Neuroscience Letters 638 (2017) 21–26

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

The expression of amphetamine sensitization is dissociable from anxiety and aversive memory: Effect of an acute injection of amphetamine

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HIGHLIGHTS

- Expression of amphetamine locomotor sensitization is not accompanied with anxiety.
- Low basal anxiety levels predict high increase in AMPH-induced locomotor activity.
- An increase in inter-trial interval attenuate the retrieval of EPM aversive memory.
- A single AMPH injection restore retrieval of EPM aversive memory.

ARTICLE INFO

Article history:
Received 18 October 2016
Received in revised form
29 November 2016
Accepted 5 December 2016
Available online 6 December 2016

Keywords:
Amphetamine
Locomotor sensitization
Anxiety
Aversive memory
Elevated plus maze

ABSTRACT

The repeated administration of amphetamine can lead to locomotor sensitization. Although the repeated administration of amphetamine has been associated with anxiety and impaired working memory, it is uncertain if expression of amphetamine sensitization is associated with modifications of emotional memories. To address this issue, rats were injected once daily with amphetamine for five consecutive days (1.5 mg/kg). After four days of withdrawal, rats were delivered an acute amphetamine injection to assess the expression of sensitization. A single exposure to an elevated plus maze (EPM), 24 h after the last injection of amphetamine, showed that amphetamine sensitization is not accompanied by anxiety. Next, aversive memory was assessed using an 11 day inter-trial interval between the EPM Trial 1 and EPM Trial 2. Rats administered with saline showed a percentage of open arms time (% OAT) in Trial 2 that was comparable to Trial 1, demonstrating a reduction in the retrieval of aversive memory. However, rats sensitized after the EPM Trial 1 showed a significant decrease in the % OAT in Trial 2. Importantly, a decrease in the % OAT in Trial 2 compared to Trial 1 was also observed after a single injection of amphetamine 24 h before Trial 2. These results show a facilitation in the retrieval of aversive memory, and suggest that a previous amphetamine injection is enough to produce a protracted activation of neural circuits necessary for the retrieval of aversive memory.

1. Introduction

Amphetamine (AMPH) is a psychostimulant drug whose abuse has been associated with the development of addiction and alterations in learning, memory, and emotions [1]. Some emotions, such as anxiety, are increased with the chronic use of AMPH as observed in clinical and pre-clinical studies. In clinical studies, Hall et al. showed that AMPH abusers reported an increase in depression and anxiety following drug usage [2]. Moreover, in preclinical studies involving rodents, a decrease in open arms time (OAT) in the elevated plus maze (EPM) has been observed after both short- and long-withdrawal following chronic AMPH exposure, indicating an increase in anxiety-like behavior [3,4]. Importantly, the repeated and chronic exposure to AMPH have been associated with the development of behavioral sensitization [5], a pre-clinical model used to indirectly study the incentive motivational effects of AMPH [6]. Although chronic AMPH exposure is associated with anxiety, it is unclear if the neuroplastic changes that accompany

Abbreviations: AMPH, amphetamine; ANOVA, analysis of variance; CAE, closed arms entries; EPM, elevated plus maze; OAT, open arms time; HR, high responder.

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http://dx.doi.org/10.1016/j.neulet.2016.12.009
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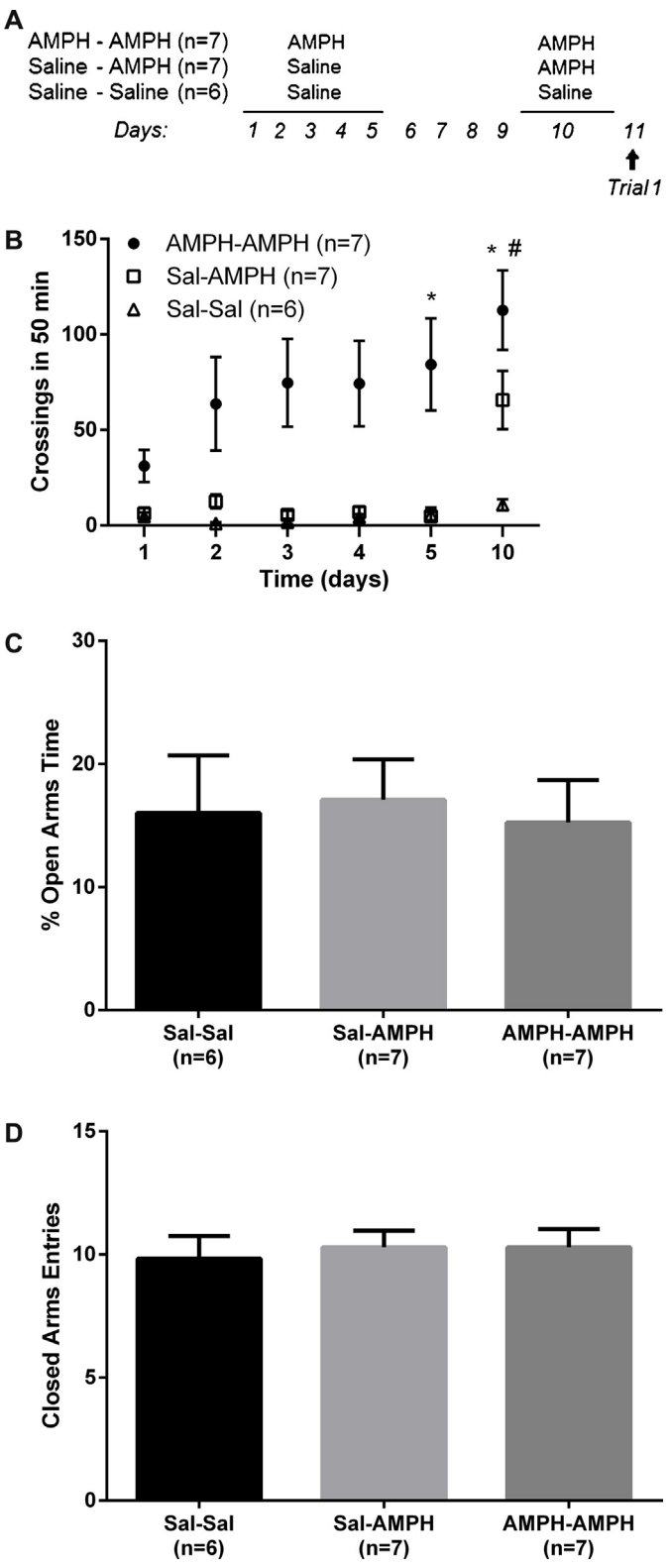

Fig. 1. Expression of amphetamine sensitization is not accompanied by anxiety-like behavior.
(A) To study anxiety-like behavior, three experimental groups were used. Rats were repeatedly injected with either AMPH or saline (day 1 to day 5). After four days of abstinence, rats were acutely injected with either AMPH or saline (day 10). An EPM Trial 1 was carried out 24 h after the last AMPH or saline injection (day 11). (B) Crossings in the locomotor activity box, an index of horizontal locomotor activity, were measured for 50 min immediately after AMPH injection (1.5 mg/kg) on days 1–5 (development phase) and day 10 (expression phase). Each data point represents mean ± SEM. * $p < 0.001$ vs day 1 of AMPH–AMPH group; # $p < 0.05$ vs day 10 of Saline-AMPH group, according to Bonferroni post-hoc test. (C) Percentage of open arms time in rats that were exposed to an EPM (Trial 1, day 11), twenty-four hours after the expression of locomotor sensitization. Statistical analysis shows no significant differences between groups (one-way ANOVA, $p > 0.05$). (D) Closed arms entries. Statistical analysis shows no significant differences between groups (one-way ANOVA, $p > 0.05$). Bars represent mean ± SEM.

the expression of AMPH-induced behavioral sensitization increases anxiety-like behavior. Given that anxiety-like behavior emerges immediately after a chronic treatment of AMPH [7], it is likely that the expression of AMPH sensitization is accompanied by a decrease in EPM open arm time.

Behavioral sensitization after chronic AMPH administration has been associated with impairment in working memory and with cognitive deficits [8], whereas no effect has been observed in spatial memory tasks [9]. Consistent with this observation, Eldred and Palmiter have suggested that synaptic plasticity associated with AMPH sensitization is not involved in motor learning tasks [10]. However, whether the expression of AMPH sensitization modifies emotional memories remains to be studied. In addition to the study of anxiety-like behaviors, the EPM has been used to assess emotional memories [11]. A reduction in OAT has been observed after a second exposure to the maze, which has been related to aversive learning processes [12]. This test-retest paradigm has been used to study memory impairments produced by pharmacological manipulations [13]. Interestingly, changes in the inter-trial interval can modify the retrieval of this aversive memory; an attenuation in OAT reduction in trial 2 is observed with 8 days [14], 11 days [15] or 28 days [16] of inter-trial interval. These results suggest a temporal dependency in the retrieval of emotional memories. Although it has been reported that acute AMPH improves the retrieval of emotional memories [17–19], the effect of AMPH sensitization on emotional memories, such as aversive memory, is unclear.

We hypothesized that the expression of AMPH locomotor sensitization is accompanied by an increase in anxiety and an enhanced retrieval of aversive memory. To measure anxiety-like behaviors, an EPM Trial 1 was carried out 24 h after the expression of AMPH locomotor sensitization. To measure the effect on the retrieval of aversive memory, a second EPM trial (Trial 2) was carried out 24 h after the expression of AMPH locomotor sensitization, with an inter-trial interval of 11 days.

2. Methods

2.1. Animals

Adult male Sprague-Dawley rats (300–340 g) were grown in the Animal Care Facility of the Biological Sciences, Pontificia Universidad Católica de Chile, under the supervision of a veterinarian. During drug treatment, rats were maintained in the Animal Care Facility of the Department of Pharmacy, Pontificia Universidad Católica de Chile, following the instruction of a protocol approved by the veterinarian. Rats were housed in a colony room in groups of three per cage and were kept at a room temperature between 22–24 °C on a 12 h light/dark cycle (lights on at 7 AM, Eastern Standard Time) with access to food and water *ad libitum*. All procedures were in strict accordance with the guidelines published in the "NIH Guide for the Care and Use of Laboratory Animals" (8° Edition) and the principles presented in the "Guidelines for the Use of Animals in Neuroscience Research" by the Society for Neuroscience. Rats were handled for one week before starting the experiments.

2.2. Amphetamine locomotor sensitization

The process of amphetamine locomotor sensitization was developed according to a schedule as described previously [20]. Three treatment groups were used: for five consecutive days (days 1–5),