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Reversal of methamphetamine-induced behavioral sensitization by repeated administration of a dopamine D_1 receptor agonist

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Abstract

Repeated intermittent administration of methamphetamine (MAP) produces an enduring hypersensitivity to the motor stimulant effect of MAP, termed behavioral sensitization. Dopamine plays a critical role in the development and expression of behavioral sensitization. Here, we investigated whether a dopamine D_1 receptor agonist could reverse behavioral sensitization to MAP. Administration of MAP (1.0 mg/kg, i.p.) to rats once every 3 days for a total of 5 times (days 1−13) induced the enhancement of locomotor activity after MAP challenge (0.5 mg/kg, i.p.) on day 20, verifying the development of behavioral sensitization. The MAP-sensitized rats then received a dopamine D_1 agonist, R-(+)-SKF38393 (3.0 mg/kg, i.p.), once a day for 7 consecutive days (days 21−27). Behavioral analysis on days 30 and 41 revealed that the enhanced locomotor activity was reversed by repeated R-(+)-SKF38393 administration. Moreover, repeated R-(+)-SKF38393 administration reversed the increased dopamine release in the striatum after MAP challenge on day 41. Thus, repeated administration of the dopamine D_1 receptor agonist induces the reversal of established behavioral sensitization to MAP and of increased dopamine release in the striatum, lasting for at least 2 weeks. Dopamine D_1 receptor agonists may be useful therapeutic agents for the treatment of psychostimulant addiction.

Keywords: Sensitization; Methamphetamine; Dopamine D_1 agonist; Locomotor activity; Dopamine release

1. Introduction

In animals, repeated intermittent administration of psychostimulants such as methamphetamine (MAP), amphetamine (AMPH) and cocaine induces a progressive and enduring enhancement of locomotor activity and stereotyped behavior (Nestler et al., 2001; Ujike, 2001). This phenomenon, termed behavioral sensitization, easily reappears with the injection of small doses of psychostimulants after a long period of abstinence following initial drug exposure. Behavioral sensitization has been proposed as a useful model for the intensification of drug craving, leading to a high rate of relapse in psychostimulant addiction. Since behavioral sensitization accompanies persistent, adaptive changes in neural transmission, it may also reflect some aspects of psychostimulant psychosis and schizophrenia (Kalivas and Stewart, 1991; Robinson and Becker, 1986).

The neurobiological mechanisms underlying behavioral sensitization are thought to be associated with alterations in dopaminergic pathways (King et al., 1994a,b; Vezina and Stewart, 1989). Drugs of abuse are thought to act at the mesolimbic dopamine system, but the striatum also plays an important role for the control of locomotor activity in response to psychostimulants (Nestler et al., 2001), the reinforcement learning of rewards (Samejima et al., 2005) and the development and expression of behavioral sensitization (Hamamura et al., 1991). Most research in this field has focused on

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mechanisms underlying the development of MAP sensitization. The development of MAP sensitization is blocked by dopamine D_1 or D_2 receptor antagonism (Hamamura et al., 1991; Kuribara and Uchihashi, 1993), and the action of MAP in sensitized animals is transiently antagonized by co-administration of a dopamine D_2 receptor antagonist (Karler et al., 1991). Understanding how sensitization can be reversed is important for the development of therapeutic agents for drug abuse. Dopamine D_1 and D_2 receptor antagonists have been tested for this purpose, but so far these attempts have failed to reverse the established behavioral sensitization to MAP (Kuribara and Tadokoro, 1990; Kuribara and Uchihashi, 1994).

Recently, Li et al. (2000) reported that treatment with a dopamine D_1 receptor agonist, SKF81297, for 7 days induces a reversal of cocaine-induced behavioral sensitization and dopamine D_1 receptor supersensitivity in the nucleus accumbens. In addition, dopamine D_1 receptor agonists are reported to diminish the cocaine-seeking behavior in self-administration models (Self et al., 1996). The behavioral effects of MAP and cocaine are mediated through the increase in synaptic dopamine in the striatum and nucleus accumbens (Nestler et al., 2001). This is thought to explain the development of cross-behavioral sensitization between MAP and cocaine (Akimoto et al., 1990). However, some actions of MAP in the induction of behavioral sensitization, in particular mediated through the activation of dopamine D_1 receptors, are reported to be different from those of cocaine (Kuribara and Uchihashi, 1993; Mattingly et al., 1994; White et al., 1998). Therefore, we investigated whether repeated administration of a dopamine D_1 receptor agonist, R-(+)-SKF38393, is able to reverse the established behavioral sensitization to MAP and the increased dopamine release in the striatum after MAP challenge.

2. Methods

2.1. Animals

Male Wistar rats (Kyudo Co. Ltd., Saga, Japan), weighing between 230 and 250 g at the start of the experiment, were used. They were housed in groups of four under a constant temperature (23 ± 2 °C) and a 12-h light/dark cycle (light period: 07:00–19:00 h). The rats were given free access to food and water throughout the experiments. All rats used in this study were handled in accordance with the Declaration of Helsinki and with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the U.S. National Institutes of Health, and the specific protocols were approved by the Committee of Animal Care of the Graduate School of Kyushu University to ensure the ethical use of animals. Attempts were made to minimize the number of animals used and their suffering.

2.2. Drugs

Drugs were obtained from the following sources; methamphetamine (MAP) from Dainippon Pharmaceuticals Ltd. (Osaka, Japan) and the dopamine D_1 receptor agonist, R-(+)-SKF-38393 hydrochloride, from Sigma–Aldrich (St. Louis, MO, USA). The drugs were dissolved in saline.

2.3. Experimental schedule

Rats were injected with MAP (1.0 mg/kg, i.p.) or saline (SAL) once every 3 days for a total of five times (days 1–13) in their home cages. After a 6- or 7-day withdrawal period, all rats were challenged with SAL on day 19 and MAP (0.5 mg/kg, i.p.) on day 20, and their locomotor activity was recorded. They subsequently received either the selective dopamine D_1 agonist, R-(+)-SKF38393 (1.0 or 3.0 mg/kg, i.p.), or SAL once a day for 7 days (on days 21–27) in their home cages. After a 3-day or 14-day withdrawal period (day 30 or day 41), the rats were challenged with MAP (0.5 mg/kg, i.p.), and their locomotor activity and dopamine release were determined. The experimental schedule and the group of rats, subdivided into 5 groups (SAL/SAL, SAL/3 SKF, MAP/SAL, MAP/1 SKF, MAP/3 SKF), are shown in Fig. 1.

2.4. Measurement of locomotor activity

The number of horizontal and vertical (or rearing) movements was determined as activity counts using an area sensor (F5B; Omron, Kyoto, Japan). Rats received repeated drug or SAL injection in their home cages except when challenged with MAP. On the day of MAP challenge, rats were habituated to the activity cages for 60 min before the injection of MAP, and locomotor activity was recorded for 90 min after the injection of MAP.

2.5. Measurement of dopamine release

On day 17, the rats were anesthetized with sodium pentobarbital (40 mg/kg, i.p.) and fixed on a stereotaxic apparatus. A guide cannula (0.5-mm outer diameter, AG-8; Eicom Co., Kyoto, Japan) was placed just above the striatum (0.2 mm anterior, 2.6 mm lateral from the bregma and 4.2 mm ventral from the

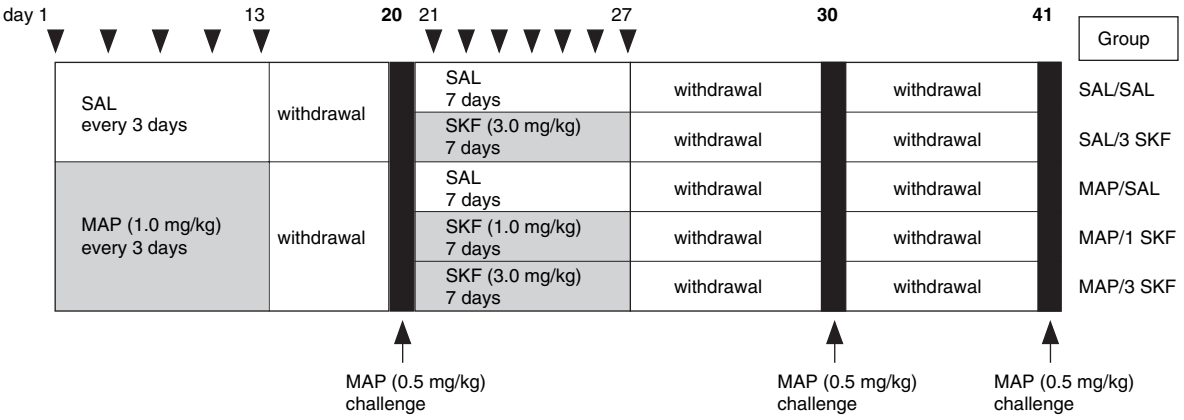

Fig. 1. Experimental schedule for the development of methamphetamine (MAP) sensitization and repeated administration of R-(+)-SKF38393 (SKF). Rats were subdivided into five treatment groups; saline (SAL)/SAL, SAL/3.0 mg/kg SKF38393 (SAL/3 SKF), MAP/SAL, MAP/1.0 mg/kg SKF38393 (MAP/1 SKF), MAP/3 SKF. Locomotor activity was recorded for 90 min after MAP challenge (0.5 mg/kg) on day 20, 30 and 41, and dopamine release was measured in the striatum on day 30 and 41 using microdialysis.