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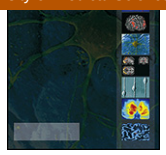

Intrahippocampal administration of D2 but not D1 dopamine receptor antagonist suppresses the expression of conditioned place preference induced by morphine in the ventral tegmental area

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HIGHLIGHTS

- Intra-CA1 D2 dopamine receptors are involved in the expression of morphine-induced CPP.
- Blockade of D1 receptors in CA1 had no effect on the expression of morphine-CPP.
- Intra-CA1 injection of D1/D2 receptor antagonists alone could not induce CPP.

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ABSTRACT

The ventral tegmental area (VTA) as a major source of dopamine neurons projecting to cortical and limbic regions has a crucial role in reward and addiction. The current study assessed the role of D1 and D2 receptors within the dorsal hippocampus (CA1) in the expression of conditioned place preference (CPP) by intra-VTA morphine in the rats. In the present study, 160 adult male albino Wistar rats weighing 220–290 g were bilaterally implanted by two cannulae into the CA1 and VTA. The CPP paradigm was done and animal displacement, conditioning score and locomotor activity were recorded. For blocking the dopamine D1/D2 receptors in the dorsal hippocampus, SCH23390 (0.02, 0.05, 0.2 and 0.5 μg per side) or sulpiride (0.25, 0.75, 1.5 and 3 μg per side) were microinjected into the CA1, just 5 min before the CPP test on the post-conditioning day. All animals received intra-VTA morphine (1 μg per side) during 3-days conditioning phase. Our results showed that sulpiride (1.5 and 3 μg) but not SCH23390 in the dorsal hippocampus significantly decreased the expression of CPP induced by intra-VTA morphine ($p < 0.001$). Intra-CA1 administration of these antagonists alone, in all doses, could not induce CPP. We suggest that D2 receptors in the CA1 region of hippocampus have a key role in the expression of CPP induced by morphine at the level of the VTA and there is a relationship between dopaminergic D2 receptors and opioidergic systems in these areas in reward circuit.

1. Introduction

It is now well established that almost all drugs of abuse converge on a common circuitry in the brain which includes the ventral tegmental area (VTA), nucleus accumbens (NAc), hippocampus, hypothalamus and prefrontal cortex [15]. The mesolimbic dopaminergic system is necessary for the acquisition of morphine-induced CPP [35,34]. The hippocampus and the VTA form a dopaminergic loop, which may regulate some kind of information into the long-term memory that affects hippocampal-dependent learning [17]. Dopamine D1 receptors have an important role in functional interaction between the VTA and the hippocampus [22]. Activation of the VTA increases dopamine (DA) release in the hippocampus and seems to have a pivotal role in hippocampal plasticity [11,30]. The VTA is an important site for synaptic modifications involved in learning and memory to associate morphine exposure with a specific environment [9]. It has also been suggested that the VTA is an important area for reward-related learning [35] through the dopaminergic projections to the NAc and hippocampus.

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Dopamine conducts its action by activating two group-specific receptors, D1-like and D2-like, both of which belong to the family of G-protein coupled receptors [20]. These two types of dopamine receptor are found in both the hippocampus [20] and the VTA [2]. It has been reported that microinjections of D1 antagonists into the VTA can disrupt the development of amphetamine sensitization, suggesting that DA systems within the midbrain mediate the neuroadaptations that are responsible [32]. Evidently, blockade of D1 receptors disrupts morphine induced conditioned place preference, whereas such effect is unseen with the D2/D3 receptors [1,16,28]. Moreover, morphine does not induce place preference in mice lacking D2 receptors [19]. Acute injections of either D1 or D2 receptor antagonists have been reported either not to affect heroin self-administration or to affect only at doses that also affect motor function or response rate [31]. Opiates augment DA release by suppressing GABA inhibitory input to DA neurons in the VTA [9,12].

The hippocampus receives dopaminergic input from the substantia nigra and the VTA [27]. Dopamine receptors in the dorsal hippocampus have an important role in mediating morphine reward [24] and the hippocampal CA1 region receives a dopaminergic input from the VTA [10,11]. Previous studies showed that the hippocampus is important for learning tasks, such as conditioned place preference (CPP), that use positive reinforcement [13,18,24]. Several studies suggest that both D1- and D2-like receptors in the CA1 region of the dorsal hippocampus are involved in reward-related learning and have an important role in the acquisition and expression of morphine-induced place preference [24]. In our previous study, we found that both D1 and D2 receptors have key role in the development of morphine induced CPP at the level of the VTA [4]. Hence, the aim of this work was to identify the effect of inhibition of the dopamine D1/D2 receptors located in the rat dorsal hippocampus (CA1) on expression of condition placed preference followed by morphine administration into the ventral tegmental area.

2. Materials and methods

2.1. Animals

One hundred and sixty adult male albino Wistar rats (Pasteur Institute, Tehran, Iran) weighting 200–300 g were used in these experiments. Animals were caged in group of 3–4 at $23 \pm 1\,^{\circ}C$, 60% humidity, and maintained in a 12-h light/dark cycle (light on 07:00) with food and water freely available. Each animal was used only once. All experiments were executed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institute of Health Publication No. 80-23, revised 1996).

2.2. Stereotaxic surgery

Animals were anesthetized with intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg) and implanted with two ipsilateral chronic indwelling guide cannulae, one inside the VTA and one inside the dorsal hippocampus (CA1). These cannulae were secured in place using two stainless steel screws anchored to the skull and dental acrylic cement. The related coordinates were determined from Paxinos and Watson [33] as 3–3.5 mm posterior to the bregma, ±1.8–2 mm lateral to the midline, and 2.8–3 mm ventral of the dorsal surface of the skull for CA1 and 4.7–5 mm posterior to the bregma, ±0.8–0.9 mm lateral to the midline and 8.2–8.4 mm from the top of skull for the VTA (guide cannulae were 1 mm above the appropriate injection place).

2.3. Drugs

Morphine sulfate was obtained from TEMAD (Tehran, Iran). SCH23390 (D1 receptor antagonist) and sulpiride (D2 receptor antagonist) were purchased from Tocris Bioscience (Bristol, UK). Morphine and SCH23390 were dissolved in physiological saline and Sulpiride was dissolved in dimethyl sulfoxide (DMSO; Sigma–Aldrich, Germany). All drugs prepared immediately before use.

2.4. Conditioning place preference apparatus and paradigm

2.4.1. Apparatus

The testing apparatus consisted of three wooden compartments [3,6,7,21]. Two compartments were identical in size (30 cm × 30 cm × 40 cm) but differed in shading and texture. Compartment A was white with black horizontal stripes 2 cm wide on walls and also had a textured floor. Compartment B was black with vertical white stripes 2 cm wide and had a smooth floor. The third compartment (C) was a passage painted in red (30 cm × 15 cm × 40 cm). It protruded from the rear of two large compartments and connected the entrances to them.

2.4.2. Behavioral testing

Conditioned place preference consisted of a 5-day schedule with three phases: pre-conditioning, conditioning and post-conditioning.

2.4.2.1. Pre-conditioning phase. During this phase (day 1), each animal was placed in compartment C with the guillotine door removed to allow access apparatus for 10 min. In this phase, we recorded each animal displacement.

2.4.2.2. Conditioning phase. It consisted of six, 30-min sessions (three for saline and three drug pairing) in a 3-day schedule. These sessions were conducted twice each day (from day 2 to day 4) with a 6-h interval. On each day, separate groups of animals received a conditioning session with morphine and another received saline. During 30-min session intervals for morphine/saline, the animals were confined to one compartment by closing the removable wall. Treatment compartment and order of presentation of morphine/saline were counterbalanced for either group.

2.4.2.3. Post-conditioning or testing phase. This phase was carried out on day 5 (the preference test day), 1 day after the last conditioning session, in a morphine free state. Each animal was tested only once. The removable wall was raised and rat could access the entire apparatus for 10 min. The mean time spent for each rat in both compartments during a 10-min period was recorded by a 3CCD camera (Panasonic Inc., Japan) and analyzed by the Ethovision software (Version XT7, Noldus Information Technology, the Netherlands) in order to calculate the conditioning score as the preference criteria; the time spent in the drug-paired place minus the time spent in saline-paired place. In control and experimental groups, total distance traveled was also recorded.

2.5. Experimental design

Twenty groups of animals were used (8 rats in each group) in these experiments. During the conditioning phase animals received a bilateral microinjection of the morphine sulphate (1 μg per 0.3 μl saline) or saline (0.3 μl) into the VTA [4]. Later on, 5 min prior to start of the trial session, different doses of the SCH23390 or sulpiride were bilaterally microinjected into the CA1 region of hippocampus (0.5 μl per side).

2.5.1. Effect of D1 receptor antagonist, SCH23390, pretreatment on the expression of intra-VTA morphine-induced place preference

In this set of experiments, in order to assess possible effects of blockade of the D1 receptors in the CA1 on the intra-VTA morphine induced CPP, we applied different doses of SCH23390 (0.02, 0.05, 0.2 and 0.5 μg) or saline (0.5 μl per side) in morphine-treated animals on the test day. In saline-treated groups, animals received saline (0.3 μl per side) during the conditioning days and same doses of SCH23390 or saline were administered prior to test sessions.

2.5.2. Effects of D2 receptors antagonist, sulpiride, pretreatment on the expression of morphine-induced place preference in the VTA

Similar to the aforementioned groups, during the conditioning period animals received either morphine sulphate (1 μg per 0.3 μl) or saline (0.3 μl) into the VTA and on the test day, different doses of sulpiride (0.25, 0.75, 1.5 and 3 μg per side) or DMSO (0.5 μg per side) as vehicle were microinjected into the CA1 region of hippocampus.

2.6. Statistics

Data are expressed as mean ± SEM (standard error of mean). One-way analysis of variance (ANOVA) and randomized blocks model followed by *post hoc* analysis (Newman–Keuls test) were used to compare the conditioning scores or locomotor activity obtained in all control and experimental groups, as needed. *p*-Values less than 0.05 were considered to be statistically significant.

2.7. Histological verification

Upon finishing each experiment, animals were deeply anesthetized with ketamine and xylazine. Then, they were transcardially perfused with 0.9% saline and 10% formaldehyde solution prior to sectioning. The neuroanatomical location of cannulae tips was confirmed by using the rat brain atlas [33]. The data reported here are only from animals in which the placements of cannulae tips were histologically verified (Fig. 1A and B).

3. Results

3.1. Effects of intra-CA1 administration of D1 receptor antagonist, SCH23390, on the expression of morphine-induced CPP in the VTA

Administration of different doses of SCH23390 (0.02–0.5 μg) in saline- and morphine-treated groups caused no significant alterations on the CPP scores in each experimental group. One-way ANOVA followed by Newman-Keuls test did not indicate any significant alterations in CPP scores after SCH23390 administration in the saline- and morphine-treated groups (Fig. 2A; left and right panels). One-way ANOVA indicated that none of the groups for saline- or morphine-treated animals showed significant changes in locomotor activity (Fig. 2B).

3.2. Effects of intra-CA1 administration of D2 receptor antagonist, sulpiride, on the expression of morphine-induced CPP in the VTA

Fig. 3A (right panel) shows that administration of different doses of sulpiride (0.25–3 μg per side) significantly decreased the conditioning scores in morphine-treated rats. One-way ANOVA followed by Newman-Keuls multiple comparison test [$F(4,39) = 7.399$, $p = 0.0002$] indicated that sulpiride in two doses (1.5 and 3 μg) decreases the place preference to morphine microinjected into the VTA ($p < 0.001$). Meanwhile, Fig. 3A (left panel) shows that intra-CA1 administration of sulpiride only, on the test day, was unable to alter conditioning scores in saline-treated animals. On the other hand, none of the groups for saline- or morphine-treated animals revealed significant differences in distance traveled (Fig. 3B) during 10-min test period. Thus, the different doses of sulpiride used in this set of experiments did not affect the conditioning scores due to changes in the locomotor activity on the test day.

4. Discussion

The purpose of this study was to evaluate the development of conditioned place preference paradigm after administration of morphine in ventral tegmental area and the involvement of D1 and D2 receptors within the hippocampus in the CPP induced by morphine. The major findings are: *(a)* Intrahippocampal administration of D2 receptor antagonist, Sulpiride, suppresses the expression of

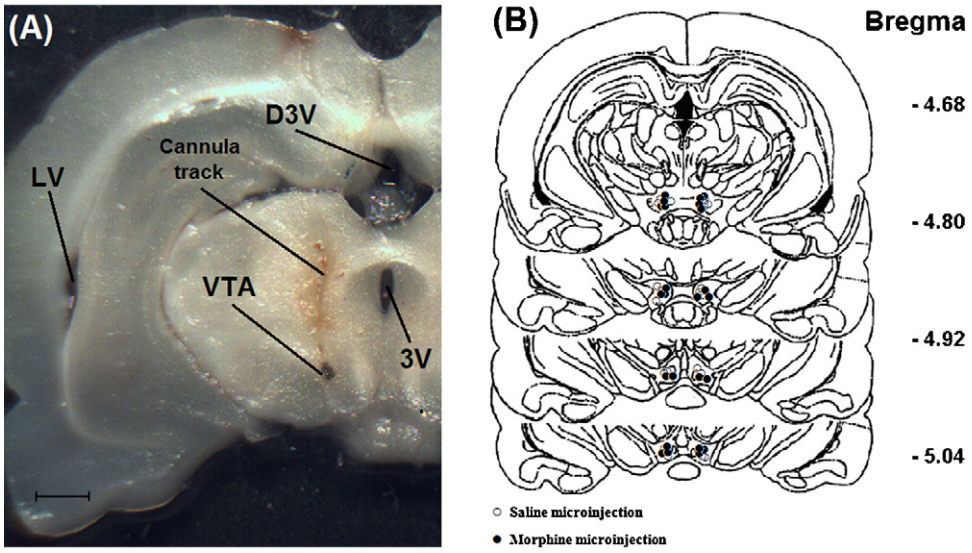

Fig. 1. A photomicrograph of representative (A) morphine microinjection site in the ventral tegmental area and (B) four coronal schematic sections showing microinjection sites in the nucleus cuneiformis (○ = saline microinjection and ● = morphine microinjection). All microinjections were performed bilaterally (not shown in this picture). 3V, 3rd ventricle; D3V, dorsal 3rd ventricle; LV, lateral ventricle; and VTA, ventral tegmental area. Scale bar is 1 mm.

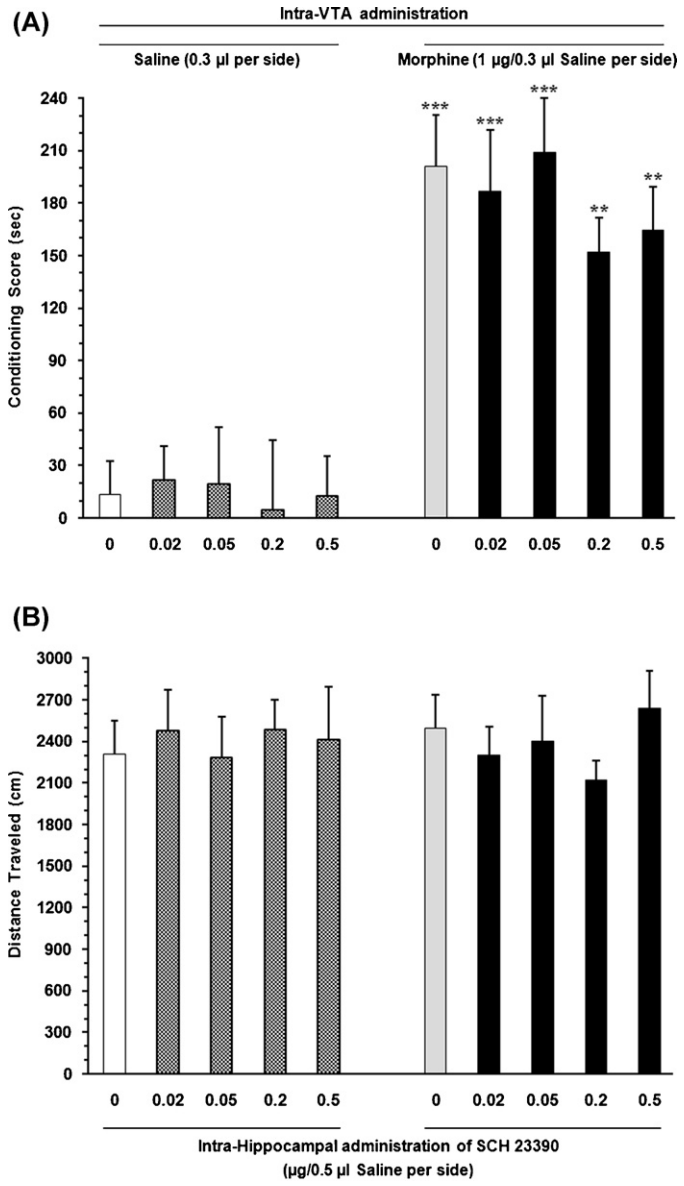

Fig. 2. Intrahippocampal administration of D1 receptor antagonist (SCH23390) in the test day had no effect on the conditioning scores (A) and administration of saline in the VTA along with SCH23390 in the hippocampus CA1 region failed to induce conditioned place preference in rats (left). Microinjection of morphine sulphate in the VTA in the hippocampus induced conditioned place preference but blockade of the D1 receptors (SCH23390) in CA1 region of the hippocampus had no effect on the conditioning scores (right). (B) Data analysis of the distance traveled by the rat on the test day suggests that results were not due to effects on motor activity. Traveled distance is measured on the test day simultaneously by software for 10-min period. $^{**}p < 0.01$ and $^{***}p < 0.001$ compared to respective group in saline-treated animals.

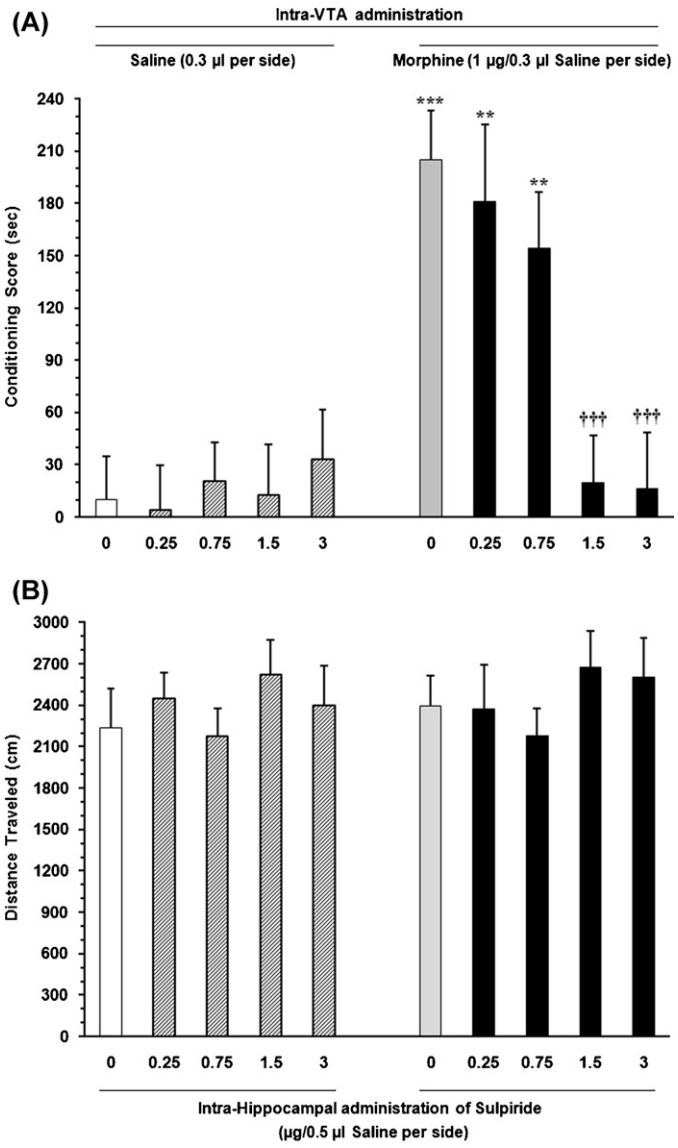

Fig. 3. Intra-hippocampal administration of D2 receptor antagonist (Sulpiride) could significantly decreased the conditioning scores (A) in the test day. However, administration of saline into the VTA along with sulpiride in the CA1 region failed to induce conditioned place preference in rats (left). Microinjection of morphine sulphate into the VTA induced conditioned place preference but blockade of the D2 receptors in CA1 region of the hippocampus significantly reduced the conditioning score in two higher doses (right). (B) Data analysis of the distance traveled by the rat on the test day proved that animals had no motor deficit. Points represent mean ± SEM for 8 animals. $^{**}p < 0.01$ and $^{***}p < 0.001$ compared to respective group in saline-treated animals. $^{\dagger\dagger\dagger}p < 0.001$ compared to respective control group in morphine-treated animals.

CPP induced by morphine in the VTA; *(b)* SCH23390 as a D1 receptor antagonism could not suppress the expression of conditioned place preference induced by morphine in the VTA. Our data provided evidence that D2 receptors in the CA1 region of hippocampus have a pivotal role in the expression of CPP induced by morphine at the level of the VTA and it supports the relationship between dopaminergic D2 receptors and opioidergic systems in these areas in reward circuit. Acquas et al. showed that systemic administration of dopamine antagonists block the motivational properties of rewarding as well as aversive stimuli [1]. In line with their work several studies have been conducted to clarify the role of different dopamine receptors, especially D1 and D2, in all aspects of reward related behaviors. In agreement with our results, Maldonado et al. indicated that the D2 receptor plays a crucial role in the motivational component of drug addiction [19]. On the other hand, it has been shown that the specific D1 dopamine-receptor antagonist SCH2339 blocked the place-preference induced by morphine, nicotine and diazepam [1]. Our recent study also revealed that D1 and D2 antagonist inhibit the acquisition of morphine induced CPP [4].

A study on freely moving animals showed that endogenous DA, which depends on the activity patterns of DA midbrain neurons, appears as a key regulator in specific synaptic changes observed at certain stages of learning and memory and of synaptic plasticity [11]. Also, it has been shown that the VTA is an important site for synaptic modifications involved in the learning and memory of environmental cues predicting reward [8]. Previous studies

showed that the mesolimbic dopaminergic system that projects from the VTA to NAc is critical for initiation of opioid reinforcement [14,25,26] and the reward-related effects of drugs of abuse [5,23]. In 2005, Lisman and Grace supported a model whereby the hippocampal-VTA loop regulates the entry of information into long-term memory, and activation of VTA dopaminergic pathway to the hippocampus produces an enhancement of LTP and learning [17]. Although hippocampus is known to participate in associative processes such as declarative memory, and not typically considered an integral component of the reward pathway, but it might be expected to play a significant role in the mechanism leading to development of drug addiction. In fact, the hippocampus plays an important role in the formation of contextual memory between the environment and the rewarding effect of abused drugs. The dopaminergic neural transmission in the hippocampus seems to be critical for such memory [24]. Since injection of dopamine receptor agents into the hippocampus did not initiate rewarding effects, it seems that the hippocampus by itself is not a place of rewarding but it cooperates with other parts [24]. Hippocampal excitatory outputs regulate the activity of VTA dopaminergic neurons through a polysynaptic pathway [5,33]. Moreover, this link between hippocampus-dependent memory formation and neuromodulation by reward has been confirmed by the fMRI findings [36].

Recently, Tanaka et al. showed that the protein level of the dopamine D1 receptor and its prerequisite mRNA in the hippocampus increases in animals that show a clear preference for the environment paired with cocaine. They concluded that the alteration of dopamine D1receptor in the hippocampus is related to the induction of drug-induced contextual memory [29]. In addition results of our previous research showed that administration of dopamine D1 and D2 receptor antagonists into the CA1 prior to administration of morphine into the VTA in conditioning phase inhibit morphine-induced CPP [4]. This finding have led us to investigate if the memory is formed during conditioning phase, is there possibility to be affected by dopamine receptors suppression on the test day? Our results show that administration of D2 but not D1 receptor antagonists into the CA1 suppress the expression of CPP induced by intra-VTA morphine. In support of our results, Rezayof and colleagues showed that blockade of dopamine D1 or D2 receptors in the CA1 region of the dorsal hippocampus abolished the acquisition and expression of CPP induced by systemic administration of morphine [24]. Although this research suggests the action of D1 receptor in the expression of CPP, it cannot be considered as conflicting evidence since morphine was administrated subcutaneously. Their findings may differ from our results because of activation of opiate receptors outside of the VTA. In conclusion, although there is memory formation during acquisition, memory retrieval is impaired. It means that animals have a problem in memory recovery and getting something back. Therefore, we propose that D2 but not D1 receptors play an important role in the hippocampus in memory retrieval and development of reward-related behaviors. However, further behavioral experiment such as Morris water maze and also electrophysiological and molecular investigations would be necessary to better understanding mechanisms by which dopamine receptors within the hippocampus modulate the mesolimbic dopaminergic system in reward circuit.

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