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Prevention of drug priming- and cue-induced reinstatement of MDMA-seeking behaviors by the CB_1 cannabinoid receptor antagonist AM251

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ABSTRACT

Background: 3,4-Methylenedioxymethamphetamine (MDMA), a methamphetamine (METH) derivative, exhibits METH-like actions at monoamine transporters and positive reinforcing effects in rodents and primates. The purposes of the present study were to determine whether cross-reinstatement would be observed between MDMA and METH and if the cannabinoid receptor, a receptor known to play critical roles in the brain reward system, could modulate MDMA craving.

Methods: Rats were trained to press a lever for intravenous MDMA (0.3 mg/infusion) or METH (0.02 mg/infusion) infusions under a fixed ratio 1 schedule paired with drug-associated cues (light and tone). Following drug self-administration acquisition training, rats underwent extinction training (an infusion of saline). Reinstatement tests were performed once the extinction criteria were achieved.

Results: In MDMA-trained rats, the MDMA-priming injection (3.2 mg/kg, i.p.) or re-exposure to MDMA-associated cues reinstated MDMA-seeking behavior. Additionally, a priming injection of METH (1.0 mg/kg, i.p.) also reinstated MDMA-seeking behavior. In contrast, none of the MDMA doses reinstated METH-seeking behavior in the METH-trained rats. The CB_1 cannabinoid receptor antagonist AM251 markedly attenuated the MDMA-seeking behaviors induced by MDMA-priming injection or re-exposure to MDMA-associated cues in a dose-dependent manner.

Conclusions: These findings show that MDMA has obvious addictive potential for reinstating drug-seeking behavior and that METH can be an effective stimulus for reinstating MDMA-seeking behaviors. Furthermore, based on the attenuating effect of AM251 in the reinstatement of MDMA-seeking behaviors, drugs that suppress CB_1 receptors may be used in treatment of MDMA dependence.

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA) is a primary component of 'Ecstasy' tablets, a popular recreational drug among young adults in many parts of the world (Parrott, 2004). This drug is a methamphetamine (METH) derivative and exhibits METH-like actions at monoamine transporters, increasing synaptic levels of serotonin (5-HT) and dopamine (DA; Rothman and Baumann, 2003). A previous clinical study reported that MDMA clearly had abuse potential because a high percentage of its users met the DSM-IV criteria for either dependence or abuse (Cottler et al., 2001). It has also been reported that MDMA exhibits positive reinforcing effects in rodents (Trigo et al., 2006) and primates (Lile et al., 2005) in a drug self-administration paradigm.

A reinstatement model by a drug self-administration paradigm has been used as a model for relapse in drug-seeking behavior in humans. In this model, similar stimuli that induce cravings in humans, such as exposure to abusive drugs, drug-associated cues, or stress, are used to reinstate drug-seeking behavior in animals with a history of drug self-administration. Cross-reinstatement by a drug other than the self-administered drug is most commonly observed within a given drug class (Shalev et al., 2002). For example, the reinstatement of cocaine-seeking behavior in cocaine self-administered animals appeared by both direct and indirect dopaminergic agonists such as amphetamine, methylphenidate, or bromocriptine, which have similar pharmacological effects to cocaine (Shalev et al., 2002). Although MDMA has a similar pharmacological effect to METH in its dopaminergic action, it remains

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unclear whether cross-reinstatement is observed between MDMA and METH.

Cannabis is the most commonly abused illegal drug in the world, and its main psychoactive ingredient, Δ^9-tetrahydrocannabinol (THC), produces rewarding effects in humans and non-human primates. Experimental findings suggest a major involvement of the endocannabinoid system in both reward functions and drug abuse in the brain (Yamamoto and Takada, 2000; Yamamoto et al., 2004). Regarding the craving, the cannabinoid CB_1 receptor antagonist AM251 or SR141716A, which are known as specific receptors for Δ^9- THC, attenuates the reinstatement of METH-seeking behavior induced by METH-associated cues or METH-priming injections (Anggadiredja et al., 2004; Hiranita et al., 2008), indicating that CB_1 receptors may have a facilitating role in METH craving.

Touriño et al. (2008) reported that the increase in locomotor activity and body temperature induced by acute MDMA is lower or abolished in CB_1 receptor knockout mice. Judging from this finding, it is suggested that the CB_1 receptor has an important role in MDMA response.

In this study, we determined whether cross-reinstatement would be observed between MDMA and METH in rats with a history of MDMA or METH self-administration. Furthermore, given the critical roles of CB_1 receptors in METH-seeking behavior, the involvement of CB_1 receptors in the reinstatement of MDMA-seeking behavior was also investigated.

2. Methods

2.1. Subjects

Adult male Wistar rats (10-weeks-old, Kyudo, Tosu) weighing 300–320 g were used in this study. Rats were housed in a temperature- and humidity-controlled environment under a 12-h light/dark cycle (lights on at 7:00 a.m.). Before surgery, the animals had unlimited access to food and water and were housed 3–4 animals/cage. Each rat was housed individually after surgery, and food was limited to 15–20 g/day/body following 5 days for recovery. The procedures used were conducted in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the Declaration of Helsinki and the Faculty of Pharmaceutical Science, Nagasaki International University Publication, enacted in 2009.

2.2. Drugs

3,4-Methylenedioxymethamphetamine HCl (MDMA; provided courtesy of Dr. Iwamura, Department of Organic Chemistry, Matsuyama University) or methamphetamine HCl (METH; Dainippon Sumitomo Pharma, Osaka) were dissolved in a saline solution, while AM251 trifluoroacetate (Sigma, St. Louis, MO), a CB_1 cannabinoid receptor antagonist, was dissolved in a mixture of DMSO, Tween-80 and saline (1:1:18, respectively).

2.3. Food training

Two days prior to the start of food training, rats received a restricted diet to achieve weight loss to approximately 90% of their normal weight and were trained to press levers for 45-mg food pellets (Bio-Serv, Frenchtown, NJ). The training took place on a fixed ratio 1 (FR1) schedule during which no stimuli were presented. Lever-pressing training ceased when the rats could obtain 30 pellets within 250 s for three consecutive sessions.

2.4. Surgery

Following completion of the food training, the rats were anesthetized with isoflurane (Mylan Pharmaceuticals, Osaka) prior to surgical implantation of the indwelling intravenous (i.v.) catheters. Catheters were constructed from Silastic laboratory grade tubing (0.5 mm i.d., 1.0 mm o.d., Kaneka Medix, Osaka). The catheter was implanted into the right jugular vein and was secured in place with silk sutures around the silicon nodule. The Silastic tubing ran under the skin to an exit point in the mid-scapular region. Rats were infused i.v. with 0.2 ml of heparinized saline (30 U/ml) daily during the experiment to prevent blockage of the catheter.

2.5. Drug self-administration

2.5.1. Intravenous drug self-administration. Drug self-administration training was conducted in standard operant chambers ($30 \times 20 \times 24$ cm; Neuroscience, Tokyo) with two fixed levers (5 cm above the chamber floor). A house light was located on the upper side of the wall on the same side as the levers, and stimulus lights were located 4 cm above the levers. The self-administration apparatus was enclosed in a ventilated, sound-attenuating chamber. Drug was delivered using a computer controlled infusion pump located inside of the sound-attenuating chamber. The entire system was computer integrated using the MED PC 4 system (Med Associates, St. Albans, VT). Rats self-administered MDMA ($n = 32$) or METH ($n = 11$) during 2-h sessions on 20 or 10 consecutive days, respectively. The animals were connected to the drug infusion line, and the session was initiated. Each session began with illumination of the house light, which remained lit for the entire session.

Responses on the active lever resulted in the delivery of an MDMA (0.3 mg/0.1 ml) or METH (0.02 mg/0.1 ml) infusion over 6-s; this training was accomplished using an FR1 schedule. Responses on another lever (inactive lever) had no programmed consequences, but were recorded. Each infusion was paired with both the stimulus light and a tone (2.9 kHz, 85 dB) for 26-s as drug-associated cues, delivered via a programmable audio generator (Neuroscience, Tokyo). Following drug delivery and stimulus presentation, responses on the active lever had no programmed consequences (no drug or stimulus delivery) for 20 s, but lever responses were recorded.

2.5.2. Extinction and reinstatement test. Following self-administration training, rats underwent daily 1-h extinction sessions. During the extinction sessions, active lever responses resulted in an infusion of saline instead of drug without presentation of the drug-associated cues. Prior to reinstatement testing, the animals underwent 5–15 extinction days. If necessary, additional days of extinction were given until the rats reached response criteria of less than 10 active lever responses/day on 2 consecutive days. After extinction criteria were met, the reinstatement test was conducted under saline infusions carried out for 1-h on an FR1 schedule. In the cue-induced test, immediately after the onset of the session, rats were re-exposed to the drug-associated cue, and each press on the active lever resulted in the presentation of the drug-associated cues. In the drug-primed test, each response during the test session resulted in the infusion of saline without the presentation of the cues. In MDMA-trained rats, MDMA (1.0 and 3.2 mg/kg) or METH (1.0 mg/kg) as a priming injection was injected intraperitoneally (i.p.) 30 min before the test. In METH-trained rats, MDMA (3.2, 5.6 and 10 mg/kg, i.p.) or METH (1.0 mg/kg, i.p.) was administered. In an antagonist experiment of MDMA-trained rats, AM251 (0.32 and 3.2 mg/kg, i.p.) was also injected 30 min before the test. The doses of AM251 were selected based on previous reports (Xi et al., 2006; Nawata et al., 2010).