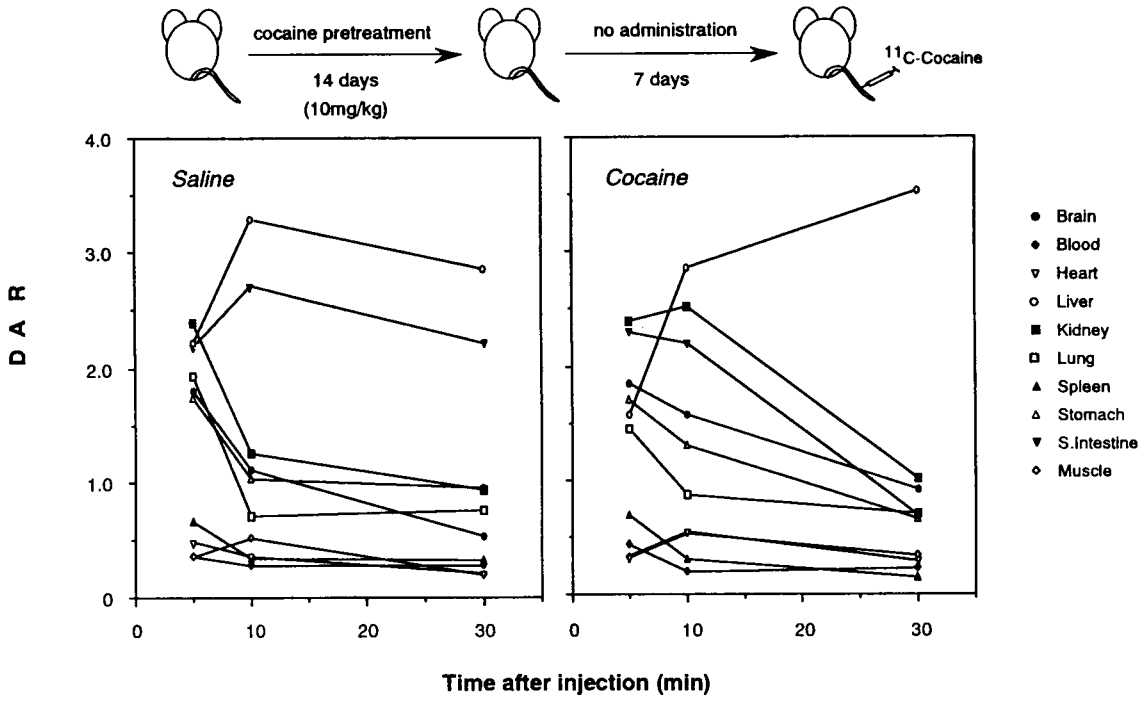

Fig. 1. Tissue distribution of [^{11}C]cocaine in the cocaine-sensitization mice

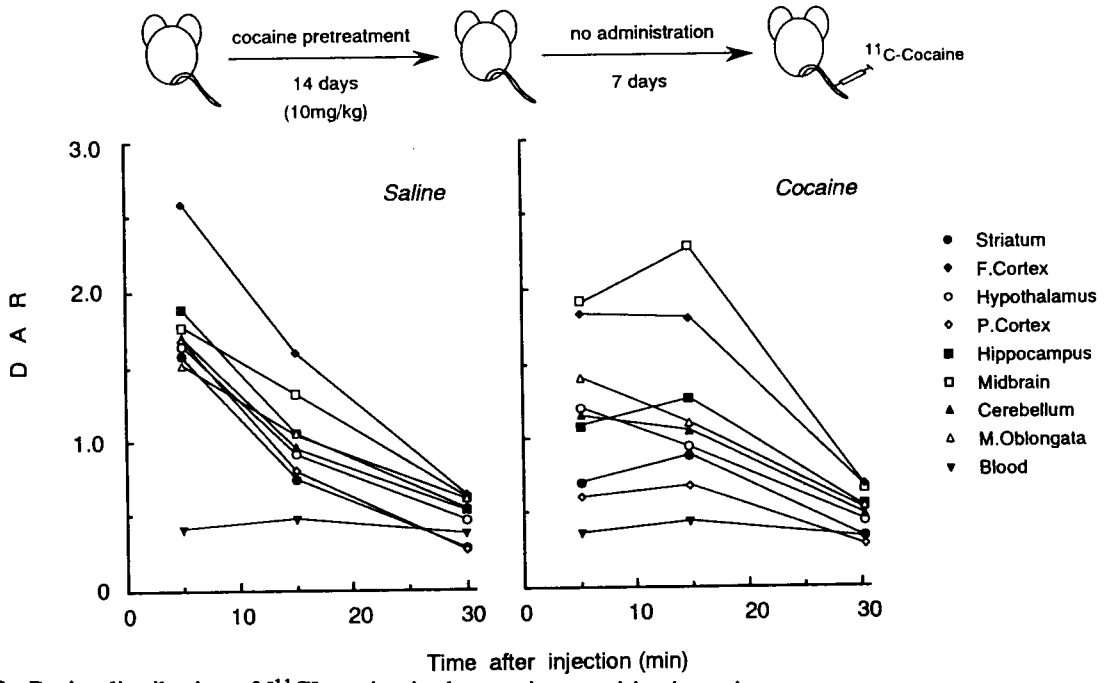

Fig. 2. Brain distribution of [^{11}C]cocaine in the cocaine-sensitization mice

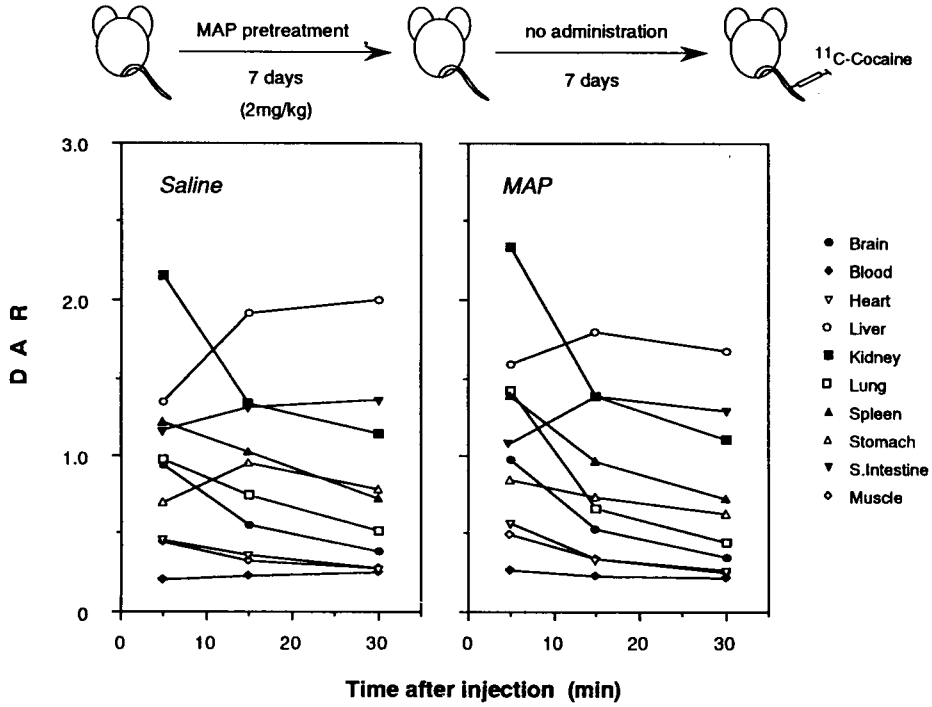

Fig. 3. Tissue distbution of [^{11}C]cocaine in the methamphetamine-sensitization mice

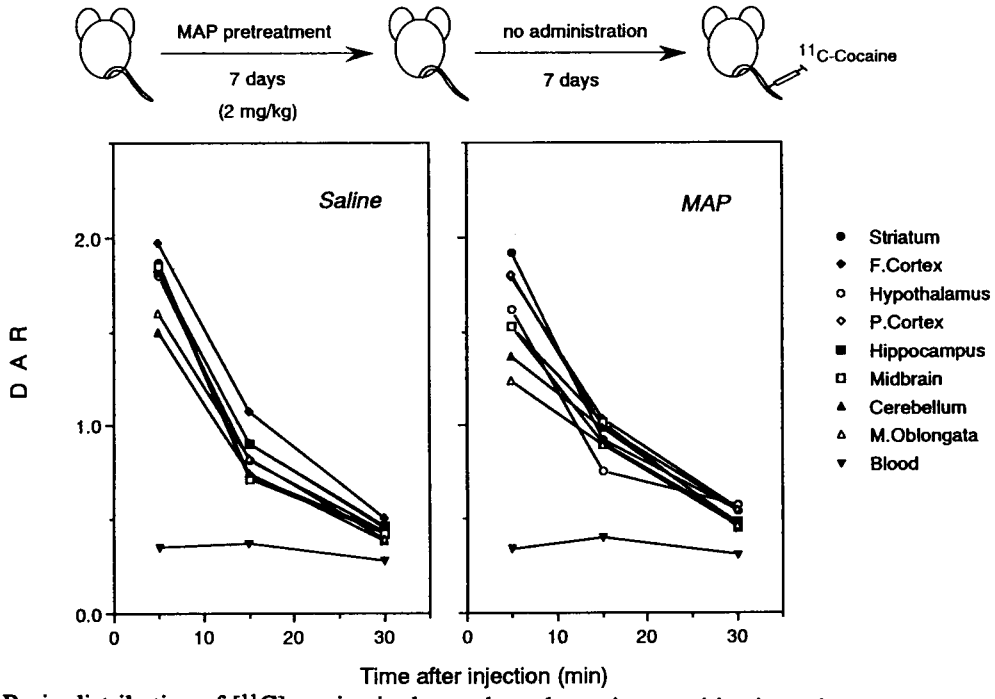

Fig. 4. Brain distribution of [^{11}C]cocaine in the methamphetamine-sensitization mice