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Research report

Repetitive administration of aripiprazole enhances locomotor response to methamphetamine in mice

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ABSTRACT

Dopamine receptor partial agonists have been proposed as potential candidate agents to treat psycho-stimulant abuse. Aripiprazole is a dopamine D2/D3 receptor partial agonist that is currently used as an antipsychotic drug in clinical settings. This study aimed to examine whether aripiprazole can suppress the methamphetamine-induced locomotor response in mice that is used as an indicator for potential clinical use. In ICR mice pre-exposed to methamphetamine (1 mg/kg subcutaneous injection once daily for 7 days), we found that mice receiving repetitive treatments with aripiprazole (1, 5, and 10 mg/kg, respectively; intraperitoneal injection once daily for 1 week) showed a significantly enhanced locomotor response upon re-exposure to methamphetamine (0.5 mg/kg), compared with animals that received a vehicle treatment. Furthermore, we found that methamphetamine-naïve mice receiving repetitive treatment with aripiprazole (5 mg/kg intraperitoneal injection once daily for 1 week) also showed a significantly enhanced locomotor response to acute challenge with methamphetamine (0.5 mg/kg), compared with animals receiving the vehicle treatment. The enhanced locomotor response to methamphetamine in both methamphetamine-pre-exposed and methamphetamine-naïve mice lasted at least four weeks in this study. Our data suggest that aripiprazole may enhance the effects of methamphetamine, so caution should be exercised when prescribing to individuals with histories of stimulant use.

1. Introduction

Methamphetamine is one of the most popular illegal drugs of abuse in Taiwan. There has also been an increasing rate of methamphetamine addiction in the United States and other countries in recent years [21,44]. Methamphetamine is highly addictive with a high relapse rate after abstinence. Methamphetamine addiction can have serious consequences on personal health and public security [36]. Current pharmacotherapy for methamphetamine addiction has only limited effectiveness, and there is an urgent need for effective drugs to treat methamphetamine-related health issues, including drug craving, withdrawals, and psychosis [24,36,43].

Several lines of study have indicated that aberrant dopamine neurotransmission in the brain is associated with the propensity for and the development of drug addiction, and also underlies the pathophysiology of drug craving, withdrawal symptoms, and psychiatric disturbances [8,27,44]. Hence, several studies have proposed that dopamine receptor partial agonists that can modulate the dopamine neurotransmission system are potential therapeutic agents to treat psycho-stimulant addiction [10,29,30]. Aripiprazole is the first dopamine receptor partial agonist that is currently used to treat schizophrenia [6,18]. Due to its unique pharmacological property of stabilizing the dopamine neurotransmission in the brain [12,39], aripiprazole was proposed as a potential therapeutic candidate for stimulant dependence [40]. Aripiprazole has been shown to attenuate the discriminative-stimulus and subject-rated effects of amphetamine in humans [19,41], decrease the desire for and the use of cocaine in schizophrenic patients co-morbid with cocaine dependence [2], and reduce craving in alcohol dependence [22]. In animal studies, aripiprazole was shown to block reinstatement of cocaine seeking [9], and improve the decreased motivation during acute withdrawal of amphetamine in rats [37]. Taken together, these studies indicated that aripiprazole is a promising candidate for the treatment of stimulant addiction.

Repetitive use of methamphetamine can induce sensitization of neuronal circuits in the brain, which may be the neurobiological basis of drug craving and psychosis in methamphetamine addicts

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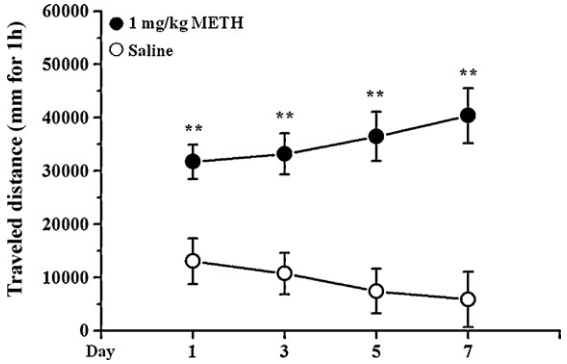

Fig. 1. The locomotor activity of ICR mice receiving a once-daily subcutaneous injection of methamphetamine (1 mg/kg) or saline for seven consecutive days. Asterisks (**) indicate a p value is less than 0.01.

[3,16,35,46]. Repetitive administration of methamphetamine in rodents also induces behavioral sensitization, which is characterized by the enduring augmentative locomotor activity and stereotyped behaviors upon subsequent drug exposure. Behavioral sensitization in rodents has been considered as an animal model for the drug craving and psychosis of stimulant addiction in humans [13,33–34]. Hence, agents that can reverse stimulant-induced behavioral sensitization in animals are considered as potential candidates to treat stimulants addiction [38]. Aripiprazole has been shown to block acute methamphetamine-induced hyperactivity in rodents, like the other antipsychotic drugs [26,42], but the effect of aripiprazole on methamphetamine-induced behavioral sensitization has not been studied. The purpose of this study was to evaluate the effects of aripiprazole on methamphetamine-induced behavioral sensitization in mice.

2. Materials and methods

2.1. Animals

Male Institute of Cancer Research (ICR) mice (25–30 g) were housed in a temperature and humidity-controlled environment with a 12-h light/dark cycle, and had free access to food and water. All experimental procedures were approved by the Institutional Animal Care and Use Committee, and all the animals were taken care of according to the Karolinska Institute's Animal Care Guidelines.

2.2. Drugs

Methamphetamine hydrochloride was provided by the National Bureau of Controlled Drugs, Department of Health, Taiwan, and dissolved in saline. Aripiprazole was kindly provided by Otsuka Pharmaceutical, Tokushima, Japan, and dissolved in 20% dimethylformamide, then adjusted to pH 5–6.

2.3. Measurement of locomotor activity

Each mouse was placed in a transparent acrylic animal cage (42 cm length × 42 cm width × 30 cm height) and allowed a 30 min habituation period before methamphetamine treatment. Locomotor activity was then measured for a period of 60 min immediately after methamphetamine injection, using an infrared sensor system (VersaMax; AccuScan Instruments, Inc., Ohio, USA). The total distance traveled was generated by the VersaDat program (VersaMax; AccuScan Instruments, Inc., Ohio, USA).

2.4. Experimental procedures

To demonstrate the locomotor response of methamphetamine (1 mg/kg), a total of 32 ICR mice were randomly assigned to two groups. One group (n = 16) received a subcutaneous injection of 1 mg/kg of aripiprazole (once daily for 7 days), and the other group (n = 16) received a saline injection as controls. The travel distance of each animal was recorded for one hour immediately after injection, and the results are shown in Fig. 1.

To assess the effect of aripiprazole on methamphetamine-pre-exposed animals, we designed an experimental scheme as shown in Fig. 2. Three doses of aripiprazole were tested in this study, i.e., 1, 5, and 10 mg/kg, respectively. For the experiment with each dose, eight animals were randomly assigned to two groups; each animal received a subcutaneous (s.c.) injection of methamphetamine (1 m/kg) once daily for 7 days. From the eighth day, the animals in the experimental group (n = 4) received an i.p. injection of aripiprazole (1, 5, or 10 mg/kg) once daily for 7 days, while the control animals (n = 4) received a vehicle injection once daily for one week. At days 15, 23, 31, and 39, all animals were challenged with a single injection (s.c.) of methamphetamine (0.5 mg/kg). The travel distance of each animal was recorded for 1 h immediately after the challenge injection of methamphetamine. The experiment was repeated once, and the data were pooled together for analysis.

To examine the effect of aripiprazole on methamphetamine-naïve mice, eight animals were randomly assigned to two groups. Each animal received an s.c. injection of saline once daily for 7 days. From the eighth day, one group of animals received an i.p. injection of aripiprazole (5 mg/kg) once daily for 7 days, while the other group of animals received a vehicle i.p. injection as a control once daily for one week. At days 15, 23, 31, and 39, each animal was challenged with a single injection (s.c.) of methamphetamine (0.5 mg/kg), and travel distance was recorded as described. The experiment was repeated once, and the data were pooled together for analysis.

2.5. Data analysis

The Student's t-test was used to compare the mean between two groups. One-way analysis of variance (ANOVA) was performed to compare the mean among three groups, and post hoc analysis using the Scheffe test was applied when appropriate. A p value of less than 0.05 was considered statistically significant.

3. Results

We first demonstrated that ICR mice receiving an injection of methamphetamine (1 mg/kg) showed significantly higher locomotor activity than the control animals, as shown in Fig. 2. In the following experiments, we found that in methamphetamine-pre-exposed mice, the animals that received repetitive treatment with aripiprazole (1 mg/kg) had a significantly enhanced locomotion response to acute methamphetamine challenge compared with those that received the vehicle treatment. The enhanced locomotor response to methamphetamine persisted for at least 4 weeks as shown in Fig. 3a. The effect of aripiprazole was observed in mice that received different doses (5 and 10 mg/kg) using the same experimental regimen. The results are shown in Fig. 3b and c, respectively. Comparing the peak-effect of different doses of aripiprazole treatment, we found that a dose of 5 mg/kg had the most prominently enhanced locomotor effect upon re-exposure to methamphetamine, compared with the other two doses; the data are summarized in Table 1. Furthermore, we observed that methamphetamine-naïve mice receiving repetitive treatment with aripiprazole (5 mg/kg for 1 week) also showed a significantly enhanced locomotor response to acute challenge with methamphetamine, as compared with the control animals that received the vehicle treatment. The enhanced response persisted for 4 weeks, as shown in Fig. 3d. Finally, in saline-pre-treated animals that received repetitive aripiprazole (5 mg/kg) treatment for 1 week, we observed an enhanced locomotor response to acute challenge with methamphetamine that was almost indistinguishable from that of the methamphetamine-pre-exposed animals that received the same repetitive aripiprazole treatment (5 mg/kg, for 7 days) and acute methamphetamine challenge; the data are shown in Fig. 4.

3.1. Discussion

Antipsychotic drugs such as haloperidol and clozapine were shown to block the induction of behavioral sensitization to amphetamine in rodents [14,23]; however, established behavioral sensitization cannot be ameliorated by haloperidol and other dopamine antagonists [14–15]. In this study, contrary to our expectations, we found that there was a significantly increased locomotion response to methamphetamine challenge in methamphetamine-pre-exposed mice after repetitive treatment with aripiprazole, compared with that in animals receiving a vehicle treatment. In addition, we also observed that the enhanced locomotion response to acute methamphetamine challenge occurred in methamphetamine-naïve mice that received