

Alteration in Biodistribution of 11C-Methamphetamine and 11C-Cocaine

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Introduction

Behavioral sensitization induced by repeated administrations of methamphetamine and cocaine to experimental animals is widely used as an experimental model of stimulant-induced psychosis ^{1,2)}. Because methamphetamine- and cocaine-induced behavioral hypersensitivity is accompanied by an increased releasability of dopamine in the striatum and nucleus accumbens, enhanced synaptic transmission of dopamine neurons has been implicated in such behavioral sensitization, but the precise mechanism of this long-term increase in dopamine releasability is unknown.

In the present study, we investigate the alterations in the biodistributions of ^{11}C -methamphetamine and ^{11}C -cocaine in methamphetamine-, cocaine-sensitized animals to study the mechanism involved in increased dopaminergic transmission and behavioral sensitization.

Materials and Methods

Chemicals

d-Methamphetamine hydrochloride and cocaine hydrochloride were kindly supplied by Eishin Co. Ltd., Sendai, Japan. *dl*-Amphetamine ⁴⁾ and norcocaine ⁵⁾ were prepared in our laboratory. Other chemicals used were of reagent grade purchased from Wako Pure Chemical Co. Ltd., Osaka Japan.

Animals

In all experiments male ddY mice approximately 7-8 weeks old weighing 25-30 g each were used. A 12hr light-dark cycle was maintained and free access to food and water was provided.

Preparations of ^{11}C -methamphetamine and ^{11}C -cocaine

^{11}C -Methamphetamine ⁶⁾ and ^{11}C -cocaine ⁷⁾ were prepared from the reaction of ^{11}C -CH₃I with amphetamine and norcocaine described previously. The specific activities of ^{11}C -methamphetamine and ^{11}C -cocaine were about 3.0 Ci/mmol and 22 Ci/mmol at the time of

the injection and the radiochemical yields were about 20-40 % and 47-58 %, respectively. The radiochemical purity of these chemicals was determined to be > 99 %.

Animal experiments

In *in vivo* studies, ^{11}C -methamphetamine hydrochloride or ^{11}C -cocaine hydrochloride was injected into the tail vein and the mice were decapitated at 1, 5, 15, 30 and 60 min after the injection. The eight brain areas (striatum, frontoparietal cortex, posterior cortex, hippocampus, hypothalamus, midbrain, cerebellum, medulla oblongata) were dissected according to the method of Glowinski and Iversen (1966)⁸⁾ and were 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).

The effect of repeated treatment and termination of nonradioactive methamphetamine or cocaine on the uptake of ^{11}C -methamphetamine or ^{11}C -cocaine were investigated in each brain region. In the sensitization model, the treatment of nonlabeled methamphetamine (2mg/kg) was continued for 3 days and then the mice were free from methamphetamine for 3 successive days. Cocaine (10mg/kg) was injected for 14 days and terminated for 7 successive days. In the control, saline was injected for 6 days (for methamphetamine) and 14 days (for cocaine) instead of the administration of nonlabeled drugs.

Result and Discussion

Distribution of ^{11}C -methamphetamine

At various intervals after the injection, the radioactivities in the eight sections of the brain were compared (Fig. 1). The uptake was always low in the blood. At 5 to 15 min after the injection, each brain section showed a high affinity to ^{11}C -methamphetamine in proportion to the total brain uptake. High value was observed after 5 min in the hypothalamus, posterior cortex, frontoparietal cortex, striatum and medulla oblongata, and after 15 min, in the hippocampus, posterior cortex and striatum. Furthermore, the striatum, hypothalamus and hippocampus showed higher values than those of other sections at 60 min.

In the sensitization model of methamphetamine, we also compared the distributions between the saline-treated control and the groups treated by nonlabeled methamphetamine for 3 or 6 days (3 days or 6 days group), and the results are described in Fig. 2. The amount of ^{11}C -methamphetamine was increased in each region except in the frontoparietal cortex and the striatum by a high-dose of non radioactive methamphetamine treatment in comparison with that of the saline treated controls for 6 days, suggesting quantitative alternation by continuous methamphetamine-treatment. By terminating methamphetamine treatment for 3 days (quitting group), the uptake of ^{11}C -methamphetamine was decreased to the level of the controls in each brain section. But in the striatum the activity was significantly increased. These results suggest that the termination of methamphetamine treatment may change the affinity of striatum to methamphetamine.

Distribution of ^{11}C -cocaine

The distribution of ^{11}C -cocaine in the brain of sensitization mice after *i.v.* injection of ^{11}C -cocaine are shown in Fig. 3. The uptake of carbon-11 by each section of brain was very fast and reached a maximum within 5 min in the control groups. In the sensitization model, no regional differences in the variation of the ^{11}C -cocaine uptake were observed. But the peaks of the ^{11}C -cocaine uptake were delayed from 5 to 10 min after the *i.v.* injection in most regions.

We reported previously that the cocaine uptake and egress from the mice brain were rapid in comparison with methamphetamine⁷⁾. Such differences in the time course of the distribution in brain between cocaine and methamphetamine could influence the pharmacological effect on drug abusers.

The termination of methamphetamine or cocaine abuse presents symptoms resembling schizophrenia, called "kindling". Though both methamphetamine and cocaine induce these phenomena, no similar changes of the brain distribution of these compound were observed. The behavioral sensitization may be induced by a different mechanism by each drug. Methamphetamine-induced behavioral hypersensitivity appears to be, at least partially, due to an increased releasability of dopamine in the striatum and nucleus accumbens⁹⁾. In addition, Akiyama et al.¹⁰⁾ reported that subchronic methamphetamine treatment causes some functional changes in the dopamine transporting systems that are involved in dopamine release and uptake on presynaptic dopamine terminals. But the precise mechanism of this long-term increase in dopamine releasability is unknown. We are currently interested in the relation between these changes in the response and the mechanism of kindling. It suggests that subchronic methamphetamine administration may result in a long-term change in the presynaptic cell membrane at the nerve terminal which may in turn cause an increase in both methamphetamine and dopamine uptake accompanied by an increased release of dopamine at the synaptic cleft.

Summary

^{11}C -labeled methamphetamine and cocaine were synthesized by *N*-methylation of amphetamine and norcocaine with $^{11}\text{CH}_3\text{I}$ to assist in the imaging of various local distributions by positron emission tomography (PET). The alterations of the organ- and regional-distributions of ^{11}C -cocaine were investigated in mice at various times after *i.v.* injection. As a result, we observed a significant increase in ^{11}C -methamphetamine radioactivities in the striatum and hypothalamus in the mice pretreated with methamphetamine for 3 days. Moreover, in the sensitization model of cocaine, we found no regional differences but the peaks of ^{11}C -cocaine uptake was delayed from 1 min to 5-15min after the *i.v.* injection in most brain regions.

These findings demonstrated that some differences existed in the localization of these drugs in sensitization models. Such variations may play important roles in stimulant-derived psychosis.

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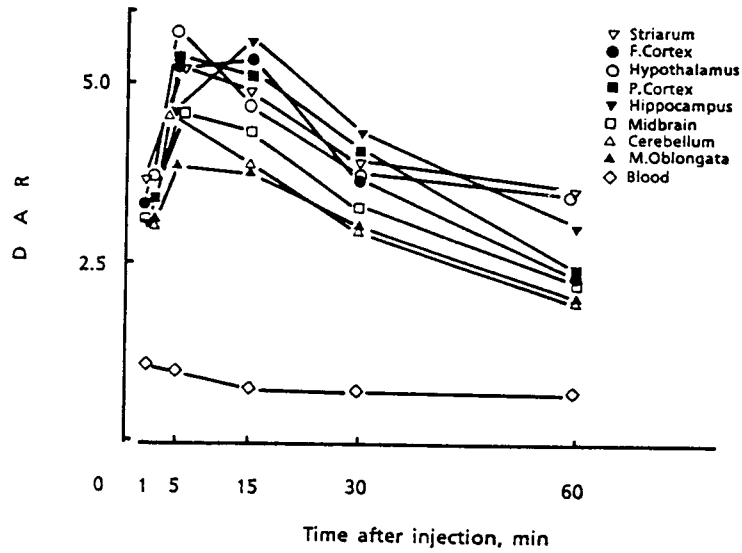


Fig. 1. The regional distributions of ^{11}C -methamphetamine in the mice brain. Each point represents the average value of triplicate samples.

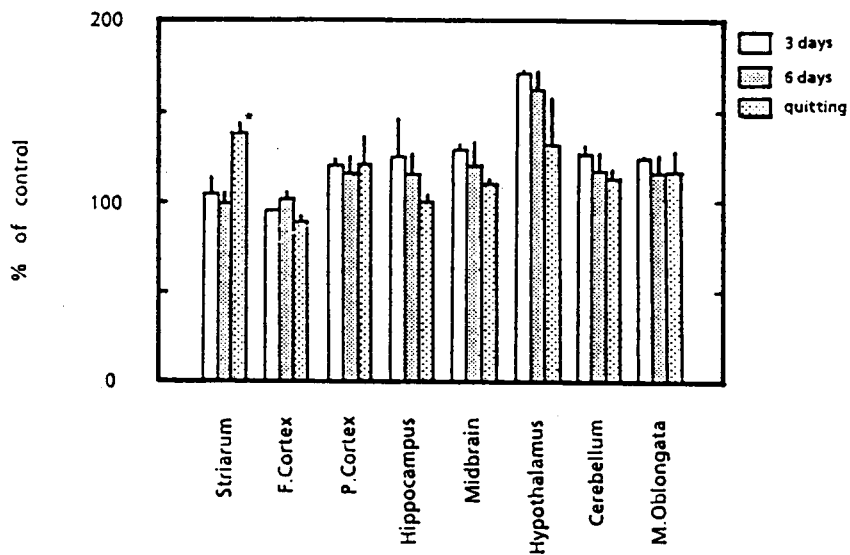


Fig. 2. The effects of terminating nonlabeled methamphetamine treatment on the regional distributions of ^{11}C -methamphetamine in the mice brain. The experimental results are shown % ratios to the uptake of control group (repeated treatment saline for 6 days) and represent the average value of triplicate samples. p Values were obtained from t tests *, p < 0.05

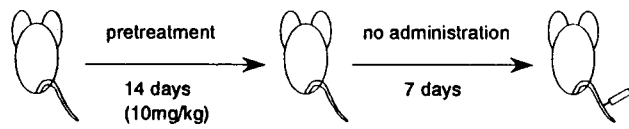
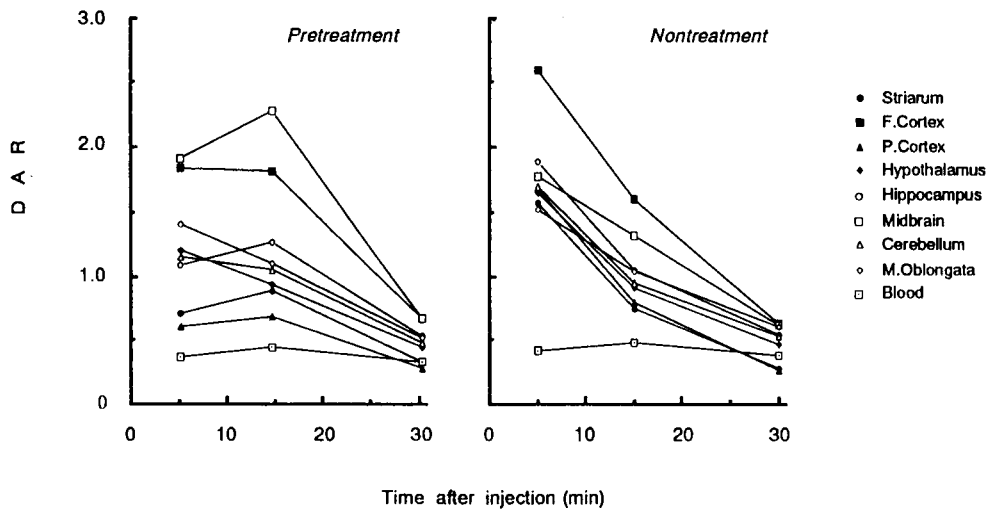


Fig. 3. The effects of terminating nonlabeled cocaine treatment on the regional distributions of ^{11}C -cocaine in the mice brain. Each point represents the average value of triplicate samples.