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Effects of spatial memory on morphine CPP and locomotor sensitization in mice

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HIGHLIGHTS

- We investigated the relationship between spatial memory and addiction.
- The study employed the CPP and behavior sensitization models simultaneously.
- Mice with low spatial memory ability were more susceptible to addiction.

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ABSTRACT

Drug addiction is associated with memory processes. We simultaneously measured conditioned place preference (CPP) and locomotor sensitization to investigate the influence of spatial memory retrieval on morphine reward and psychomotor excitement. According to their performance in space probe trial involving the Morris water maze mice were assigned to high (including morphine and saline subgroups, H-Mor and H-Sal) and low spatial memory retrieval ability groups (L-Mor and L-Sal). Morphine (10 mg/kg) produced significant CPP in L-Mor and H-Mor mice, although, L-Mor mice showed a significantly greater response to morphine. During the development period of behavior sensitization, no significant group-by-day interaction was found. However, locomotor activities of L-Mor mice were also significantly higher than H-Mor mice during the expression period of behavior sensitization. Our findings suggested that the spatial memory retrieval ability of mice influences morphine CPP, as well as behavioral sensitization. Thus, spatial memory might be implicated in drug addiction.

1. Introduction

Drug addiction is a complex phenomenon characterized by compulsive drug seeking, drug use, and craving [1]. Addiction is considered as a disease of "pathological learning", suggesting a pathological usurpation of the neural mechanism of learning and memory that under normal circumstances serve to shape survival behaviors related to the pursuit of rewards and the cues that predict them [6]. Because of the unique and stable characteristics of addiction, it has been referred to as "addiction memory" [3,11] or "aberrant memory" [1].

Associative learning is involved in drug addiction; and has an important role in the mechanism of relapse. Relapses often occur when drug-addicted people are exposed to drug-associated cues (people, places, paraphernalia), even after a period of abstinence [2,6,15,17,20]. In contrast, people who became addicted to heroin were able to stop drug use when returning to the distinct context [14]. In addition, abundant evidences have also demonstrated the correlation between drug addiction and memory. For example, heterozygous mice with latent learning impairment in the water-finding task did not develop morphine dependence [12]. Activation of the hippocampus, a structure classically associated with spatial learning and memory, had a promoting effect on morphine CPP [13,19]. Numerous studies have confirmed that cognitive processes of animals improve immediately following administration of nicotine [9]. However, pre-training administration of morphine impaired memory formation in the mouse step-down inhibitory avoidance test [10]. Also prenatal cocaine exposed mice exhibit a deficit in recall of an extinguished cue-conditioned fear [8].

Drug addiction and memory processes share common neurobiological mechanisms. They may be modulated by the same neurotrophic factors, share certain intracellular signaling cascades to induce the expression of specific genes, and are accompanied by adaptive changes in neuronal morphology with a similar diversity in synaptic plasticity (e.g., long-term potentiation, long-term depression) [5,11].

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Another study demonstrated inter-individual variations in spatial learning ability (spatial navigation learning in the Morris water maze) influenced the morphine-reward effect as demonstrated by CPP; morphine-induced CPP was more strongly associated with poor-response mice than good-response mice [18]. However, it is not clear whether individual differences in spatial memory retrieval are intrinsically related to the morphine reward effect and morphine psychomotor excitement. Individual variation in behavioral responses may account for the individual differences in vulnerability to drug addiction in mice. In this study, we simultaneously measured CPP and locomotor sensitization to examine the effects of spatial memory retrieval ability on morphine reward and psychomotor effects in mice.

2. Material and methods

2.1. Animals

Male Kunming mice ($n = 72$; 25 ± 2 g, Vital River Laboratory Animal Technology Co., Ltd., Beijing, China) were housed in standard lab Plexiglas cages ($45 \times 30 \times 25$ cm, length × width × height, 6 mice/cage) in a temperature-controlled ventilated colony room on a 12-h light/12-h dark cycle (experiments were conducted during the light period) with food and water available. All animal procedures were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the local Committee of Animal Use and Protection.

2.2. Morris water maze task

2.2.1. Apparatus

The Morris water maze consisted of a steel circular pool (98 cm in diameter, 60 cm in height) partially filled with water (23 ± 1 °C). Ink was used to render the water opaque. The pool was divided into four quadrants with four starting locations labeled north (N), east (E), south (S), and west (W) at equal distances on the rim. An invisible escape platform was submerged 1 cm below the surface and placed in the center of the north quadrant.

2.2.2. Procedure

On day 1, each mouse was placed in the Morris water maze for 2 min to adapt to the new environment. Training sessions occurred on days 2–4. Twice a day, each mouse was given three consecutive training trials to find the hidden platform. Each mouse was gently placed in the water with the nose pointing toward the wall in the center of the E, S, and W quadrant by turns, which varied from trial to trial. Latency to find the platform was recorded up to 90 s. The mouse was allowed to remain on the platform for 15 s, and then was removed from the maze to its home cage. If the mouse did not find the platform within 90 s, the latency was assigned as 90 s, and the animal was placed on the platform for 15 s.

Day 5 was the probe trial day. The escape platform was removed from the pool. Each mouse was allowed to search for the platform in three trials, each beginning with the E, S, and W quadrant by turns and lasting 60 s. Time spent searching for the platform in the N quadrant, where the hidden platform was previously located, was recorded and the average time spent in the N quadrant over three trials was defined as the memory score. The mice were divided into low, middle, and high memory groups according to their memory scores. As indicated in Table 1, the high and low memory groups were assigned to morphine (H-Mor/L-Mor) and saline (H-Sal/L-Sal) groups. All mice were tested in the following CPP and behavior sensitization experiments.

2.3. Conditioned place preference and behavior sensitization

2.3.1. Apparatus

The CPP apparatus consisted of two chambers ($40 \times 40 \times 50$ cm, length × width × height) separated by a guillotine door that could be removed to allow access to both chambers or inserted to confine the animal to a single chamber. The white chamber had a white wall with black stripes and a textured floor. The black chamber had a black wall and a smooth floor. Naïve rats tend to display a slight preference for the black chamber; thus, the white chamber was morphine-paired and the black chamber was saline-paired. Four pairs of CPP apparatus were used in this study, in which CPP and behavior sensitization experiments were performed simultaneously. A video camera was mounted above the chambers and connected to a computer to record residence time in the morphine-paired chamber during the CPP test and locomotor activity in the CPP development and behavioral sensitization expression stages. The videos were analyzed with LA analysis software (Institute of Psychology, Chinese Academy of Sciences, Beijing, China).

2.3.2. Procedure

The CPP procedure consisted of three phases: (1) preconditioning, (2) conditioning, and (3) postconditioning. The preconditioning phase was performed on days 6–7. The guillotine door was open and the mice were adapted to the chambers for 15 min daily. The average residence time in the morphine-paired chamber over both days was defined as the CPP pretest score. The behavior sensitization pretest was performed on days 8–9. All mice were placed in the morphine-paired chamber for 60 min after receiving a saline injection and locomotor activity was measured. The average locomotor activity over both days was defined as the baseline locomotor activity.

Conditioning was performed on days 10–15. In each group, half of the mice were placed in the morphine-paired chamber in the morning and in the saline-paired chamber in the afternoon. The order was reversed for the other half of the mice in each group. Immediately before being confined in the morphine-paired chamber, each mouse was injected with morphine (10 mg/kg). Immediately before being confined in the saline-paired chamber, each mouse received an injection of 1 mL/kg physiological saline. The mice remained in the chamber for 45 min. Thus, each mouse received two trials daily with at least 6 h separating the drug and saline training sessions. The H-Sal and L-Sal mice were treated with saline in each trial and saline-paired with both chambers. The computer recorded the locomotor activity of each mouse in the morphine-paired chamber, representing the development of behavior sensitization.

On day 16 (postconditioning phase), half of the mice in each group were placed in the saline-paired chamber and the other half were

Table 1
Group assignment, timeline and treatment.

Group	Treatment						
	Days 1–5 MWZ	Days 6–7 CPP pretest	Days 8–9 sensitization pretest	Days 10–15 CPP and sensitization	Day 16 CPP test	Days 17–22 withdrawal	Day 23 sensitization test
H-Sal ($n = 12$)	No	No, test (15 min)	Sal (60 min)	Sal (45 min)	No, test (15 min)	No	Mor (60 min)
H-Mor ($n = 12$)	No	No, test (15 min)	Sal (60 min)	Mor (45 min)	No, test (15 min)	No	Mor (60 min)
L-Sal ($n = 12$)	No	No, test (15 min)	Sal (60 min)	Sal (45 min)	No, test (15 min)	No	Mor (60 min)
L-Mor ($n = 12$)	No	No, test (15 min)	Sal (60 min)	Mor (45 min)	No, test (15 min)	No	Mor (60 min)

Abbreviations: Sal, saline; Mor, morphine hydrochloride; No, no treatment; MWZ, Morris water maze; CPP, conditioned place preference.

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