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ORIGINAL PAPER

Comparison of the Role of D1- and D2-Like Receptors in the CA1 Region of the Hippocampus in the Reinstatement Induced by a Subthreshold Dose of Morphine and Forced Swim Stress in Extinguished Morphine-CPP in Rats

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Abstract
Reward-seeking and relapse to drug use are two characteristics of addiction and reports have indicated the role of hippocampal structures in reward learning. To find the best ways of treatment, the understanding of the neurobiological mechanisms of reward and its involved factors is a must. For this reason, in the present study, we aimed to investigate the role of D1- and D2-like dopamine receptors and compared their activities in the CA1 region, focusing on the reinstatement induced by forced swim stress (FSS) or the combination of FSS and a subthreshold dose of morphine in extinguished morphine-CPP in rats. The rats were bilaterally implanted by two separate cannulas into the CA1 region. The animals received different doses of SCH23390 or sulpiride (0.5, 2, and 4 µg/0.5 µl vehicle/side) into the CA1 region on the reinstatement day and were tested for FSS-induced reinstatement or the combination of FSS and a subthreshold dose of morphine in separate groups. Our findings indicated that the D1- and D2-like receptor antagonists attenuated the reinstatement induced by the combination of FSS and the subthreshold dose of morphine. The behavioral results were more prominent in the groups of animals that received SCH23390 as compared to sulpiride. The data may suggest a role for the dopamine receptors in the CA1 region in relapse to drugs of abuse, which may be induced by exposure to a stressor.

Keywords Reward · Stress-induced reinstatement · D1-like dopamine receptor · D2-like dopamine receptor · CA1 region of hippocampus · Forced swim stress

Introduction

Opiates have long been under research for their ability to produce addiction. Another reason for the huge attention paid to opiates is the similarities between opiate addiction and addiction to other addictive drugs such as alcohol and some psychostimulants [1]. Research has shown resemblances between the mechanisms of action of addictive drugs and normal forms of learning and memory [2]. However, this form of learning is maladaptive as it leads to serious unfavorable social and economic consequences [3]. Relapse is an important characteristic of addiction, and as such, the disorder cannot be successfully treated without considering the problem of relapse [4]. The dopaminergic system is one of the candidates for the treatment of addiction to drugs like cocaine, nicotine, and alcohol [5].

Previous reports have shown the role of different hippocampal structures in learning and memory in general [6], learning under anxiety [7], and specifically in reward form of learning in the CPP model [8]. The role of D1-like receptors in the hippocampus (HIP) was found in 1990 [9]. The involvement of the HIP in reward-association learning has been shown [10] and among different regions of the HIP, the CA1 role in the formation and/or expression of a CPP has been emphasized [11–14].

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The conditioned place preference (CPP) paradigm is a model to test the rewarding properties of drugs as well as drug-related conditioned responses and can measure dopamine-mediated learning in rodent laboratory models [15]. The CPP paradigm is used for both the evaluation of CPP and the reinstatement of an extinguished CPP [16, 17]. A learned conditioned response is suppressed during the extinction period, in which an inhibitory learning is formed [18]. In reinstatement, the drug-related conditioned responses appear in an animal with the experience of drug-taking [19]. Different factors may trigger the reinstatement including acute exposure to the administered drug [20], drug-related cues [21], food deprivation [22], and stress [23]. We applied the forced swim stress (FSS) to model emotional stress and applied the combination of FSS and a subthreshold dose of morphine to investigate their effects on the induction of the reinstatement [24].

To find the best ways of treatment, the understanding of the neurobiological mechanisms of reward and the involved factors is a must. We have recently denoted that D1- and D2-like dopamine receptors are possible role players in the acquisition and reinstatement of morphine-CPP [14] and have shown the interplay between stress and reward in the nucleus accumbens (NAc) [25]. To further investigate the role of dopaminergic receptors in the CA1 region, as a target of VTA dopaminergic projections [26], we compared the role of D1- and D2-like dopamine receptors in the CA1 region, focusing on the reinstatement induced by forced swim stress and its combination with a subthreshold dose of morphine in extinguished morphine-CPP in rats.

Materials and Methods

Animals

In total, 103 adult male Wistar rats purchased from Pasteur Institute of Iran (weight 250 ± 20 g; age 7–8 weeks at the time of surgery) were used in this study. The animals were kept 5–6 per large cage with free access to chow and tap water in a room with a 12:12 h light/dark cycle (lights on 07:00 a.m.) and controlled temperature at 23 ± 1 °C. All the experiments were conducted according to the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication no. 80-23, revised 1996) and were approved by the Research and Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.PHNS.REC.1396.127). All efforts were made to minimize animal suffering and reduce the number of animals used to obtain reliable results.

Drugs

We used the following drugs in this study: morphine sulfate (Temad, Iran) that was dissolved in saline (0.9% NaCl) and was injected subcutaneously at two different concentrations: 5 mg/kg, when injected in the conditioning phase, or 0.5 mg/kg, when injected in the reinstatement phase. SCH23390 (Tocris Bioscience, UK), as a D1-like dopamine receptor antagonist, was dissolved in saline. Sulpiride (Tocris Bioscience, UK), as a D2-like dopamine receptor antagonist, was dissolved in 12% dimethyl sulfoxide (DMSO; Sigma, Germany). Both antagonists were injected at the doses of 0.5, 2, and 4 µg/0.5 µl vehicle [27, 28]. The control animals received vehicles (either saline and/or 12% DMSO).

Stereotaxic Surgery and Drug Administration

One week after purchase, the rats were anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg) and were placed in a stereotaxic apparatus (Stoelting, USA). The incisor bar was positioned at ± 3.3 mm and the ear bars positioned symmetrically. The scalp was cleaned and incised on the midline. Then, a hole was drilled through the skull and two stainless-steel guide cannulae (9 mm length, 22 gauge) were bilaterally implanted 1 mm above the hind portion of the dorsal hippocampus (the CA1 region). Stereotaxic coordinates for the CA1 region of the dorsal hippocampus, according to the atlas of the rat brain, were: AP = − 3.2, ML = ± 1.9 mm, DV = 2.9 mm from the surface of the skull [29]. A stylet was introduced into each guide cannula to prevent possible obstruction. The animals spent a week of recovery from surgery.

Conditioned Place Preference Apparatus and Paradigm

The conditioned place preference (CPP) paradigm is a form of classical conditioning used for the measurement of the reinforcing or aversive properties of a drug and reveals the memory or learning of simple stimulus-reward association [30]. The apparatus is made of three Plexiglas compartments (30 × 30 × 40 cm). Two compartments with equal size but different in texture and cue (the walls in each compartment are striped horizontally or vertically and each compartment has a different floor) are connected via a third smaller compartment, the neutral box (the walls and floor of which are made of simple Plexiglas with no cue). The neutral box is separated with a top-sliding door from the two main compartments. The whole experimental process was performed under controlled light conditions and any aggravating noise was avoided. An unbiased conditioning

and a counterbalanced compartment assignment were used [31]. The CPP procedure consisted of a 5-day schedule with three distinct phases (Fig. 1a) as follows:

Pre-conditioning Phase

On day 1, each rat was placed in the neutral box and the sliding door was removed to allow free movement of the rat in all the compartments for 10 min. The time spent in each compartment was monitored by a video camera (Panasonic Inc., Japan) and measured using the Ethovision software (version 7), a video tracking system for automation of behavioral experiments (Noldus Information Technology, The Netherlands). Animals that stayed more than 70% of the total test time in one compartment were excluded (five in total).

Conditioning Phase

On the next day (day 1 of the acquisition phase, days 2–4), each rat received a morphine dose (5 mg/kg; sc) and was confined to the morphine-paired compartment for 30 min (sliding door closed). After 6 h, each rat received a subcutaneous injection of saline and was placed in the saline-paired compartment. On the following day, the process changed and the rats received saline in the morning followed by morphine injection after 6 h to avoid the effects of conditioning to the time of drug administration. The third-day procedures of this phase were performed the same as the first day of this phase [32].

Post-conditioning Phase

On the fifth day (the expression phase), the rats were tested under morphine-free condition by being placed in the neutral box and given free access to all the compartments for 10 min. Time spent in each compartment was recorded as stated before. The conditioning score (the CPP score) was calculated as the difference of time spent in the morphine- and saline-paired compartments [33].

Extinction Phase

In the extinction phase, which was after the post-conditioning phase, the time spent by each rat in the CPP apparatus was measured every day and the procedure continued until the CPP scores in this phase showed 50% decline compared to the CPP score of the post-conditioning day of the same animal (the extinction latency). Hence, the extinction latency for each rat represents the number of days required to reach half of the CPP scores maintained on the post-conditioning day [32].

Reinstatement

Considering that we have already measured the effect of a subthreshold dose of morphine (0.5 mg/kg, sc) on the reinstatement phase in our laboratory [14, 25], in this study we measured the FSS-induced reinstatement, combination of FSS and the subthreshold dose of morphine (Fig. 1c), and the effects of intra-CA1 injection of D1- and D2-like receptor antagonists in the rats with extinguished morphine-CPP (Fig. 1d). The measurements were undertaken 24 h following the extinction period. In this phase, the rats received an intra-CA1 injection of D1- and D2-like receptor antagonists (SCH23390 and sulpiride) and then were given either FSS for 6 min or a combination of FSS and a subthreshold dose of morphine and their preference was immediately measured in the CPP apparatus for 10 min (Fig. 1c).

Forced Swim Stress

The FSS was undertaken following the administration of either the antagonists or vehicles. In order to induce stress, the rats were forced to swim for 6 min in a vertical plastic cylinder (50 cm high, 30 cm in diameter) filled with clean tap water (23–27 °C) up to a level of 30 cm [34].

Experimental Design

The Effect of Intra-CA1 Administration of SCH23390 on the Reinstatement of Extinguished Morphine-CPP

To explore the role of D1-like receptors within the CA1 region in the effects of FSS and the combination of FSS and a subthreshold dose of morphine on the reinstatement of morphine-CPP, seven groups of rats were used. The no-stress control group received intra-CA1 bilateral injections of vehicle (0.5 µl saline/side) and the subthreshold dose of morphine. The FSS control group received intra-CA1 bilateral injections of vehicle (0.5 µl saline/side) and morphine (0.5 mg/kg; sc) before the FSS test. Three groups received intra-CA1 bilateral injections of SCH23390 (0.5, 2, and 4 µg/0.5 µl saline/side) five min before the FSS test [27]. To investigate if SCH23390 will insert any effects on the reinstatement, another group of animals received the highest dose of SCH23390 (4 µg/0.5 µl saline/side) and the subthreshold dose of morphine (0.5 mg/kg; sc). All the groups in the mentioned set of experiments received a subthreshold dose of morphine (0.5 mg/kg; sc). To show the effect of FSS, by itself, on the reinstatement, a group of animals underwent the FSS test for 6 min followed by the reinstatement test without receiving the subthreshold dose of morphine injection. All the rats in the above-mentioned groups were

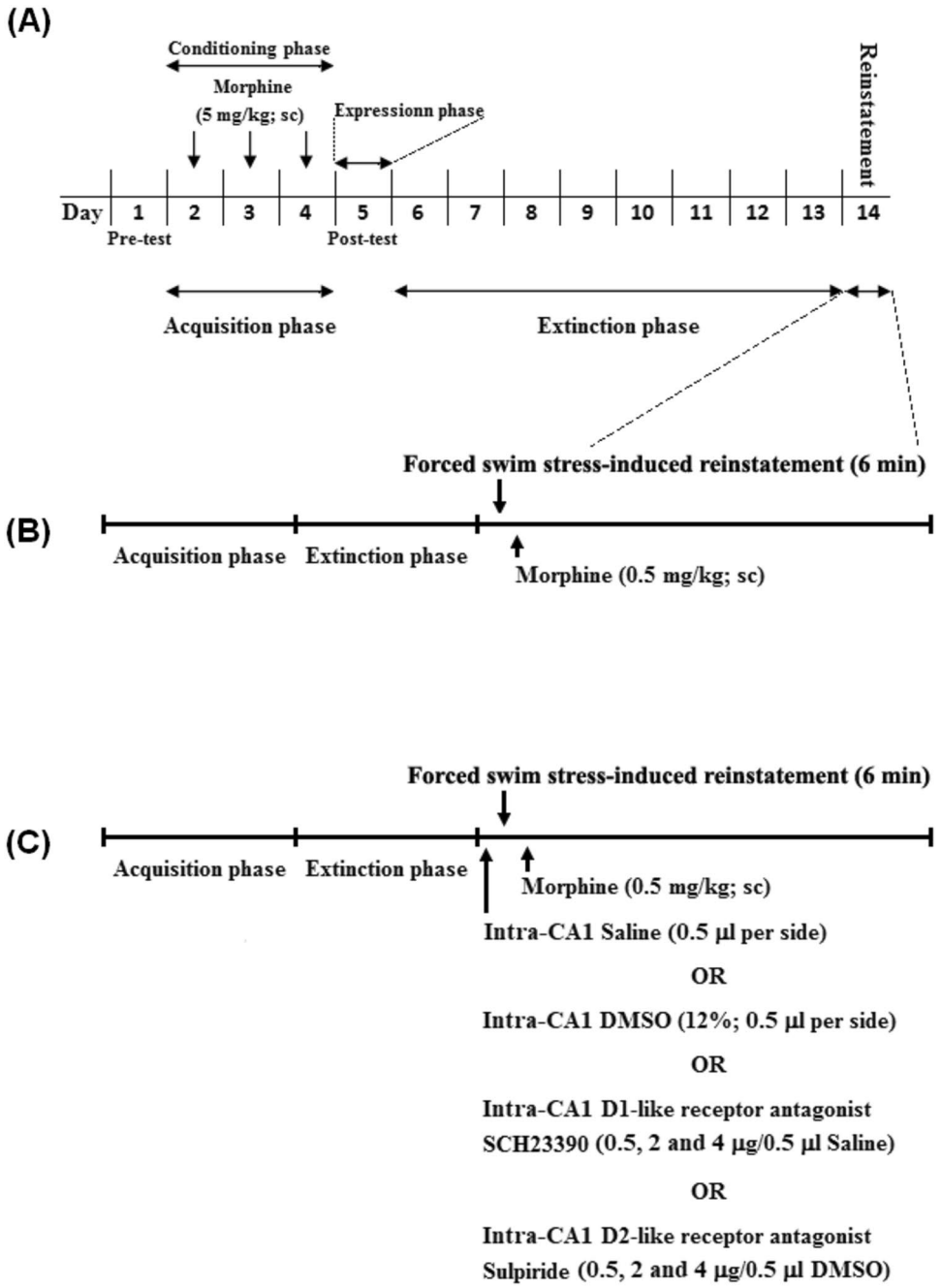

Fig. 1 The experimental protocols for the induction of morphine reinstatement by forced swim stress (FSS) and combination of FSS with a subthreshold dose of morphine in extinguished morphine-CPP in rats. **a** On the pre-test day (day 1), the time spent in each compartment was recorded for all the rats in the groups, and the animals that did not show any preference for each compartment were included in this study. In the conditioning phase, the rats received a daily injection of morphine (5 mg/kg; sc) for 3 days. On day 5 (post-test session) the CPP test was performed. The CPP score was calculated based on the time spent in the drug-paired compartment minus the time spent in the saline-paired compartment. From day 6 (the extinction phase) onward, the animals were placed in the CPP apparatus and tested for a 10-min period every day. The mentioned protocol continued until the calculated CPP scores in the extinction period were similar to those on the pre-conditioning day. **b** In another set of experiments, for investigating the effect of forced swim stress (FSS) on the reinstatement of morphine and to investigate the effect of FSS alone, the animals underwent the forced swimming test following the last day of the extinction period and received the subthreshold dose of morphine (0.5 mg/kg; sc). **c** The effect of bilateral injections of vehicles [saline or DMSO (12%)] and different doses of SCH23390, as a dopamine D1-like receptor antagonist, and sulpiride, as a dopamine D2-like receptor antagonist, into the CA1 region on the drug priming- and FSS-induced reinstatement of morphine-CPP

immediately placed into the CPP box and the CPP scores and traveled distance were measured during a 10-min period of the reinstatement test.

The Effect of Intra-CA1 Administration of Sulpiride on the Reinstatement of Extinguished Morphine-CPP

To explore the role of D2-like receptors within the CA1 region in the effects of FSS and the combination of FSS and a subthreshold dose of morphine on the reinstatement of morphine-CPP, seven groups of rats were used. The no-stress control group received intra-CA1 bilateral injections of vehicle (0.5 µl DMSO 12%/side) and a subthreshold dose of morphine. The FSS control group received intra-CA1 bilateral injections of vehicle (0.5 µl DMSO 12%/side) and morphine (0.5 mg/kg; sc) before the FSS test. Three groups received intra-CA1 bilateral injections of sulpiride (0.5, 2, and 4 µg/0.5 µl DMSO 12% per side) five min before the FSS test [27]. To investigate if sulpiride will insert any effects on the reinstatement, another group of animals received the highest dose of sulpiride (4 µg/0.5 µl DMSO 12% per side) and the subthreshold dose of morphine (0.5 mg/kg; sc). All the groups in the mentioned set of experiments received the subthreshold dose of morphine (0.5 mg/kg; sc). To show the effect of FSS, by itself, on the reinstatement, a group of animals underwent the FSS test for 6 min followed by the reinstatement test without receiving a subthreshold dose of morphine injection. All the rats in the above-mentioned groups were immediately placed into the CPP box and the CPP scores and traveled distance were measured during a 10-min period of the reinstatement test.

Histological Verification

After the reinstatement tests, the following procedures were performed: the rats were deeply anesthetized with Ketamine and Xylazine; they were transcardially perfused with 0.9% saline and 4% paraformaldehyde solution; the brains were removed and placed in a 4% formalin solution for 3 days and then cut coronally in 50-µm sections (Fig. 2). The cannula location was confirmed according to the rat brain atlas [29]. The data of the rats with a misplaced cannula was omitted from the analysis (five rats).

Locomotor Testing

The total distance traveled (in centimeters) for each animal was measured on the pre- and post-test days, and on the reinstatement day in all the groups using the locomotion tracking apparatus connected to a video tracking system (Ethovision software).

Statistics

All data are expressed as mean ± SEM. Data were analyzed by commercially available software GraphPad Prism (Version 5.0). The CPP scores in the control and experimental groups were compared using repeated measures or block randomized one-way analysis of variance (ANOVA) followed by post-hoc Newman–Keuls. P values less than 0.05 were considered to be statistically significant.

Results

The Effect of Intra-CA1 Administration of SCH23390 on the Reinstatement of Extinguished Morphine-CPP

Independent samples t-test [$t_{(12)} = 10.24$, $P < 0.001$] showed that there was a significant increase in the CPP score in animals that received FSS and the subthreshold dose of morphine under baseline conditions (Fig. 3a-left panel). To examine the effect of the dopamine D1-like receptor antagonist on the reinstatement induced by FSS or the combination of FSS and the subthreshold dose of morphine, the rats received three different doses of SCH23390 into the CA1 region. One-way block randomized ANOVA followed by the Newman–Keuls test [$F_{(3,27)} = 14.77$, $P < 0.001$; $\eta^2 = 0.65$; Fig. 3a-left and middle panels] revealed a significant difference in the reinstatement of morphine-CPP between the group that received stress and the vehicle and the animals that received either of the two highest doses of SCH23390 (2 and 4 µg/0.5 µl saline/side; $P < 0.01$ and $P < 0.001$). In addition, one-way block randomized ANOVA [$F_{(2,20)} = 0.1612$, $P = 0.8452$; Fig. 3a-left and right panels] revealed no substantial differences in the CPP scores between the no-stress saline group and the animals that either received the highest doses of SCH23390 (4 µg/0.5 µl saline) or those that did not receive a priming dose of morphine on the reinstatement day but received FSS. This reveals that the antagonist and the FSS, per se, did not have an effect on the reinstatement of morphine-CPP. The statistical analysis showed that intra-CA1 administration of the dopamine D1-like receptor antagonist did not have an effect on the locomotor activity [$F_{(6,48)} = 0.2886$, $P = 0.9391$; Fig. 3b].

The Effect of Intra-CA1 Administration of Sulpiride on the Reinstatement of Extinguished Morphine-CPP

Independent samples t-test [$t_{(12)} = 6.379$, $P < 0.001$] showed that there was a significant increase in the CPP score in animals that received FSS and the subthreshold dose of morphine under baseline conditions (Fig. 4a-left panel).

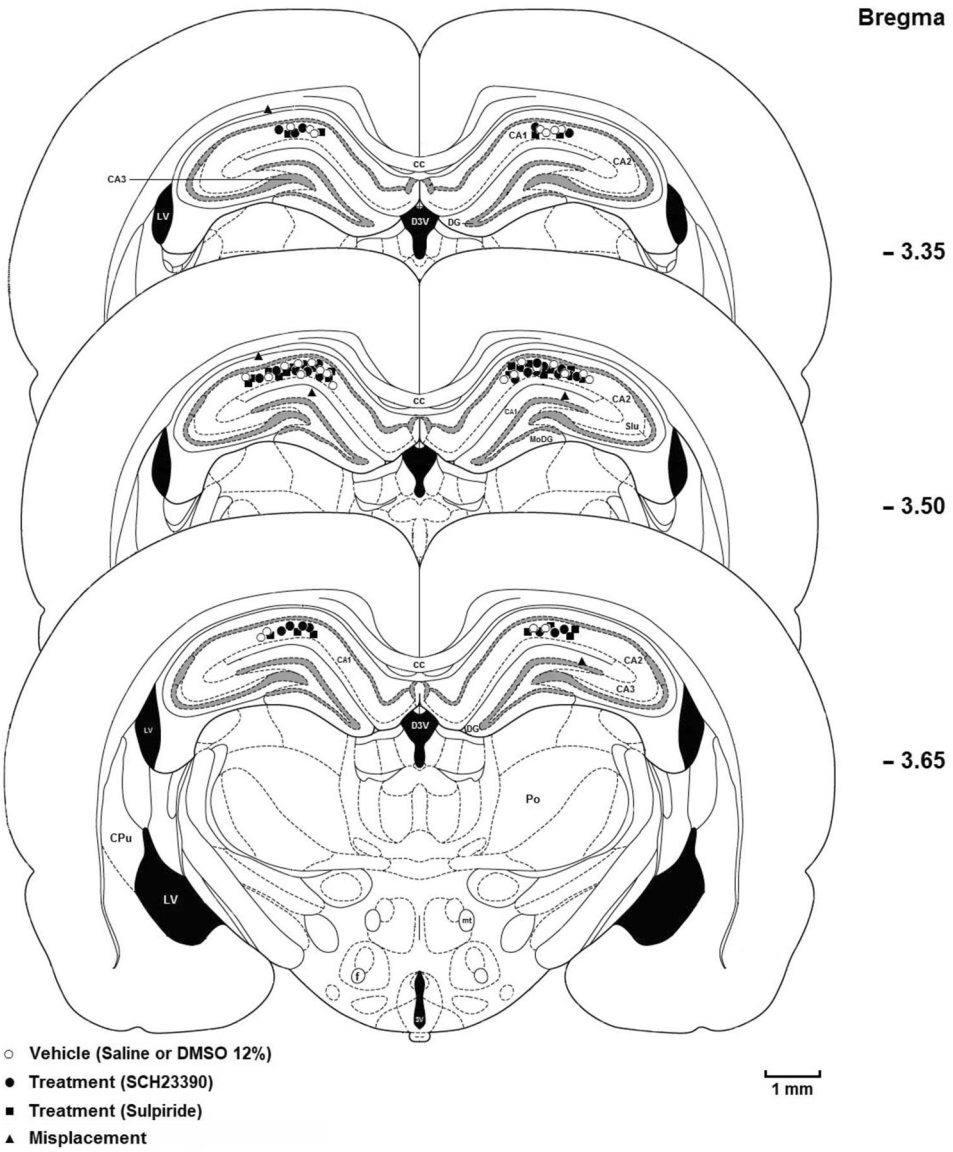

Fig. 2 Coronal schematic sections show the microinjection sites in the CA1 region of the hippocampus [open circle: vehicle (saline or DMSO 12%); filled circle: SCH23390; filled square: sulpiride, filled triangle: misplaced injections). *CA1* field CA1 of the hippocampus, *CA2* field CA2 of the hippocampus, *CA3* field CA3 of the hippocampus, *DG* dental gyrus, *MoDG* molecular layer dental gyrus, *SLu* stratum lucidum hippocampus, *cc* corpus callosum, *CPu* caudate putamen (striatum), *D3V* dorsal third ventricle, *Po* post thalamic nuclear group, *LV* lateral ventricle, *mt* mammillothalamic tract, *f* fornix

To examine the effect of the dopamine D2-like receptor antagonist on the reinstatement induced by FSS or the combination of FSS and the subthreshold dose of morphine, the rats received three doses of sulpiride into the CA1 region. The one-way block randomized ANOVA followed by the Newman–Keuls test [$F_{(3,27)} = 8.493$, $P = 0.0005$; $\eta^2 = 0.52$; Fig. 5a-left and middle panels] revealed a significant difference in the reinstatement of morphine-CPP between the group that received stress and the vehicle and the animals that received either of the two highest doses of sulpiride (2 and 4 µg/0.5 µl DMSO per side; $P < 0.05$ and $P < 0.001$). One-way block randomized ANOVA [$F_{(2,20)} = 0.4113$, $P = 0.9598$; Fig. 4a-left and right panels] revealed no substantial differences in the CPP scores in the reinstatement test between the no-stress control group and the animals that either received the highest doses of sulpiride (4 µg/0.5 µl DMSO) or those that did not receive a priming dose of morphine on the reinstatement day but received FSS. This shows that the antagonist and the FSS, per se, did not have an effect on the reinstatement of morphine-CPP. Additionally, one-way block randomized ANOVA showed that intra-CA1 administration of sulpiride had no effects on the locomotor activity [$F_{(6,48)} = 0.2053$, $P = 0.9733$; Fig. 4b].

Calculation of Effective Dose 50% (ED50) of D1- and D2-Like Dopamine Receptor Antagonists Prior to the Reinstatement of Morphine-CPP

Figure 5 shows the percentage of the CPP values compared to the vehicle control group (the animals that received only saline or DMSO in the CA1), to 100%, and represent the remaining mean %MPEs (maximal possible effect;

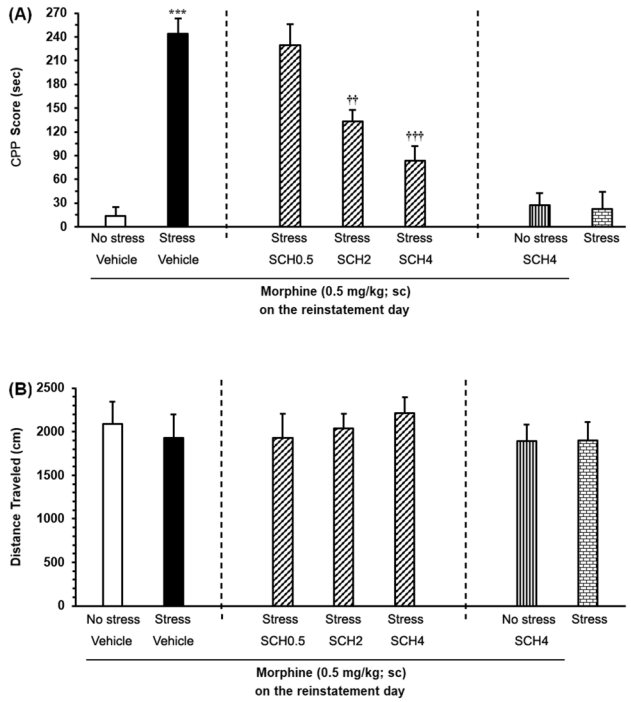

Fig. 3 The effects of the microinjections of the vehicle (saline) and different doses of SCH23390 into the CA1 region on the reinstatement induced by forced swim stress (FSS) or the combination of FSS and the subthreshold dose of morphine. **a** Left panel, the no-stress and FSS animals. Both groups received saline as the vehicle into the CA1 region. Middle panel, the animals were exposed to FSS and received different doses of SCH23390 into the CA1 region (0.5, 2, and 4 µg/0.5 µl saline/side) and morphine (0.5 mg/kg; sc) on the reinstatement day. Right panel, the FSS animals received the highest dose of SCH23390 into the CA1 region alone on the reinstatement of morphine (0.5 mg/kg; sc). **b** Shows the locomotor activity of all the groups in this set of experiments. All data are expressed as mean ± SEM for 7 rats. ***P < 0.001 compared with the "No stress-Vehicle" control group. ††P < 0.01 and †††P < 0.001 compared with the "Stress-Vehicle" control group

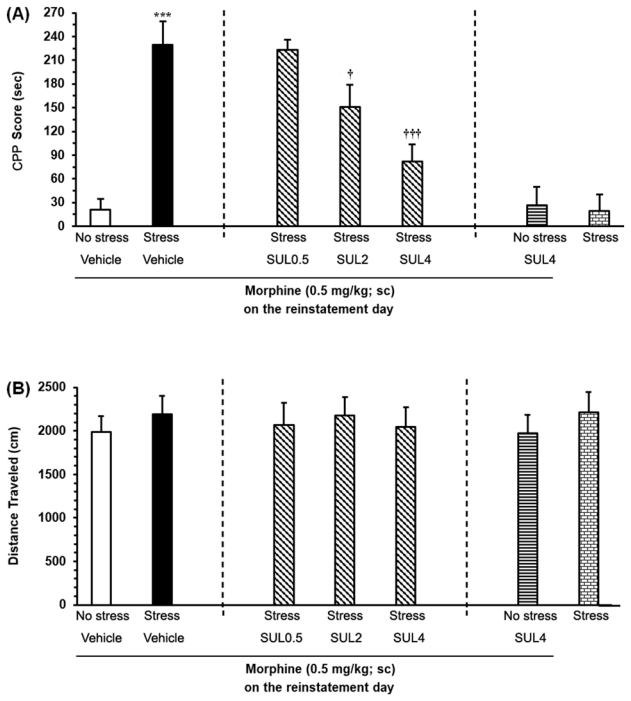

Fig. 4 The effects of the microinjections of the vehicle (DMSO) and different doses of D2-like receptor antagonist, sulpiride, into the CA1 region on the reinstatement induced by forced swim stress (FSS) or the combination of FSS and the subthreshold dose of morphine. **a** Left panel, the no-stress and FSS animals. Both groups received DMSO as the vehicle into the CA1 region. Middle panel, the animals were exposed to FSS and received different doses of sulpiride into the CA1 region (0.5, 2, and 4 µg/0.5 µl DMSO 12% per side) and morphine (0.5 mg/kg; sc) on the reinstatement day. Right panel, the FSS animals received the highest dose of sulpiride into the CA1 region alone on the reinstatement of morphine (0.5 mg/kg; sc). The FSS animals did not receive the priming dose of morphine. **b** Shows the locomotor activity of all the groups in this set of experiments. All data are expressed as mean ± SEM for 7 rats. *** P < 0.001 compared with the "No stress-Vehicle" control group. †P < 0.0.05, †††P < 0.001 compared with the "Stress-Vehicle" control group

the animals that received different doses of SCH23390 or sulpiride into the CA1) as a percent change in their effects to create an effective dose 50% (ED50, g) of SCH23390 (2.33) and sulpiride (2.97) on the reinstatement of morphine-CPP. The data show that SCH23390 caused prominent changes in preventing the FSS-induced reinstatement.

Discussion

The purpose of this study was to explore the role that dopaminergic receptors play in the CA1 region, focusing on the reinstatement induced by either FSS or a combination of FSS and a subthreshold dose of morphine in extinguished morphine-CPP in rats. The experiments did not include any anatomical controls. The findings of this research can be summarized as follows: (1) FSS, per se, did not reinstate drug-related conditioned responses. (2) The FSS-induced reinstatement of a subthreshold dose of morphine was attenuated by the blockade of D1- and D2-like receptors within the CA1 region. (3) The highest dose of SCH23390 or sulpiride (both 4 µg/kg), per se, could not make a significant change in the morphine-induced CPP scores. Application of SCH23390, at similar doses with sulpiride, produced prominent behavioral results as compared to sulpiride.

The dopaminergic neurons in ventral tegmental areas (mainly in the ventral half and in the upper and lower borders) project to the CA1 region [35] and the CA1 region expresses both D1- and D2-like receptors [36]. Previous work in our laboratory has revealed a prominent role for both of these receptors in the CA1 region in the induction of morphine reward and we have reported that SCH23390 and sulpiride (D1- and D2-like receptor antagonists) could

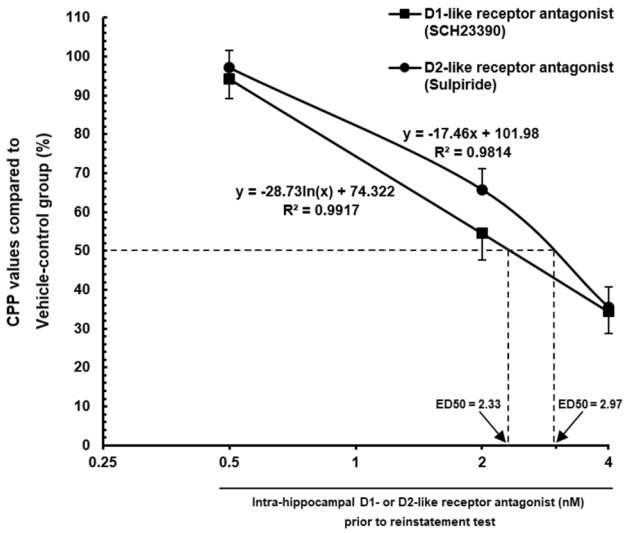

Fig. 5 The log dose–response curve for SCH23390, as a D1-like dopamine receptor antagonist, and sulpiride, as a D2-like dopamine receptor antagonist, in the CA1 region. In this figure, we tried to set the mean %MPEs (maximal possible effect) of the vehicle-control group (the animals that received only saline or DMSO in the CA1) to 100%, and represent the remaining mean %MPEs (the animals that received different doses of SCH23390 or sulpiride into the CA1) as a percentage of changes in their effects to create an effective dose 50% (ED50, g) of SCH23390 (2.33) and sulpiride (2.97) on the reinstatement of morphine-CPP

attenuate morphine reinstatement [14]. In vitro studies have reported the involvement of the dopaminergic afferents into the CA1 region in the long-term memory formation and the long-term continuance of LTP was blocked using antagonists of D1- and D2-like receptors [37]. So, dopamine plays a key role in both memory consolidation and synaptic mechanisms of storage like synaptic plasticity [38]. A line of evidence has also proved the involvement of the CA1 region in the drug-priming induced reinstatement and the effect of context on drug reinstatement [14, 39]. In morphine-dependent animals that were in their extinguished phase, forced swim stress showed an interaction with dopaminergic receptors of the CA1 region of the dorsal hippocampus and both D1- and D2-like dopamine receptors antagonists (SCH23390 and sulpiride, respectively), reduced the effect of FSS in a dose-dependent manner. Previous findings in our laboratory also confirmed the role of dopaminergic receptors in the CA1 region in the acquisition and reinstatement of morphine-induced CPP and its rewarding effect [14, 40]. The involvement of dopamine D1- and D2-like receptors in forced swim stress has also been shown by a number of other studies in the NAc [25, 41]. For example, Sadeghzadeh et al. reported a prominent role for the D2-like receptors within the NAc in morphine priming-induced reinstatement of morphine CPP and concluded that stress- and priming-induced reinstatement can be dissociated pharmacologically [22]. It should also be noted that not only the distribution of D1-like and D2-like receptors is uneven in various regions of the hippocampus [42, 43], but variation also exists in their affinity and distribution at cellular and subcellular level [44]. All these factors, at least partly, may be accountable for the variation we observed in the behavioral results when we applied SCH-23390 and sulpiride at similar doses. Our literature review did not identify any studies exploring the effects of above-mentioned antagonists on the FSS. Such possibility cannot be excluded from the results of the present study.

As addiction is a maladaptive form of learning [45] and the CA1 region of the hippocampus is one of the key player in learning [46, 47], memory formation in the hippocampus may be involved in the induction or relapses under different circumstances [48]. In addition, previous studies in humans have shown that exposure to stress can potentiate the susceptibility to relapse to drugs during abstinence [49, 50]. The present study took a further step to reveal the involvement of the CA1 region in the interaction between morphine-addiction relapse and stress.

The increase in dopamine release following acute stress and its involvement in memory function has been shown in brain areas like the prefrontal cortex [51, 52]. We here showed that both SCH23390 and sulpiride, as dopamine D1- and D2-like receptor antagonists, could attenuate the reinstatement of morphine-CPP under the induction of acute stress caused by forced swim stress.

Although the role of a hippocampal-VTA loop in the transfer of information into the long-term memory has been reported [53], the possible role of other neurotransmitter systems should not be neglected due to the fact that dopamine antagonists caused a reduction instead of a complete blockade of the reinstatement. The hypothalamic–pituitary–adrenal axis activates following acute stress and glucocorticoid hormones are released subsequently [54]. Hence, the possible involvement of glucocorticoid and mineralocorticoid receptors should also be taken into consideration. Collectively, the results of the current study suggest an involvement of the dopamine receptors within the CA1 region in FSS-induced reinstatement and the comparison of the effect of SCH23390 with sulpiride displayed a greater effect for SCH23390. Pharmacological differences, diffusion properties, and different distribution of the D1- and D2-like receptors may be involved in the observed results.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

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