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Comparison of single *versus* repeated methamphetamine injection induced behavioral sensitization in mice

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HIGHLIGHTS

- Single METH injection produced similar magnitude sensitization as repeated injection.
- Sensitized locomotion peaked 8 days after a single METH injection.
- Single METH-induced sensitization lasted at least 21 days.

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ABSTRACT

Repeated exposure to drugs of abuse produces a persistent behavioral sensitization to stimulants, which is often used to study drug-associated behavioral plasticity. Interestingly, even a single exposure to some drugs of abuse is sufficient to elicit long-lasting behavioral sensitization. However, few studies have directly compared the magnitude of sensitization between single *versus* repeated drug treatments. This study examined the magnitude and duration of single methamphetamine (METH) injection-induced behavioral sensitization and compared it to the more typical repeated drug injection-induced sensitization in mice. Different groups of mice were injected with METH (0.5, 1.0, 2.0 mg/kg, i.p.) only once or daily for 7 consecutive days. A challenge dose of METH (1.0 mg/kg, i.p.) was tested 7 days later. The time-course of a single METH injection-induced behavioral sensitization was assessed where METH (2.0 mg/kg, i.p.) was injected and a challenge dose of METH (1.0 mg/kg, i.p.) was tested after different drug-free periods. Single METH injection produced similar magnitude of behavioral sensitization as compared to repeated injection. Such a sensitized locomotor response peaked 8 days after METH injection and lasted for at least 21 days. This long lasting behavioral alteration induced by single METH injection suggests the value of future studies to explore the underlying neural mechanisms, particularly in comparison to those underlying repeated METH-induced sensitization.

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Methamphetamine (METH) is a highly abused central nervous system stimulant with high reinforcing properties [16], and its prolonged use results in dependence and psychosis [12]. Repeated administration of METH leads to a progressive increase in drug response on re-exposure to the drug. Behavioral sensitization, the main characteristics of which are progressively intensifying, persistent and stimulant-inducible response during re-exposure, is thought to play a key role in certain aspects of drug addiction such as compulsive drug-seeking behavior [2,17,19]. Thus, behavioral sensitization in rodents is widely used as a model for the study of behavioral plasticity associated with repeated drug treatment [4,17]. The degree of drug-induced behavioral sensitization depends on various factors such as dose, dosing regimen and environmental context. For instance, repeated drug exposure with long intervals is more effective to induce sensitization as compared to chronic exposure to either high and/or escalating dosage with short intervals [17,23]. Interestingly, even a single exposure to cocaine [5,7], amphetamine [18,22] and morphine [6,10,21] can produce long-lasting behavioral and neurochemical sensitization.

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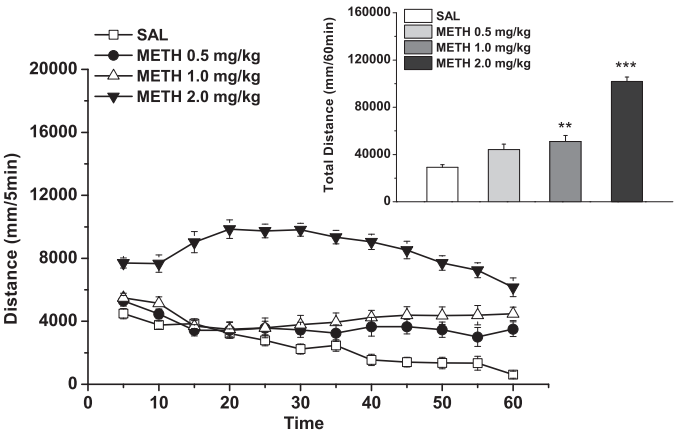

Fig. 1. Dose–effect relationship of single METH injection-induced hyperactivity in mice. Mice were injected with saline or METH (0.5, 1.0, 2.0 mg/kg, i.p.) and then placed individually in the test chambers to record the locomotion for 60 min. Data are expressed as mean ± S.E.M. $^{**}P < 0.01$, $^{***}P < 0.001$ *vs.* saline group. $n = 11–12$ per group.

Although the majority of the literature utilizes repeated treatment regimen to induce behavioral sensitization, few studies have systematically compared the magnitude of sensitization induced by single or repeated drug treatment. This study attempted to address this issue by directly comparing two treatment regimens for their ability to induce behavioral sensitization.

Male C57BL/6J mice (initial body weight 18–20 g) were obtained from the Institute of Laboratory Animal Science, Chinese Academy of Medical Sciences and housed (5–6 per cage) in temperature- and humidity-controlled (22 ± 1 °C and 50 ± 10%) environment with 12/12 h light/dark cycle (lights on at 08:00 AM) and free access to food and water. All mice were habituated to the housing conditions for 1 week before experiments. During test days, the animals were kept in the test room at least 30 min before recording their locomotor activity. All experiments were conducted in Dr. Jian-Hui Liang' lab in National Institute on Drug Dependence (China), according to the NIH Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23, revised 1996) and were approved by the Peking University Animal Care and Use Committee.

Locomotor activity was measured in four identical chambers (25 cm × 25 cm × 45 cm) situated in a sound-attenuating cabinet and the total distance of horizontal locomotor activity was recorded with a video camera placed above the chamber and analyzed with the Digbehv software (DigBehv-LG Ver 2.0, Shanghai Jiliang Software Technology Co. Ltd., Shanghai, China). METH–HCl was provided by National Institute on Drug Dependence (China). The drug was dissolved in 0.9% saline and administered intraperitoneally in a volume of 10 ml/kg.

For acute studies, mice were injected with saline or METH (0.5, 1.0, 2.0 mg/kg, i.p.) and then immediately put into test chambers individually to monitor the locomotor activity for 60 min (Fig. 1). For studies that compared acute or repeated (7 daily injection) METH injection-induced sensitization, mice were injected with saline or METH (0.5, 1.0, 2.0 mg/kg, i.p.) only once or daily for 7 consecutive days, but the locomotion was only monitored on Day 1 or both Day 1 and Day 7 (data not shown). All mice were re-tested one week later after a challenge dose of 1.0 mg/kg METH (Fig. 2A and B). For studies that examined the duration of single METH injection-induced behavioral sensitization, mice were injected with saline or METH (2.0 mg/kg, i.p.) and then left for 60 min in the test chambers on Day 1 (data not shown). After various drug-free periods (housed in the home cages with no treatment or test), mice received the challenge injections of METH (1.0 mg/kg, i.p.) on Day 2, 3, 4, 8, 15, 22 and the locomotor activity was recorded for 60 min (Fig. 3).

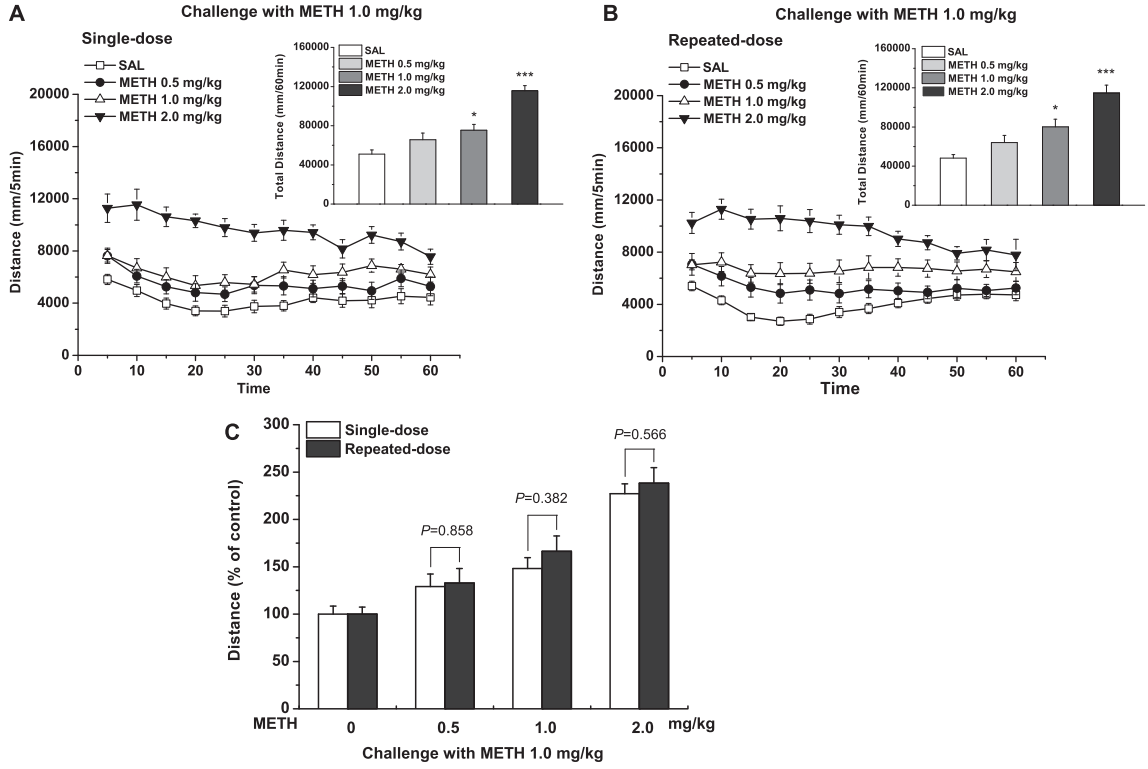

Fig. 2. Locomotor response to 1 mg/kg METH challenge in mice injected with a single or repeated dose of METH. (A) Single-dose METH injection-induced behavioral sensitization; (B) repeated-dose METH injection-induced behavioral sensitization; (C) comparison of the locomotor sensitization induced by single and repeated dose injection of METH. The data were normalized to the corresponding saline group (SAL + METH 1.0 mg/kg, taken as 100%) and were expressed as mean ± S.E.M. $n = 11–12$ per group. See Fig. 1 for other details.