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RESEARCH ARTICLE

The Effects of 4-Methylethcathinone on Conditioned Place Preference, Locomotor Sensitization, and Anxiety-Like Behavior: A Comparison with Methamphetamine

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Abstract

Background: 4-Methylethcathinone is a drug that belongs to the second generation of synthetic cathinones, and recently it has been ranked among the most popular "legal highs". Although it has similar in vitro neurochemical actions to other drugs such as cocaine, the behavioral effects of 4-methylethcathinone remain to be determined.
Methods: The addictive potential and locomotor potentiation by 4-methylethcathinone were investigated in rats using the conditioned place preference and sensitization paradigm. Methamphetamine was used as a positive control. Because synthetic cathinones can have psychological effects, we also examined anxiety-like behavior using the elevated plus maze.
Results: A conditioning dose of 10 mg/kg 4-methylethcathinone was able to induce conditioned place preference and reinstatement (following 2 weeks of withdrawal). Acute or repeated injections of 4-methylethcathinone at 3 or 10 mg/kg failed to alter locomotor activity. At 30 mg/kg, however, acute 4-methylethcathinone increased locomotor activity compared with saline, while chronic 4-methylethcathinone induced a delayed and attenuated sensitization compared with methamphetamine. Additionally, repeated daily injections of 4-methylethcathinone (30 mg/kg) reduced, whereas methamphetamine increased time spent by rats in the open arm of an elevated plus maze compared with saline injections. Interestingly, a 2-week withdrawal period following chronic injections of 4-methylethcathinone or methamphetamine increased time spent in the open arm in all rats.
Conclusions: The rewarding properties of 4-methylethcathinone were found to be dissociated from its effects on locomotor activity. Additionally, chronic 4-methylethcathinone use may trigger abnormal anxious behaviors. These behavioral effects caused by 4-methylethcathinone appear to last even after a withdrawal period.

Keywords: 4-methylethcathinone, CPP, locomotor sensitization, elevated plus maze

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Introduction

Synthetic cathinones have become increasingly popular as novel psychoactive substance in the smuggling and trading of illicit drug since the early 2010s, seriously raising public concerns in China and other countries. In particular, 4-methylethcathinone (4-MEC) has recently been identified as very popular among the seized cathinone derivatives, according to a disclosure issued by the Ministry of Public Security in China. Further, it is ranked as one of the most common designer drugs according to a review published by the WHO Expert Committee on Drug Dependence (World Health Organization, 2014). Since 2014, 4-MEC has been listed in Catalog I of the controlled psychotropic drugs in China (China Food and Drug Administration, 2013) and in temporary control (Schedule 1) of the Controlled Substances Act in the U.S. (United States Department of Justice, 2014).

As one of cathinone derivatives, 4-MEC shares structural characteristics with phenylethylamine, 3,4-methylenedioxy-methamphetamine (MDMA), and methamphetamine (METH) (De Felice et al., 2014). Pharmacological assays in vitro showed that 4-MEC inhibits monoamine uptake and displays stronger affinity for serotonin transporter (SERT) though weaker affinity for norepinephrine or dopamine transporter (DAT) compared with METH (Simmler et al., 2014). Additionally, 4-MEC acts as a serotonin releaser similar to MDMA (Saha et al., 2015). According to those pharmacological findings, 4-MEC is hypothesized to have rewarding, psychedelic, and stimulant-like effects in vivo. While it has recently been reported that 4-MEC produces discriminative stimulus effects similar to cocaine and methamphetamine (Gatch et al., 2015), its profile in other types of addiction-related behaviors is unknown.

Therefore, the present study investigated conditioned place preference (CPP) and locomotor sensitization using 4-MEC. CPP and locomotor activity are paradigms commonly employed to determine the rewarding and psychomotor properties of drugs, respectively (Bardo and Bevins, 2000; Steketee and Kalivas, 2011). Because synthetic cathinones can influence other types of mental disorders (Ross et al., 2012), we further evaluated the effects of 4-MEC on anxiety-like behavior using the elevated plus maze.

Materials and Methods

Animals

All procedures were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Peking University Animal Care and Use Committee. Male Sprague Dawley rats (250 g on arrival; Vital River Laboratories, Beijing, China) were housed in groups of 4 to 5 in a temperature- and humidity-controlled environment with a 12-hour-dark/-light cycle. Experiments were conducted during the dark cycle. Rats received food and water ad libitum. Separate and naive groups of rats were used for each experiment.

Drugs

METH and 4-MEC were provided by Drug Intelligence and Forensic Center of Ministry of Public Security, China. Both drugs were dissolved in 0.9% saline and were injected i.p. at a volume of 1 mL/kg.

CPP Paradigm

The detailed procedure of CPP paradigm has previously been described (Xu et al., 2015). In brief, the present CPP employed an unbiased paradigm. The CPP apparatus was made of smooth black plastic and consisted of 3 distinct compartments separated by guillotine doors. The 2 end-compartments, referred to as the conditioning compartments, were identical in size (28 × 23 × 20 cm) but differed in tactile and visual aspects (tactile: stainless-steel grid floor vs stainless-steel mesh floor; visual: 5 low-power red light bulbs forming a radial shape vs square shape). The central compartment was smaller in size (14 × 23 × 20 cm). The position and the movement of the rat throughout experimentation were measured by 2 infrared light beams (3 cm above floor) in each compartment. A computer recorded these data. On days 1, 3, 5, and 7, the rats received 4-MEC (1, 3, or 10 mg/kg, i.p.) or METH (1 mg/kg, i.p.). On days 2, 4, 6, and 8, the rats received saline. After each injection, the rats were immediately confined to the drug-paired or saline-paired compartment for 45 minutes. On days 9 and 24 (ie, 2 weeks after withdrawal), the rats were placed in the central compartment without receiving any injection and were allowed to explore the entire apparatus freely for 15 minutes. The CPP score was calculated by the time spent in the drug-paired compartment minus the time spent in the saline-paired side on the test day.

Locomotor Activity and Sensitization

All rats were first habituated to the locomotor chambers (40 × 40 × 45 cm) for 3 days (120 min/d). Rats were then injected once daily either with saline, 4-MEC (3, 10, or 30 mg/kg), or METH (1 mg/kg) for 7 consecutive days. Two weeks after the last injection, each rat received the same drug (Shen et al., 2009). After each injection, rats were immediately placed in the locomotor chamber for 120 minutes. All locomotor activities were recorded and quantified by an automatic path-tracking and analysis system (Zhongshidichuang Sci. and tech., Beijing, China).

Elevated Plus Maze Test

The elevated plus maze was utilized to evaluate anxiety-like behavior based on the rats' natural fear of open, unprotected, and elevated spaces (Hogg, 1996; Singh et al., 2011). It consisted of 2 open arms (42 × 15 cm) crossed at right angles with 2 closed arms of the same size with an open roof and was elevated 70 cm above the floor. The closed arms had walls 22.5 cm high, with the exception of the central square of the maze (15 × 15 cm), where the open and closed arms crossed. All procedures were conducted in a quiet and dim room (the light intensity of the central square of the maze was ~10 lux). Thirty-five minutes after each injection (saline, 4-MEC [3, 10, or 30 mg/kg], or METH [3 mg/kg]), each rat was placed in the central square of the maze with its nose facing an open arm and was allowed to freely explore the maze for 5 minutes. The total distance travelled and time spent in each arm or the central square were measured and recorded by the path-tracking and analysis system (Zhongshidichuang Sci. and tech.).

Statistics

All data are shown as mean ± SEM and were analyzed using 1- or 2-way ANOVA followed by Bonferroni posthoc tests. Student's unpaired t test was used where appropriate. Values of $P < .05$ were considered statistically significant. All statistical tests were conducted using Graphpad Prism software.

Results

4-MEC Induced CPP Dose Dependently

The rats underwent CPP training (1, 3, or 10 mg/kg of 4-MEC; or 1 mg/kg of METH) for 8 days. They then received CPP test on day 9

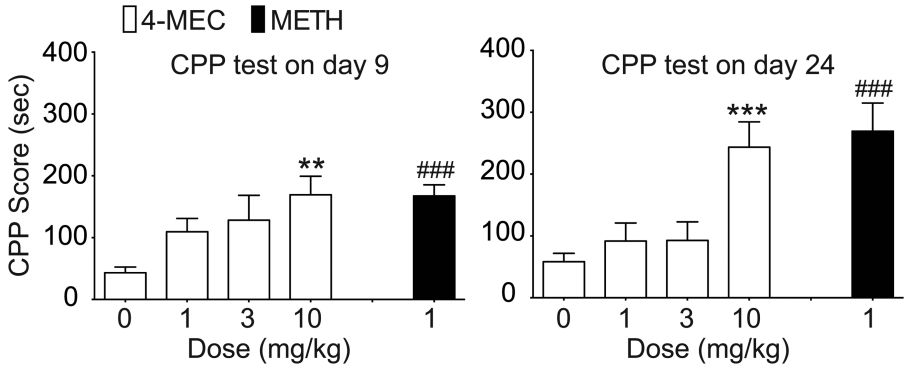

Figure 1. 4-Methylethcathinone (4-MEC) induced conditioned place preference (CPP) dose dependently. The rats trained with 10 mg/kg 4-MEC or methamphetamine (METH) displayed significant CPP and context-associated reinstatement. **P < .01, ***P < .001, comparing 4-MEC with saline groups, Bonferroni's posthoc test. ###P < .001, comparing METH with saline group, Student's *t* test. n = 8/group.

and reinstatement test on day 24 (ie, 2-week withdrawal period; n = 8/group). The rats trained with 10 mg/kg 4-MEC displayed significant CPP (Figure 1A; 1-way ANOVA of CPP scores within the 4-MEC groups, $F_{(3,28)} = 3.607$, $P = .026$) and context-associated reinstatement (Figure 1B; 1-way ANOVA of CPP scores within the 4-MEC groups, $F_{(3,28)} = 7.628$, $P < .001$). No difference was observed between rats that received 4-MEC (10 mg/kg) or METH (1 mg/kg) on CPP and reinstatement tests ($t_{(14)} = 0.051$, $P = .960$; $t_{(14)} = 0.421$, $P = .680$, respectively).

4-MEC Elicits Delayed and Attenuated Expression of Locomotor Sensitization

Because the minimum effective dose of 4-MEC that induced CPP in rats was 10 mg/kg in the first experiment, we raised the dose range of 4-MEC to 3 to 30 mg/kg in subsequence experiments to investigate whether 4-MEC is able to induce locomotor sensitization and/or anxiety-like behavior.

We first compared the effects of acute injection of 4-MEC at different doses against saline or METH (1 mg/kg) on locomotor activity. The rats treated with 30 mg/kg 4-MEC or METH displayed significantly increased locomotor activity (Figure 2A; 1-way ANOVA of total distance within the 4-MEC groups, $F_{(3,32)} = 6.246$, $P < .01$). The within-session time-binned locomotor activities of rats injected with saline, 4-MEC (30 mg/kg), or METH (1 mg/kg) is shown in Figure 2B. Although there was no difference between the 4-MEC (30 mg/kg) and METH (1 mg/kg) groups in the total distance travelled ($t_{(16)} = 1.152$, $P = .266$), within-session data showed that 4-MEC-treated group exhibited an enhanced locomotor activity from 10 to 30 minutes, whereas METH-treated group showed increased activity from 15 to 95 minutes postinjection (Figure 2B; 2-way repeated-measures ANOVA, treatment × time interaction: $F_{(96, 1128)} = 5.481$, $P < .0001$).

Rats receiving repeated daily injections of METH (1 mg/kg) exhibited considerable locomotor sensitization, indicated by the significant increase in total distance travelled following each METH injection over 7 consecutive days and at rechallenge on day 22 (Figure 3A; 1-way repeated-measures ANOVA, $F_{(7,49)} = 8.265$, $P < .001$). Repeated daily injections of 4-MEC (3, 10, or 30 mg/kg) failed to cause any increase in locomotor activity over consecutive sessions, although the highest dose (30 mg/kg) of 4-MEC significantly increased locomotor activity at rechallenge (Figure 3A; 2-way repeated-measures ANOVA, dose × day interaction: $F_{(21, 224)} = 2.066$, $P < .01$). These results suggest that a high dose of 4-MEC is able to produce a delayed and attenuated development of sensitization that is a key characteristic of

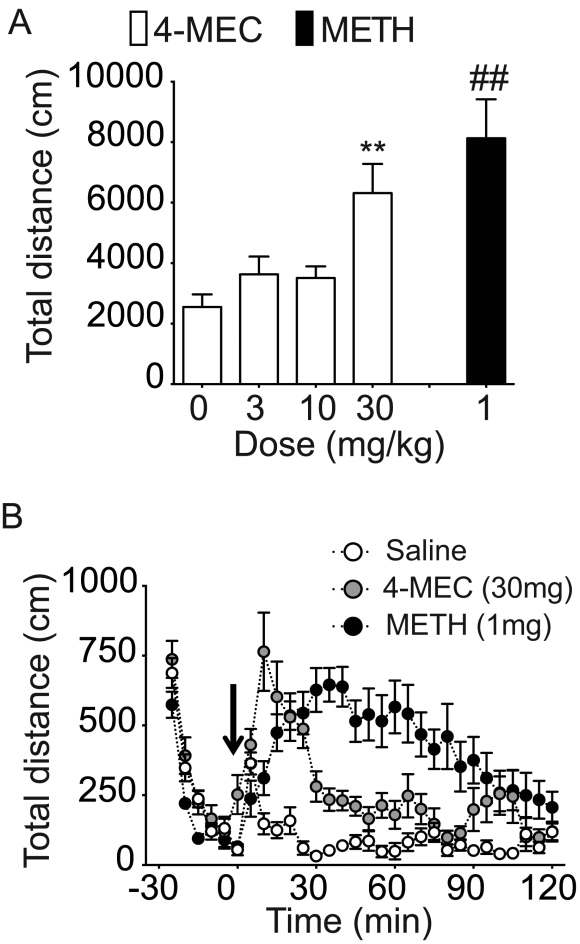

Figure 2. Locomotor response to acute saline, 4-methylethcathinone (4-MEC), or methamphetamine (METH). (A) Acute 4-MEC (30 mg/kg) or METH (1 mg/kg) significantly increased locomotor activity. **P < .01, comparing 4-MEC with saline groups, Bonferroni's posthoc test. ###P < .001, comparing METH with saline group, Student's ttest. (B) The temporal pattern of locomotor response to acute 4-MEC (30 mg/kg) or METH (1 mg/kg). Each point represents the average distance travelled in 5-minute bins. A Bonferroni's posthoc test revealed that 4-MEC (30 mg/kg) enhanced locomotor activity from 10 to 30 minutes, while METH enhanced locomotor activity from 15 to 95 minutes compared with saline injection. The arrow indicates the time of injection. n = 10–12/group.

most psychostimulants. The within-session time-binned locomotor response following rechallenge is shown in Figure 3B. The 4-MEC (30 mg/kg) group exhibited an enhanced locomotor

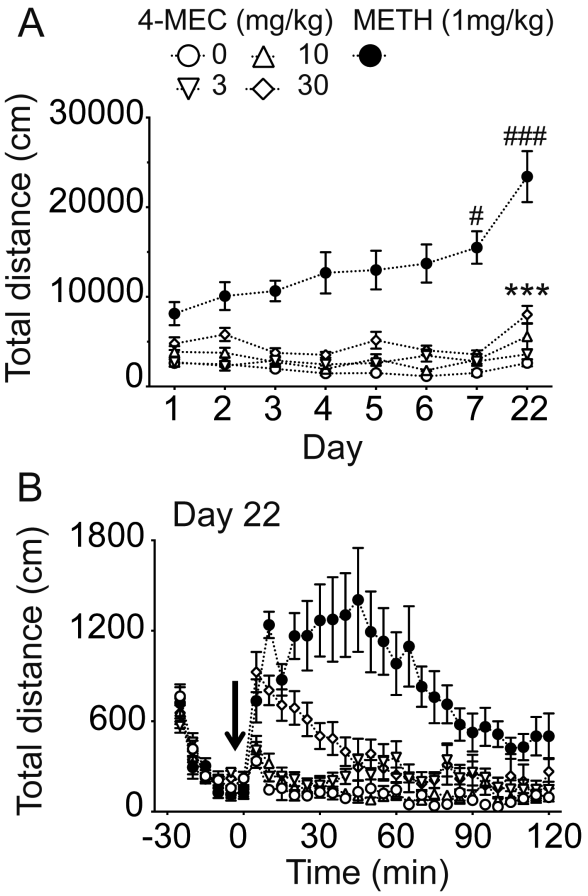

Figure 3. 4-Methylethcathinone (4-MEC) elicits delayed and attenuated expression of locomotor sensitization. (A) Total distance during the 120-minute test after saline, 4-MEC, or methamphetamine (METH) administration. ***$P < .001$, compared with day 1 (4-ME C, 30 mg/kg); #$P < .05$, ###$P < .001$, compared with day 1 (METH, 1 mg/kg), Bonferroni's posthoc test. n = 8–10/group. (B) The temporal pattern of locomotor response in rats when re-challenged 4-MEC or METH after withdrawal. Each point represents the average distance travelled during 5 min bins. Bonferroni's posthoc tests revealed that 4-MEC (30 mg/kg) enhanced the locomotor activity from 5 to 35 minutes and METH from 5 to 100 minutes compared with saline injection. The arrow indicates the time of injection.

activity from 5 to 35 minutes, while the METH group showed an enhanced locomotor activity from 5 to 100 minutes postinjection (Figure 2B; 2-way repeated-measures ANOVA, treatment × time interaction: $F_{(96, 936)} = 5.209$, $P < .0001$).

4-MEC-Withdrawn Rats Spent More Time in the Open Arm of Elevated Plus Maze

The design for the elevated plus maze experiment is shown in Figure 4A. Rats received the test the day before the first drug injection, then 35 minutes following the first and last injections (3, 10, or 30 mg/kg for 4-MEC; 3 mg/kg for METH), then after 2 weeks of withdrawal. Notably, the higher dose of METH was used here to ensure altered elevated plus maze behavior according to previous studies (Tamaki et al., 2008; Kitanaka et al., 2010). At test following the last injection, rats treated with chronic METH showed significantly longer total distance travelled ($t_{(14)} = 2.446$, $P = .028$), longer percent of travel distance in the open arm ($t_{(14)} = 4.386$, $P < .001$), and percent time spent in the open arm ($t_{(14)} = 3.393$, $P < .01$) relative to chronic saline group (Figure 4B). In contrast, rats treated with 30 mg/kg of 4-MEC had shorter total travel distance (1-way ANOVA within the 4-MEC groups, $F_{(3,28)} = 4.281$, $P = .013$) and spent significantly less percent of travel distance ($F_{(3,28)} = 10.90$, $P < .001$) and percent time spent ($F_{(3,28)} = 11.78$, $P < .001$) in the open arm compared with the chronic saline group (Figure 4B). Strikingly, after 2 weeks of withdrawal, all 4-MEC- or METH-treated rats exhibited significant increases in percent travel distance ($F_{(3,28)} = 9.625$, $P < .001$; $t_{(14)} = 4.070$, $P < .01$, respectively) and percent time spent ($F_{(3,28)} = 15.27$, $P < .001$; $t_{(14)} = 3.675$, $P < .01$, respectively) in the open arm compared with rats chronically treated with saline.

Discussion

CPP is commonly employed to assess the rewarding properties and the abuse potential of drugs in animals (Bardo and Bevins, 2000; Tzschentke, 2007). The present study clearly demonstrated that 4-MEC induced CPP in a dose-dependent manner. Our finding, combined with other recent studies that report how 4-MEC dose-dependently produces discriminative stimulus effects similar to METH (Gatch et al., 2015; Naylor et al., 2015), strongly indicates the abuse liability of 4-MEC. Notably, the dose of 4-MEC (10 mg/kg) enabling CPP is similar to its "threshold-lowering" dose of intracranial self-stimulation observed by a previous study (Watterson et al., 2014). This effective dose of 4-MEC that induced CPP is considerably higher compared with METH, which may be because 4-MEC is 4 times less potent than METH as a DAT inhibitor (Simmler et al., 2014). The enduring rewarding properties of 4-MEC were shown when 4-MEC-induced CPP was still observed after 2 weeks of withdrawal following CPP training. An interesting observation is that the CPP score appears to increase after the withdrawal period compared with the day after the last injection in both the 4-MEC and METH groups. The enhanced CPP score may relate to the incubation of craving effect, which has been observed after various withdrawal periods following the self-administration of different drugs of abuse (Pickens et al., 2011).

Repeated exposure to psychostimulants produces behavioral sensitization, which is characterized by an enhanced motor-stimulant response to subsequent drug challenges (Steketee and Kalivas, 2011). Behavioral sensitization can be attributed to direct pharmacological action of the drug as well as to learned associations between the environment and the drug experience (Pierce and Kalivas, 1997). It is therefore a useful animal model for studying drug addiction and psychostimulant-induced psychosis. Intriguingly, we found that repeated 4-MEC treatments at 10 mg/kg produced neither development nor expression of locomotor sensitization, although this dose was sufficient for CPP induction. It is well known that addictive drugs such as METH, cocaine, and morphine at doses that induce CPP also potentiate locomotor sensitization. Nevertheless, such dissociation between the effects of 4-MEC on CPP vs sensitization may not be surprising, because sensitization does not always correlate with CPP (Eisener-Dorman et al., 2011; Gregg et al., 2013) or with the reinstatement of drug-seeking behavior (Knackstedt and Kalivas, 2007). Notably, rats chronically treated with 30 mg/kg of 4-MEC failed to show the development of sensitization but were still able to express locomotor sensitization when rechallenged following the 2 weeks of withdrawal.

In addition to their abuse potential, synthetic cathinones often cause adverse psychiatric sequelae, including hallucinations, paranoia, panic attacks, restlessness, and anxiety (Ross et al., 2012; Valente et al., 2014). Thus, we assessed anxiety-like behavior following acute or chronic administration of 4-MEC or METH using the elevated plus maze. We observed that repeated injections of 4-MEC at 30 mg/kg significantly decreased total travel distance with reduced percentages of travel distance

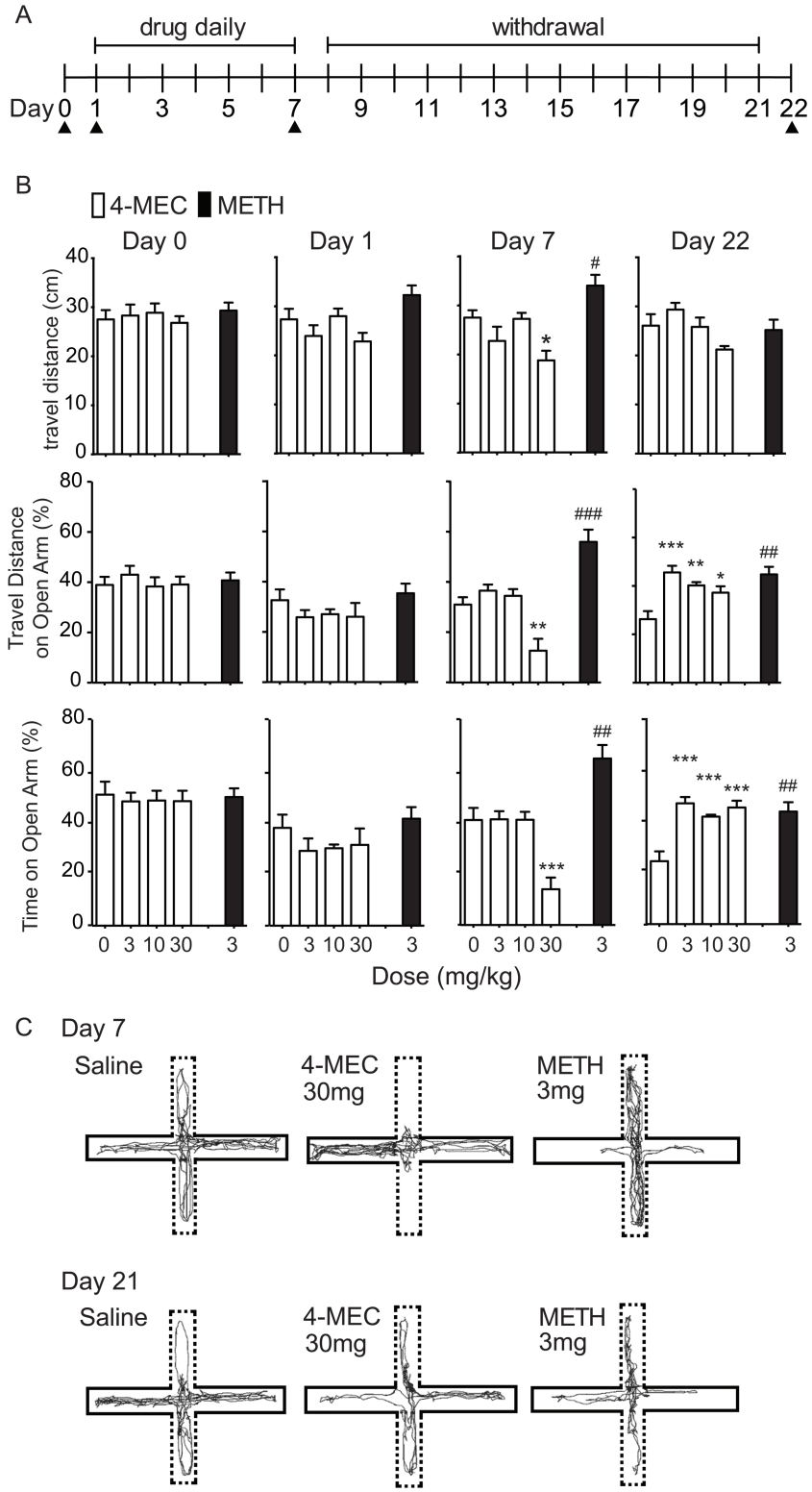

Figure 4. The effects of repeated 4-methylethcathinone (4-MEC) on anxiety-like behavior in the elevated-plus maze tests. (A) The drug treatment regiment. The triangles indicate the days of testing. (B) After repeated 4-MEC injections (ie, on day 7), rats showed less total travel distance and less percent of travel distance and time spent in the open arms compared with closed arms. Two weeks after withdrawal, all groups previously treated by 4-MEC or methamphetamine (METH) exhibited higher percent of travel distance and time spent in the open arms compared with closed arms. $^{*}P<.05$, $^{**}P<.01$, $^{***}P<.001$, comparing 4-MEC with saline groups, Bonferroni's posthoc test. $^{\#\#}P<.01$, $^{\#\#\#}P<.001$, comparing METH with saline group, Student's *t* test. n = 8–10/group. (C) Representative diagrams of travel trace during testings. Dashed lines: open arms; solid lines: closed arms.

and time spent in the open arm. This result suggests that rats repeatedly treated with a high dose of 4-MEC may be more anxious and/or less willing to explore a dangerous environment. In contrast, repeated METH injections at 3 mg/kg significantly increased exploration, which is consistent with previous reports (Tamaki et al., 2008; Pometlova et al., 2012). Interestingly,

after a 2-week withdrawal period from chronic 4-MEC or METH administration, all rats exhibited abnormally reduced anxiety as indicated by the increased percentages of travel distance and time spent in the open arm. Previous studies demonstrated that repeated psychostimulant injections induce anxiety-related behavior after 1 to 8 days of withdrawal (Perrine et al., 2008; Kitanaka et al., 2010; El Hage et al., 2012). Our present study is the first to report that chronic METH or 4-MEC injections can increase exploration and reduce anxiety in the elevated plus maze after 2 weeks of withdrawal. This effect may involve drug-related place conditioning and/or incentive sensitization to the open arm of the maze.

There is a high level of diversity in different subtypes of synthetic cathinones in their structural and pharmacological profiles; hence, the behavioral alterations caused by those different subtypes may vary. 4-MEC is a nonselective monoamine uptake inhibitor and serotonin releaser and is classified as a type of cathinone, so-called cocaine-MDMA-mixed cathinone, such as methylone and mephedrone (Simmler et al., 2014). Interestingly, a low dose of mephedrone (0.5 mg/kg) is adequate to elicit locomotor sensitization, while a much higher dose (30 mg/kg) is necessary to induce CPP (Lisek et al., 2012). Therefore, the dissociation observed between CPP and locomotor sensitization at different doses of 4-MEC may be a distinct feature of this category of synthetic cathinones.

The behavioral differences following 4-MEC or METH injections may be due to their different potency to inhibit dopamine and serotonin uptake. Compared with METH, 4-MEC is 4 times less potent as a DAT inhibitor but 3 times more potent as a SERT inhibitor (Simmler et al., 2014). A low DAT/SERT inhibition ratio possibly relates to a lower abuse potential and a more "entactogenic" MDMA-like effects of a drug (Liechti et al., 2000; Wee et al., 2005; Rothman and Baumann, 2006). This may explain how 4-MEC may have less reinforcing efficacy, as indicated by a higher dose threshold for CPP induction and attenuated development of sensitization compared with METH in the present study.

In sum, these results reveal that 4-MEC has addictive potential due to its rewarding properties. Chronic 4-MEC may not be effective in eliciting psychomotor agitation but is still able to cause significant behavioral deficits relating to anxiety that can last even after a withdrawal period. Future investigations are urgently needed to comprehensively understand the possible effects of 4-MEC and other synthetic cathinones on addiction-related behaviors and other psychiatric conditions.

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Statement of Interest

None.

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