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Research report

NMDA antagonist MK 801 in nucleus accumbens core but not shell disrupts the restraint stress-induced reinstatement of extinguished cocaine-conditioned place preference in rats

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HIGHLIGHTS

- The restraint stress-induced reinstatement of cocaine-CPP is dependent on the duration of restraint and the context.
- Systemic MK-801 blocks the development and expression of restraint stress-induced reinstatement of cocaine-CPP.
- Intra-Nac Core, but not shell, MK 801 administration blocks restraint stress-induced reinstatement of cocaine-CPP.

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ABSTRACT

Relapse is a common feature of cocaine addiction. In rodents, it can be elicited by cues, stress or the drug. Restraint stress-induced reinstatement of cocaine-conditioned place preference (CPP) is a useful model to study the mechanisms involved in stress-induced relapse of drug-seeking behavior. There is evidence that the glutamate NMDA receptors are critically involved in drug- and cue-induced reinstatement of seeking behavior and drug-CPP responses. The aim of this study was to investigate the contribution of NMDA receptors within core *vs*. shell nucleus accumbens (NAc) subregions to restraint stress-induced reinstatement of extinguished cocaine-CPP. After extinction of cocaine-conditioned preference, animals were administered MK 801 systemically or directly into intra-core or intra-shell, and restrained for 30 min or left undisturbed in their home-cages. First, we demonstrated that restraint stress-induced reinstatement of extinguished cocaine-CPP depends on the duration of restraint as well as on the context in which it is applied. Second, this effect was blocked by systemic MK 801 administration either before or after restraint. Third, intra-core but not intra-shell administration abrogated the restraint stress-induced reinstatement. These findings show that NMDA receptors within NAc core, but not shell, play a critical role in restraint stress-induced reinstatement of cocaine-CPP.

1. Introduction

Relapse to compulsive drug intake after a withdrawal period is considered a hallmark of the addiction process. Cocaine craving in human addicts can be elicited by three major factors: environmental cues associated with drug taking, a stressful life-event or re-exposure to cocaine [25,52,51]. The conditioned place preference (CPP) test has been previously described as a useful protocol for studying relapse to drug-seeking in laboratory animals [36,5,29]. Drug relapse elicited by stressful life-events has been studied in rodents using a CPP paradigm by applying different stressors such as footshock, forced swimming or, as in the current study, restraint, in order to induce reinstatement of an extinguished cocaine-CPP [55,46].

Since there are reported differences among the extinction protocols used to reinstate a drug-CPP response, the first interest of this study was to compare the two extinction procedures used so far for the reinstatement of extinguished drug-CPP. Specifically, we compared the effectiveness of a repeated test extinction procedure and a saline pairings extinction procedure to extinguish a CPP response to cocaine [36,24].

Different lengths of intermittent or continuous exposure to either footshock or restraint stress, respectively, have also been used to elicit reinstatement of cocaine-CPP response [45,30,9,3].

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Nevertheless the restraint stress studies do not provide details about the place in which restraint stress occurs, in spite of the known relevance of environment to trigger the stress-induced reinstatement of extinguished cocaine self-administration behavior (see [48]). So, the second aim of the current study was to determine the length of exposure and the environment dependence of the restraint stress needed to induce reinstatement of extinguished cocaine-CPP.

In relation to the neuroanatomical substrates of these behaviors, it is well known that the nucleus accumbens (NAc) plays a major role in mediating the reinstatement of cocaine-seeking behavior [12,26,8]. This area is composed of two major subregions, NAc core and NAc shell, with differential anatomical afferents and efferent projections [22], which may account for different aspects of the drug-rewarding process [23]. The NAc shell seems to mediate several drug-related phenomena, such as the acute effects of drug reward [38,23], the motor responses to addictive drugs [13,31] and extracellular dopamine levels after an acute intravenous administration of cocaine [41]. The NAc core seems to be important for the processing of drug-associated cues and the drug-seeking behavior [23,4,40,57,15,19].

Although several studies suggest that stress-induced reinstatement involves a specific limbic subcircuit [47,48], it is well established that the glutamatergic projection from the medial prefrontal cortex (mPFC) to the NAc core represents a common mechanism underlying cocaine priming- [35,26], cue- [18,16,42] and footshock- [11,34] induced reinstatement of extinguished cocaine self-administration behavior. It has been consistently shown that the mPFC and NAc also participate in cocaine-priming and forced-swimming stress-induced reinstatement of extinguished cocaine-CPP [45,58,29]. Furthermore, [45] also demonstrated mPFC participation in restraint stress-induced reinstatement of cocaine-CPP. Interestingly, recent work from our lab has shown that a glutamatergic mechanism within the NAc core, but not shell, underpins the cross-sensitization to cocaine induced by restraint stress [17].

Regarding the involvement of the ionotropic glutamate receptors, AMPA/kainate and NMDA, it has been demonstrated that the AMPA receptors in the NAc are critically involved in the reinstatement of cocaine-seeking behavior [40,56] and there is evidence that the NMDA receptors may also play a role in this behavior [6,27,15,10]. For example, [10] reported that systemic administration of a non-competitive NMDA antagonist, MK 801, blocked cocaine-induced reinstatement of extinguished cocaine-CPP. Moreover, [4] demonstrated that by blocking the NMDA receptor within the NAc core, the cue-induced reinstatement of cocaine seeking is attenuated. However, the participation of NMDA receptors within the NAc core *vs*. shell has not been examined yet for restraint stress-induced reinstatement of extinguished cocaine-CPP. Therefore, the third and main aim of the present study was oriented to systematically examine the influence of a systemic, intra-core or shell administration of an NMDA receptor antagonist, i.e. MK 801, on restraint stress-induced reinstatement of extinguished cocaine-CPP.

2. Materials and methods

2.1. Animals and housing

Male Wistar rats born and bred in our vivarium (IFEC- CONICET, Córdoba, Argentina), weighing 200–250 g at the beginning of the experiment, were housed four per cage in a temperature- and humidity-controlled colony room with a 12 h light/dark cycle (lights on at 7:00 a.m.). Food and water were provided ad libitum. All experimental procedures were approved by the Animal Care Committee of the Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, in accordance with the guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Drugs

Cocaine hydrochloride was purchased from the Verardo Laboratory (Buenos Aires, Argentina) and dissolved to reach a final concentration of 10 mg/ml. A dose of 10 mg/kg i.p. was employed for the conditioning phase in all experiments and a dose of 5 mg/kg i.p. for the priming injection to induce cocaine-induced reinstatement in Exp. 3. (+)- MK 801 hydrogen maleate was purchased from Sigma-Aldrich SA, (Argentina) and dissolved in sterile saline for i.p. administration and for intra-NAc microinjections, at a concentration of 1 mg/ml and 1 μg/μl respectively. The selection of the 0.1 and 0.2 mg/kg i.p. doses for MK 801 was based on [10], while the intra-core or intra-shell dose of 0.75 μg/side was based on reports from [2,1].

2.3. Conditioning place-Preference (CPP) apparatus

The procedure was conducted in four identical rectangular boxes, each containing two large acrylic chambers (25 cm × 33 cm × 37 cm) separated by a small central corridor (22 cm × 11 cm × 19 cm). One of the main chambers is painted black with a stainless steel grid floor and the other is white with a plastic mesh floor. The central corridor is transparent with an acrylic floor and separated from the two chambers by removable guillotine doors. The apparatus was placed in an experimental room, dimly lit and free of noise. Three infrared beams were placed in each large chamber to register the time spent and locomotor activity in each, using a computer-aided system (LIADE, FCEyN, Córdoba, Argentina). Locomotor activity counts were measured when two beams were consecutively interrupted.

2.4. Restraint stress session

On the day after the extinction test, a restraint stress session was performed in the central corridor of the CPP apparatus to induce reinstatement (except for Exp. 3). Briefly, each rat was placed in an acrylic mesh restrainer device (length 20 cm, width 5 cm, height 6 cm) for 30 min (except for Exp. 2) while control rats were kept in their home cages; immediately after, all animals were tested for reinstatement of cocaine-CPP. In Experiment 3, animals were restrained in the same device placed in a cage similar to the central corridor, located in a separate room from the experimental room.

2.5. Surgery and cannula placement

After four days of extinction (see Section 2.8), all rats were anaesthetized with Ketamine/xylazine (Kensol, Laboratories Holliday, Buenos Aires, Argentina) and placed in a stereotaxic frame (Stoelting, USA) with the incisor bar set at −3.3 mm below the interaural line. A 22-gauge bilateral guide cannula was then implanted, targeting the NAc core or shell using the following coordinates (in mm from bregma); AP = +1.2; L = ±1.5; DV = -7.8 for NAc core, and AP = +1.4; L= ± 0.8; DV: −7.8 for NAc shell. The guide cannula was anchored to the skull with dental cement (Meron, Voco Laboratories, Cuxhaven, Germany) and skull screws. After surgery, all rats were allowed a recovery period of at least 1 day before the extinction training continued.

2.6. Microinfusion procedure

All drug microinfusions were performed in the experimental room where the CPP apparatus was located, and rats were habituated to the infusion procedure after both the last extinction session and the extinction test (see experimental design). For drug infusion, the animals were gently hand-held while bilateral 27G microinjectors were placed in the guide cannula, projecting 1.5 mm beyond its tip. Twenty seconds later, the injector was removed to ensure total diffusion of the drug. Drug injections were conducted over one minute using an infusion pump (Harvard Apparatus, USA) mounted with 5 μl Hamilton syringes; behavioral tests began 5 min later.

2.7. Verification of cannula placement

Following the restraint stress-induced reinstatement test, animals were given an overdose of chloral hydrate (100 mg/kg) and perfused intracardially with 0.9 % saline followed by 10 % formalin. The brain was removed and 60 μm coronal sections at the NAc level were generated using a Cryostat (Leica). The sections were mounted on gelatin-coated slides and stained with cresyl violet. Animals with cannula placements outside the areas of interest, or with excessive mechanical damage, were excluded from the subsequent data analysis (placements are shown in Figs. 6 and 7).

2.8. Experimental procedure

A total of two-hundred and twenty-five male Wistar rats, aged two months, were used only once for each experiment. At the beginning of the protocol, all animals were handled for 3 days to reduce the stress associated with the manipulation. In addition, they were habituated to the test room for 30 min before the beginning of each experimental session. In all studies, the animals were conditioned and tested during the light phase of the cycle. All experiments included the following phases: a) basal: the animals were allowed to freely explore the entire apparatus during 15 min to rule out unconditioned preference for any of the compartments; b) conditioning: the animals were confined alternately to both compartments during 30 min after being administered either vehicle (4 days), or cocaine 10 mg/kg i.p. (4 days); half of the animals were first conditioned in the cocaine-associated compartment while the other half started the conditioning session in the saline-associated compartment; c) conditioning test: the animals were allowed to freely move in the entire apparatus during 15 min to confirm the presence of conditioned preference for the context previously paired with cocaine; d) extinction: on the basis of the results of Exp. 1, in the subsequent experiments the following extinction scheme was used (8 days in length): the animals were confined alternately to both contexts during 30 min after being injected with vehicle, with the last extinction session followed by a test (extinction test) to confirm the disappearance of the conditioned preference for the drug-associated context; e) restraint stress-induced reinstatement: animals were placed in the apparatus to explore it freely immediately after a 30 min restraint stress session carried out in restraint devices placed in the central corridor.

2.8.1. Experiment 1: comparison between repeated-tests and saline-pairings extinction procedures of cocaine-conditioned place preference

Exp. 1 was performed to compare the effectiveness of the main extinction procedures used in the drug-CPP paradigm to extinguish the cocaine-conditioned response under our experimental conditions: repeated-tests or saline-pairings extinction procedures, as was previously carried out by Mueller et al. (2000). For the repeated-tests extinction procedure, the day after the conditioning test, all rats were allowed to freely explore the two compartments in 15-min daily tests for a total of 12 days; the duration of permanence in each context (cocaine or saline-paired) was measured. For the saline-pairings procedure, starting on the day after the conditioning test, the animals were injected daily with saline and placed alternately in each compartment (30 min each during 4 days); the day after the last extinction session, the animals were placed in the central corridor and allowed to explore the CPP apparatus; the duration of permanence was measured to confirm the extinction of the preference for the drug-associated context.

2.8.2. Experiment 2: effect of different duration of exposure to restraint stress on inducing reinstatement of extinguished cocaine-conditioned place preference

Exp. 2 was performed to evaluate the influence of the duration of exposure of the restraint stress session on the ability to reinstate the extinguished cocaine-CPP using saline-pairing extinction procedures (an extinction procedure that was selected on the basis of the results of Exp. 1). The animals were allocated to four different groups according to the time spent in the restrainer placed in the CPP-apparatus central corridor: 0 (Non-restraint), 15, 30 and 60 min. Immediately after the restraint stress session, the stressed and non-stressed animals were tested for 15 min in the CPP apparatus.

2.8.3. Experiment 3: influence of the environment on restraint stress-induced reinstatement of extinguished cocaine-conditioned place preference

In Exp. 3 we sought to determine whether restraint stress-induced reinstatement is dependent on the environment where the restraint stress occurs. Animals were restrained 30 min either inside the central corridor of the CPP apparatus in the experimental room (INSIDE CPP-CONTEXT group), or in a cage similar to the CPP apparatus central corridor, but located in a different room (OUTSIDE CPP-CONTEXT group) and, immediately thereafter, tested for reinstatement in the experimental room. Three days later, all animals were tested for cocaine (15 mg/kg i.p.)-induced reinstatement in order to discard a failure of the OUTSIDE CPP-CONTEXT group of animals to reinstate cocaine-CPP beyond the stimulus applied to induce it.

2.8.4. Experiment 4: effect of systemic MK 801 administration prior to the restraint stress session on the development of restraint stress-induced reinstatement of extinguished cocaine-conditioned place preference

In Exp. 4 we evaluated the influence of MK 801 administered intraperitoneally prior to the restraint stress exposure (30 min) on the development of restraint stress-induced reinstatement of cocaine-CPP. Animals were assigned to six groups: vehicle non-stress (VEH-NS), vehicle stress (VEH-S), 0.1 mg/kg MK 801 non-stress (MK 0.1-NS), 0.1 mg/kg MK 801 stress (MK 0.1-S), 0.2 mg/kg MK 801 non-stress (MK 0.2-NS), 0.2 mg/kg MK 801 stress (MK 0.2-S). On the reinstatement day, all animals were injected with saline or MK 801 at the above mentioned doses 15-min before restraint stress and evaluated for reinstatement immediately thereafter. As has previously been explained, separate groups of control animals were injected with vehicle or each dose of MK 801, and were not exposed to the restraint stress session, being left undisturbed inside the experimental room in their home-cages.

2.8.5. Experiment 5: effect of systemic MK 801 administration after the restraint stress session on the expression of restraint stress-induced reinstatement of extinguished cocaine-conditioned place preference

On the basis of the results obtained in Exp. 4, we aimed to determine whether NMDA receptor-mediated glutamatergic neurotransmission participates not only in the development but also

in the expression of the restraint stress-induced reinstatement of cocaine-CPP. The experimental design was identical to Exp. 4, with the difference in the time when MK-801 was administered on the reinstatement day. In this case, once the restraint stress session ended, all animals were injected with saline or MK 801 (0.1 mg/kg i.p., a dose that was selected on the basis of the results obtained in Exp. 4) and 15 min later they were placed in the CPP apparatus to evaluate restraint stress-induced reinstatement of extinguished cocaine-CPP.

2.8.6. Experiment 6: effect of intra-core MK 801 administration on restraint stress-induced reinstatement of extinguished cocaine-conditioned place preference

This experiment was performed to determine the influence of intra-core infusions of MK 801 on restraint stress-induced reinstatement of cocaine-CPP. The experimental design was similar to Exp. 4, with the difference that, during the extinction phase (after extinction session 4 or 5), all animals were implanted with a guide cannula in the NAc core; subsequently, after a recovery period of 2 days, they continued with the extinction procedure. In this case, on the reinstatement day, they were microinfused with vehicle or MK 801 (0.75 μg/side), and 5 min later they were submitted to either a restraint stress session or left undisturbed in their home cages. Immediately after the restraint stress session, animals were tested in the CPP apparatus.

2.8.7. Experiment 7: effect of intra-shell MK 801 administration on restraint stress-induced reinstatement of extinguished cocaine-conditioned place preference

Exp. 7 was performed to evaluate whether intra-shell MK 801 administration exerts an influence on restraint stress-induced reinstatement of cocaine-CPP. The experimental design was the same as Exp. 6, except that the guide cannula implantation was aimed at the NAc shell. As in experiment 6, the extinction procedure continued after surgery recovery. On the reinstatement day, the animals were microinfused with vehicle or MK 801 (0.75 μg/side), and 5 min later either submitted to a restraint stress session or left undisturbed in their home-cages and then tested in the CPP apparatus.

2.9. Statistical analysis

Data was analyzed with StatView software. For behavioral analyses, in Exp. 1 test data is reported as the time of permanence in each context (cocaine or saline-paired). However, in order to facilitate data interpretation in subsequent experiments, the results are reported as the difference in time spent between the context associated with the drug and the context associated with saline (preference score; COC CONTEXT − SAL CONTEXT). The ability of restraint stress (or cocaine, as applicable) to elicit reinstatement was determined by the difference between the preference score on the day of testing (reinstatement induced by restraint stress) and that of the preceding session (extinction test), in accordance with the analysis performed by Vaughn et al. [54]. Statistical significance was determined by repeated measures (RM) ANOVA with post hoc multiple comparisons using the Bonferroni post-hoc test. All analyses used an acceptable significance level of $p < 0.05$ to determine significance. Data is expressed as the mean ± standard error.

As an additional measure, locomotor activity (measured as the total counts in each compartment) was reported for the restraint stress-induced reinstatement test. Group sizes are reported in the corresponding figure legends

3. Results

3.1. Methodological considerations

Initial experiments allowed us to adjust the environmental conditions to achieve an equal preference for the white and the black compartments (i.e. to consider the apparatus as “unbiased”, data not shown). The procedure itself is considered “biased”, as the animals were always conditioned with cocaine in the least preferred compartment during the basal test (either black or white indistinctly). It is noteworthy that biased place preference protocols have been used previously and have produced comparable results to other designs. Moreover, it should be noted that not all animals successfully completed all phases of the experiment (basal, conditioning and extinction tests). Thus, data from rats that displayed an initial preference for a particular chamber during the basal test (more than 66 % of the total time), or animals that did not show conditioning or extinction of the preference for a given compartment were excluded from the statistical analysis. The application of this criteria resulted in the exclusion of approximately 36 % of the animals.

3.2. Experiment 1: extinction by saline pairings, but not by repeated tests, decreases cocaine-conditioned place preference.

Fig. 1 represents the comparison between the saline-pairings and repeated-tests extinction procedures, applied following the establishment of cocaine-CPP. Fig. 1b-1 shows the results of the experiment in which animals were submitted to the repeated-testing extinction procedure. It can be seen that the time spent in the cocaine-paired context did not diminish, and the time spent in the saline-paired context did not increase, over the twelve consecutive extinction sessions, revealing a significant effect only for context (RM ANOVA for context, $F_{(1,15)} = 27.36$, $p < 0.05$). This indicates that this procedure failed to extinguish cocaine-conditioning. Fig. 1b-2 shows the results of the experiment in which animals were given repeated pairing of the two contexts with saline to induce extinction of the cocaine-CPP. During the conditioning test, animals spent more time in the context previously paired to cocaine, whereas following extinction they did not show preference for the conditioned context (Fig. 1b-2; RM ANOVA revealed a significant difference for the experimental phase x context, $F_{(1,15)} = 4.84$, $p < 0.05$; Bonferroni *post hoc* test $p < 0.05$). Thus, the decrease of cocaine-conditioning found following the saline-pairings extinction procedure was not evident after the repeated-tests procedure. On the basis of these results, the saline-pairings extinction procedure was selected for all subsequent experiments to extinguish the cocaine-conditioned preference.

3.3. Experiment 2: restraint stress-induced reinstatement of extinguished cocaine-conditioned place preference depends on the duration of exposure of the restraint stress session

We demonstrate here an influence of the duration of exposure to restraint stress on the restraint stress-induced reinstatement of cocaine-CPP (RM ANOVA for experimental phase x stress exposure $F_{(3,22)} = 14.58$, $p < 0.05$). The Bonferroni post hoc test showed that either the 30-min or the 60-min duration of restraint stress reinstated extinguished cocaine-CPP, compared to both the non-restraint stress group and the 15-min restraint stress group (Non-restraint stress x Restraint 30, $p < 0.05$; Non-restraint stress x Restraint 60, $p < 0.05$; Restraint 15 x Restraint 30, $p < 0.05$; Restraint 15 x Restraint 60, $p < 0.05$; Fig. 2 b). The analysis of locomotor activity during the restraint stress-induced reinstatement test revealed an increase in locomotion in the Restraint 60-min group (one-way ANOVA $F_{(3,21)} = 3.85$, $p < 0.05$; Fig. 2 c) while the Restraint 30-min

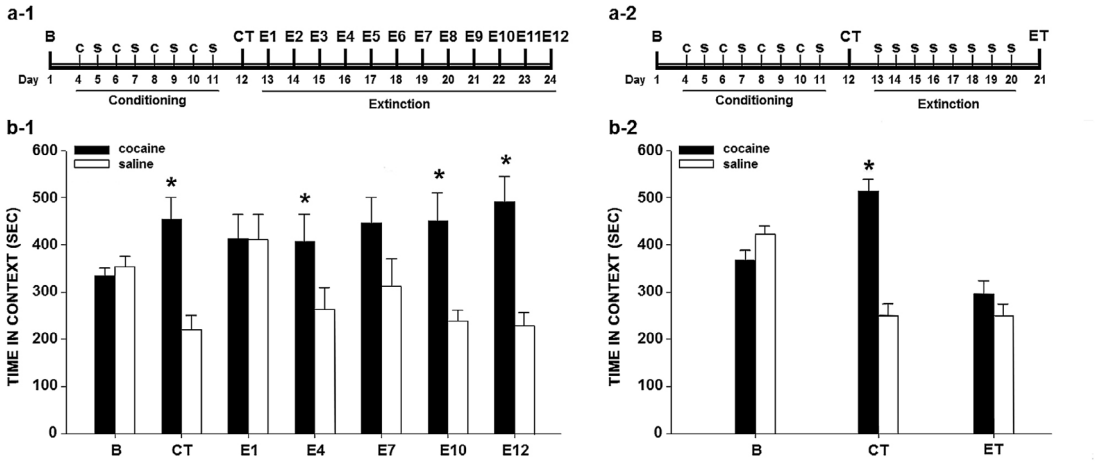

Fig. 1. (a-1) and (a-2) Experiment timeline (c = cocaine; s = saline; B = basal; CT = conditioning test; E1 to E12 = extinction sessions; ET = extinction test). (b-1) Mean (± S.E.M.) time of permanence in each context (time in context, sec) during the basal, conditioning and extinction tests of the experiment in the repeated-test extinction procedure (data is plotted for sessions 1, 4, 7, 10, 12). (N = 8) (*$p < 0.05$ compared with saline group). (b-2) Mean (±S.E.M.) time of permanence in each context (time in context, sec) during the basal, conditioning and extinction tests of the experiment in the saline-pairings extinction procedure (N = 8) (*$p < 0.05$ compared with saline group).

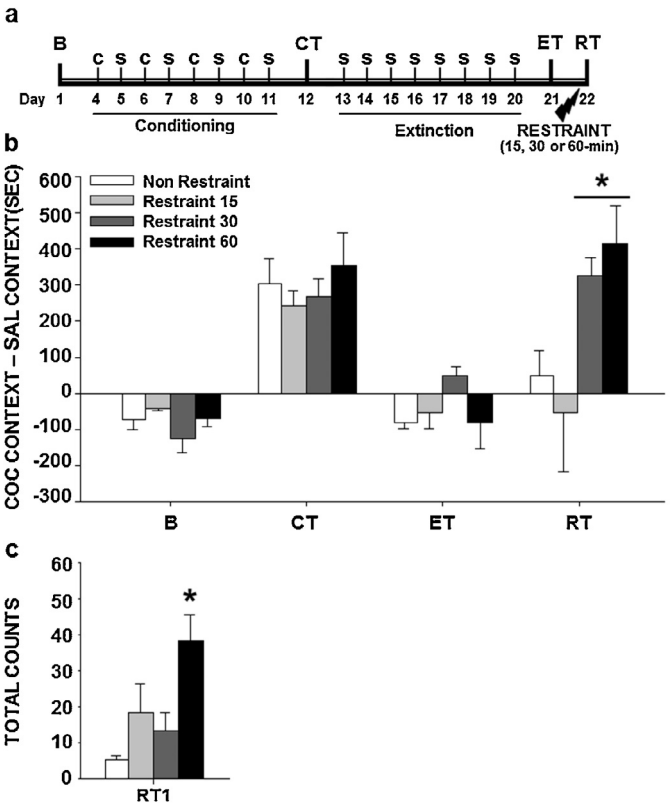

Fig. 2. (a) Experiment timeline. (c = cocaine; s = saline; B = basal, CT = conditioning test; ET = extinction test; RT = restraint stress-induced reinstatement test). (b) Difference in the preference score (mean ± S.E.M.) between the cocaine and saline-associated context for the Non-restraint stress (N = 7), Restraint-stress 15 min (N = 6), Restraint-stress 30-min (N = 6), and Restraint-stress 60-min (N = 6) groups in the basal, conditioning, extinction and reinstatement phases of the test (*$p < 0.05$ compared with Non-Restraint and Restraint-15 group). (c) Mean (±S.E.M.) total locomotor activity in both contexts during stress-induced reinstatement (*$p < 0.05$ compared with Restraint 30, Restraint 15 and Non-Restraint group).

group did not show any change compared to the remaining groups. On the basis of these results, the 30-min period of exposure to restraint stress was selected to induce reinstatement in all subsequent experiments.

An additional pilot experiment was performed in order to demonstrate that just the confinement in the central corridor of the CPP apparatus during 30 min (without restraint stress exposure) was not able to cause reinstatement of cocaine-conditioned preference by itself (data not shown). Similar values to those obtained in non-stressed control animals kept in their home cages were obtained in this pilot experiment.

3.4. Experiment 3: restraint stress-induced reinstatement of extinguished cocaine-conditioned place preference depends on the environment in which restraint stress occurs

Fig. 3 depicts the comparison of restraint stress-induced reinstatement between the animals that were restrained inside the CPP apparatus or in a similar device but outside the experimental room. The RM ANOVA for experimental phase x environment showed that a 30-min restraint stress session was able to induce reinstatement only if it is applied within the environment of the CPP apparatus ($F(1,18) = 6.92$, $p < 0.05$). Since three days after the restraint stress-induced reinstatement day, all groups of animals were able to demonstrate cocaine-induced reinstatement of extinguished cocaine-CPP (RM ANOVA for experimental phase x environment, $F_{(1,18)} = 5.35$, $p < 0.05$), it is not likely that a lack of effect of the restraint stress applied outside the CPP-context could be attributed to a failure of this group to reinstate cocaine-CPP beyond the stimulus applied to induce it. As in Exp. 2, we observed that the difference in preference scores among both groups was not related to changes in locomotor activity (Fig. 3 c).

3.5. Experiment 4: systemic MK 801 administration prior to restraint stress blocks the development of restraint stress-induced reinstatement of extinguished cocaine-conditioned place preference

Exp. 4 reveals that systemic MK 801 administration, before the restraint stress session, disrupted the development of restraint stress-induced reinstatement of extinguished cocaine-CPP (Fig. 4b; RM ANOVA for experimental phase x MK–801 x stress, $F_{(1,27)} = 4.22$; $p < 0.05$). Interestingly, MK 801 injection per se also induced an increase in the permanence of the animals in the cocaine-associated context, an effect that was evident at both doses. Moreover, a greater increase of locomotor activity was found in animals that were injected with the highest MK 801 dose (Fig. 4c). This may

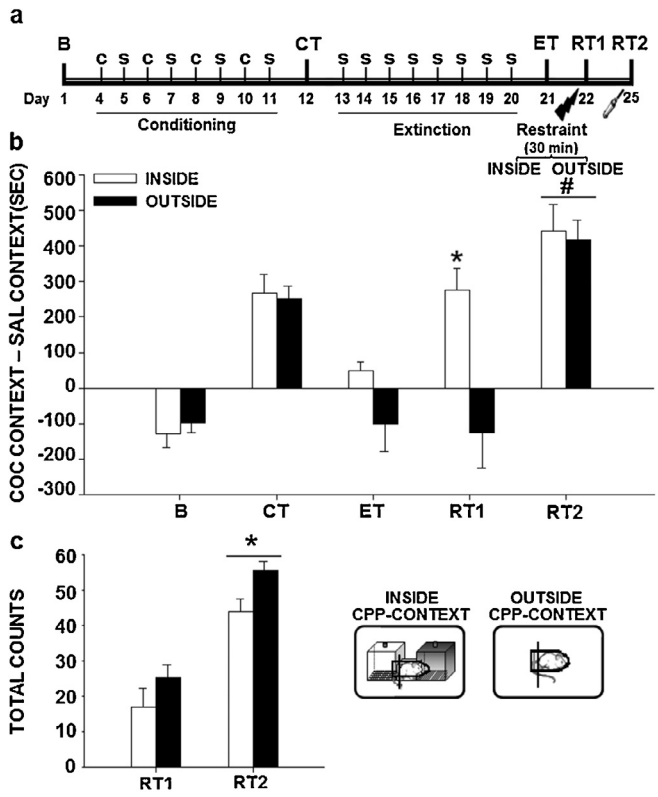

Fig. 3. (a) Experiment timeline. (c = cocaine; s = saline; B = basal; CT = conditioning test; ET = extinction test; RT1 = reinstatement test 1 induced by restraint stress; RT2 = reinstatement test 2 induced by cocaine priming). (b) Difference in the preference score (mean ± S.E.M.) between the cocaine-associated *vs.* the saline-associated context for the stress "INSIDE CPP-CONTEXT group" (N = 6) and "OUTSIDE CPP-context group" (N = 7) groups in the basal, conditioning, extinction and reinstatement (1 and 2) tests (*$p < 0.05$ compared with outside CPP-context group, #$p < 0.05$ compared both groups during ET and RT2. (c) Mean (± S.E.M.) total locomotor activity in both contexts during reinstatement 1 and 2 (*$p < 0.05$ compared with RT2).

indicate that MK 801 exerts an unspecific effect, observed in the non-restraint stress group, that is different to that involved in the suppressing effect of restraint stress-induced reinstatement of cocaine-CPP.

3.6. Experiment 5: systemic MK 801 administration after restraint stress blocks the expression of restraint stress-induced reinstatement of extinguished cocaine-conditioned place preference

The results depicted in Fig. 5 show that the expression of restraint stress-induced reinstatement of extinguished cocaine-CPP was prevented by MK 801 when it was administered immediately after the restraint stress session (RM ANOVA for experimental phase x MK–801 x stress, $F_{(1,23)} = 6.61$, $p < 0.05$; Fig. 5b). The Bonferroni post hoc test shows that MK 801 failed to induce reinstatement by itself (MK 0.1 x VEH: $p < 0.05$), which contrasts with the result observed in Exp. 4, and this is probably attributable to non-specific effects that are evident 45 min but not 15 min after MK-801 administration. Furthermore, it seems that there is a trend toward aversion following the low dose of the antagonist. However, when preference scores of the MK-NS group during reinstatement and extinction were compared, this difference did not reach an acceptable level of significance according to the Bonferroni post hoc test ($p < 0.08$). No differences were observed in locomotor activity among the different groups (Fig. 5c).

3.7. Experiment 6: intra-core MK 801 administration prevents restraint stress-induced reinstatement of extinguished cocaine-conditioned place preference

In this experiment, intra-core MK 801 microinfusions prevented restraint stress-induced reinstatement of cocaine-CPP (RM ANOVA for experimental phase x MK–801 x stress, $F_{(1,27)} = 4.22$, $p < 0.05$), showing that NMDA-dependent neurotransmission in the NAc core is involved in this phenomenon (Fig. 6b). It should be addressed that intra-core MK 801 administration did not induce reinstatement by itself in the non-restraint stress group of animals, as previously

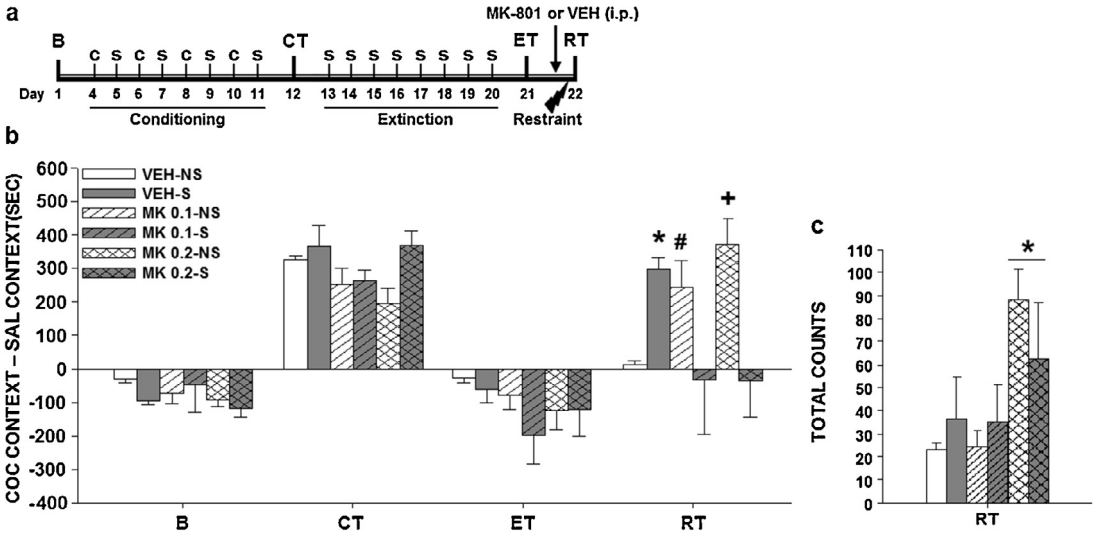

Fig. 4. (a) Experiment timeline. (c = cocaine; s = saline; B = basal, CT = conditioning test, ET = extinction test, RT = reinstatement test). (b) Difference in the preference score (mean ± S.E.M.) between the cocaine-associated *vs.* the saline-associated context for the VEH-NS=Non-stress VEH group (N = 7); VEH-S = Stress VEH group (N = 8); MK 0.1-NS = Non-stress MK 801-0.1 group (N = 6); MK 0.1-S = Stress-MK 801-0.1 (N = 7); MK 0.2-NS=Non-stress MK 801-0.2 group (N = 8); and MK 0.2-S = Stress-MK 801-0.2 group (N = 8) in the basal, conditioning, extinction and reinstatement tests in animals that were injected with vehicle (VEH) or with MK-801 (0.1 or 0.2 mg/kg) (*$p < 0.05$ compared with VEH-NS, MK 0.1-S and MK 0.2-S groups; #$p < 0.05$ compared with VEH-NS, MK 0.1-S, MK 0.2-S; +$p < 0.05$ compared with VEH-NS, MK 0.1-S, MK 0.2-S) 15 min before the restraint stress session. **(c)** Mean (± S.E.M.) total locomotor activity in both contexts during the restraint stress-induced reinstatement test (#$p < 0.05$ compared with VEH-NS, VEH-S, MK 0.1-NS, MK 0.1-S groups).

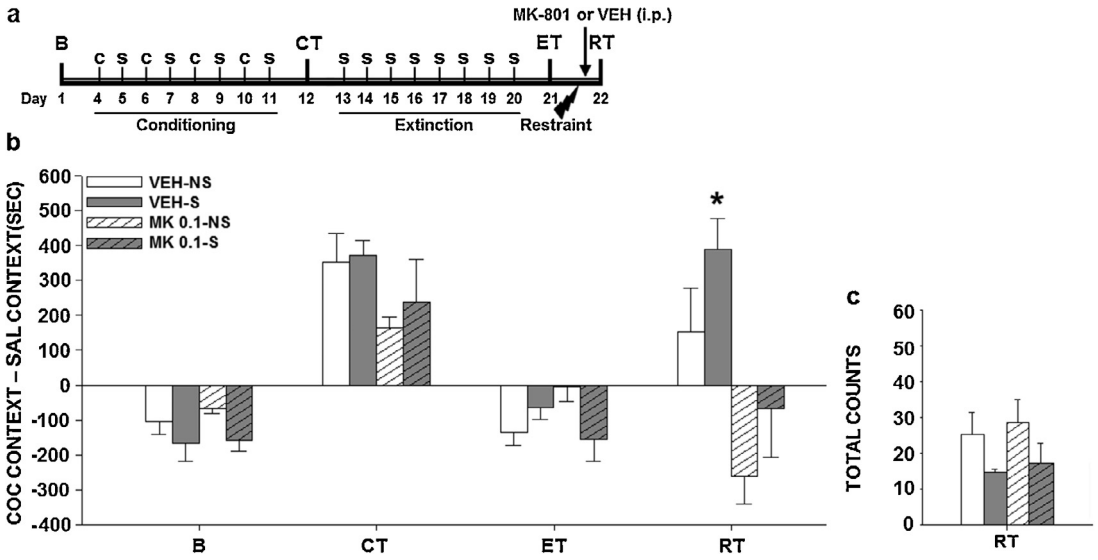

Fig. 5. (a) Experiment timeline. (c = cocaine; s = saline; B = basal, CT = conditioning test, ET = extinction test, RT = reinstatement test). (b) Difference in the preference score (mean ± S.E.M.) between the cocaine-associated *vs.* the saline-associated context for the VEH-NS=Non-stress VEH group (N = 8); VEH-S = Stress VEH group (N = 8); MK-NS=Non-stress MK 801 group (N = 7); MK-S = Stress-MK 801 group (N = 8) in the basal, conditioning, extinction and reinstatement tests in animals that were restrained (or left undisturbed in their home-cage, considered as control group) and immediately after the restraint session were injected with vehicle (VEH) or MK-801 0.1 or 0.2 mg/kg and tested in the CPP test (*$p < 0.05$ compared with VEH-NS, MK-NS and MK-S groups). (c) Mean (±S.E.M.) total locomotor activity in both contexts during the restraint stress-induced reinstatement test.

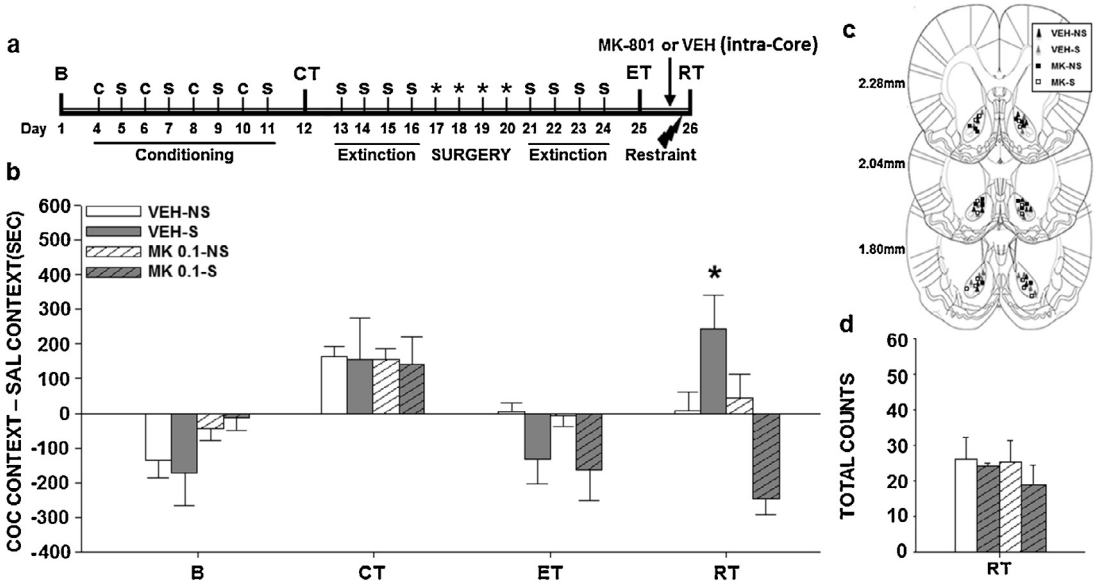

Fig. 6. (a) Experiment timeline. (c = cocaine; s = saline; B = basal, CT = conditioning test, ET = extinction test, RT = reinstatement test). (b) Difference in the preference score (mean ± S.E.M.) between the cocaine-associated *vs.* the saline-associated context for the VEH-NS=Non-restraint stress VEH group (N = 7), VEH-S = Restraint stress-VEH group (N = 8), MK-NS=Non-restraint stress MK 801 group (N = 7), MK-S = Restraint stress-MK 801 group (N = 7); in the basal, conditioning, extinction and reinstatement test in animals that were microinfused with 0.75 ug/side MK-801 or VEH 5 min before restraint stress session (*$p < 0.05$ compared with VEH-NS, MK-NS, MK-S). (c) Cannula placement in NAc core according to the atlas of Paxinos et al. (d) Mean (± S.E.M.) total locomotor in both contexts during restraint stress-induced reinstatement test.

observed in Exp. 4. No differences were observed in locomotor activity among the different groups (Fig. 6c).

3.8. Experiment 7: intra-shell MK 801 administration does not prevent restraint stress-induced reinstatement of extinguished cocaine-conditioned place preference

Fig. 7 shows that intra-shell MK 801 microinfusions did not prevent restraint stress-induced reinstatement of cocaine-CPP, revealing that, in contrast to NAc core, NAc shell NMDA-dependent neurotransmission is not involved in this phenomenon (Fig. 7b). No differences were observed in locomotor activity among the different groups (Fig. 7c).

4. Discussion

This study demonstrates the participation of NMDA receptors within the NAc core, but not in the shell, in restraint stress-induced reinstatement of extinguished cocaine-CPP. The intra-core, but not the intra-shell, administration of MK-801, an NMDA receptor antagonist, prevented the restraint stress-induced reinstatement of cocaine-CPP, which was slightly different to that observed following footshock stress-induced reinstatement of seeking behavior in a

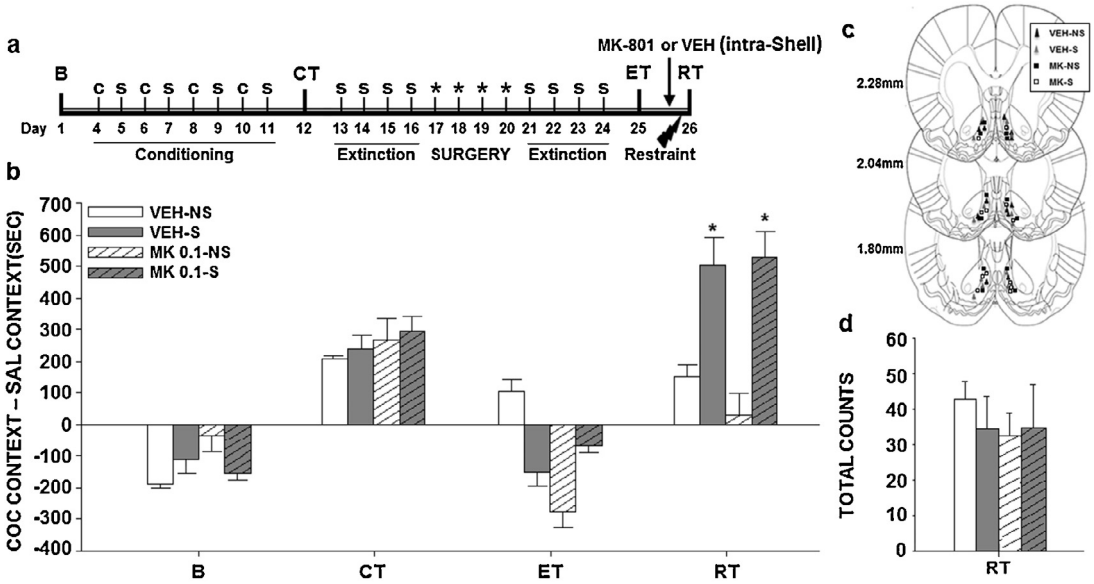

Fig. 7. (a) Experiment timeline. (c = cocaine; s = saline; B = basal, CT = conditioning test, ET = extinction test, RT = reinstatement test). (b) Difference in the preference score (mean ± S.E.M.) between the cocaine-associated *vs.* the saline-associated context for VEH-NS=Non-stress VEH group (N = 7), VEH-S = Stress-VEH group (N = 7), MK-NS=Non Stress-MK 801 group (N = 6) and MK-S = Stress-MK 801 (N = 6) group in the basal, conditioning, extinction and reinstatement tests in animals that were microinfused with vehicle (VEH) or MK-801 (0.75 ug/side) 15 min before the restraint stress session (*$p < 0.05$ compared with VEH-NS and MK-NS groups; *$p < 0.05$ compared with VEH-NS and MK-NS groups). (c) Cannula placement in NAc shell according to the atlas of Paxinos et al. (d) Total locomotor activity in both contexts during the reinstatement test.

cocaine self-administration paradigm, in which the inactivation of Nac core or shell was shown to suppress this behavior [34]. Also, we demonstrated that systemic MK 801 administration, either prior to or after restraint-stress exposure, blocked the stress-induced reinstatement of extinguished cocaine-CPP, matching that observed following a cocaine priming injection in a CPP reinstatement model [10].

Comparing two different extinction protocols, saline pairings *vs.* repeated tests, the saline-pairings extinction procedure showed a strong capability to induce extinction of the cocaine-associated context while the repeated tests procedure was not sufficiently effective. Our results agree with those reported by [24], but not with those of [36], who showed that both extinction procedures were effective to extinguish cocaine-CPP responses. This discrepancy could be attributed to the difference in the duration of the extinction sessions (20-min in [36] *vs.* 30-min in our protocol). Several factors may be also related with this discrepancy, such as different rat strains (Sprague Dawley in [36] *vs* Wistar in our study), environmental conditions, light conditions, etc. Related to this, [24] showed that effectiveness of the repeated tests procedure to induce extinction of cocaine-conditioning preference depends on the magnitude of conditioning. Interestingly, the present study also provides the first evidence about the duration- and environment-dependence of restraint stress for inducing reinstatement of extinguished cocaine-CPP. Thus, 30 and 60-min but not 15-min restraint stress session, applied in the same room where the conditioning apparatus is located, were able to induce a robust reinstatement in animals that extinguished cocaine-CPP.

The ability of stress to induce reinstatement of cocaine-CPP or cocaine self-administration has been modeled using several stressors, such as food deprivation [49], footshock [14,49,46], forced swimming [29] and restraint [49,45,9]. Restraint stress has been used to induce reinstatement of extinguished preference in CPP-trained animals for different drugs: methamphetamine [20], nicotine [30,53] and cocaine [45,9], among others. In these studies, the duration of exposure to restraint stress necessary to induce reinstatement of extinguished drug-CPP varies within a range from 15 min [45,9] o 30 min [30]. The shorter time needed to induce reinstatement of extinguished drug CPP in some of these studies compared to ours could be attributed to the use of mice or different rat strains.

Another important finding of the current study was related to whether or not the context associated with restraint stress exposure determines the reinstatement of cocaine-CPP in animals that have extinguished this response. Animals that were restrained inside the CPP apparatus exhibited reinstatement while animals restrained outside the apparatus did not. These results are consistent with a previous study by [49] in which they reported that, in cocaine self-administered rats, restraint or footshock stress did not induce reinstatement of cocaine-seeking if the restraint or footshock was applied in a novel, non-drug related environment. Given the importance of environment in drug addiction, our findings help to support the face validity criterion of the restraint stress-induced reinstatement of cocaine-CPP responses.

4.1. Role of NMDA receptors in restraint stress-induced reinstatement of cocaine-CPP: a differential role for NAc core and shell

NMDA-dependent glutamatergic transmission in the forebrain reward circuits is actively involved in the regulation of drug-rewarding effects and the ability of cue, drug priming and stress to induce reinstatement of extinguished drug-CPP. Previous studies demonstrate the participation of NMDA receptors in cocaine- and amphetamine-induced CPP [28,44]. Moreover, [10] demonstrated that the systemic administration of MK 801 blocks cocaine priming-induced reinstatement in cocaine-CPP animals. Additionally, Ma et al. [32] reported that, in animals submitted to morphine-CPP, the NMDA receptor 2 B subunit (NR2B) selective antagonist, ifenprodil, blocked morphine priming-induced reinstatement but not forced-swimming stress-induced reinstatement, and consistently, these authors demonstrate that NR2 B protein levels were elevated in the NAc of rats that had reinstated.

Our findings provide new insights into the contribution of NMDA receptors within the NAc core, but not within the shell, to the mechanism of the relapse of drug-seeking behaviors elicited by

exposure to acute restraint stress. Specifically, the non-competitive blockade of NMDA receptors by the administration of MK 801 was able to disrupt restraint stress-induced reinstatement of extinguished cocaine-CPP when the drug was administered either systemically or directly into the NAc core, but not into the NAc shell, thereby identifying the NAc core as a critical site at which NMDA receptors are needed to underpin the restraint stress-induced reinstatement of cocaine-CPP responses.

Our data agree with recent findings reported by [19], who suggested that the NAc core and shell participate differentially in the two processes related to cocaine-taking and −seeking during escalation, abstinence and re-escalation of cocaine self-administration. They reported that while in the NAc core is an increased recruitment of coding neurons after abstinence and through re-escalation, in the NAc shell they found a decrease in firing of the neurons. Moreover, recent studies from [56] demonstrate that, although the functional integrity of both the NAc core and the shell is required for reinstatement of cocaine-seeking behavior, the neuropharmacological mechanisms that underlie this phenomenon are different. Thus, while in the NAc core the administration of either an AMPA/kainate or an mGluR1 receptor antagonist (CNQX or JNJ16259685, respectively) disrupts the reinstatement of cocaine-seeking, only the AMPA/kainate antagonist, but not the mGluR1 antagonist, exerts an influence within the NAc shell. In other studies, it was also shown that the NAc core, but not the NAc shell, is critical for cue-induced reinstatement [16] but not for drug-context-induced reinstatement of cocaine-seeking behavior [7], suggesting that the core and shell subregions of the NAc contribute differently to the reinstatement of cocaine-seeking, depending on the type of stimulus used to elicit this behavior. McFarland et al. [34] demonstrated that footshock stress-induced reinstatement of cocaine-seeking behavior requires the functional integrity of NAc core or shell, but the effect of inhibition of the dorsal prefrontal cortex (PFCd) on NAc glutamate release associated with footshock-induced reinstatement was found only for the NAc core. Our work provides new insights into the role of glutamatergic transmission within the NAc core, but not in the shell, in restraint stress-induced reinstatement of cocaine-CPP, similarly to that observed in cue-induced, but not in context-induced, reinstatement.

Despite the clear suppression effect of MK 801 on restraint stress-induced reinstatement of cocaine-CPP, it should be mentioned that systemic MK 801, at both doses, induced *per se* a reinstatement in non-restrained animals. In the same way, [37] showed that a higher systemic dose of MK 801 induces an amphetamine-sensitized response by itself, but, when MK-801 is administered prior to an acute restraint stress exposure, the development of restraint stress-induced sensitization to amphetamine was blocked. Additionally, in a previous study from [15], the intra-core or intra-shell administration of the competitive NMDA antagonist AP-5 induced reinstatement of cocaine self-administration behavior. However, in the current study, the intra-core or intra-shell administration of MK 801 did not induce any effect per se, although the intra-core administration of MK 801 did block the restraint stress-induced reinstatement of extinguished cocaine-CPP. The difference between our current findings and those of [15] could be attributed to the use of a competitive instead of a non-competitive antagonist, Sprague-Dawley instead of Wistar rats, and a different behavioral paradigm to determine cocaine-seeking behavior. Interestingly, in our study the increase of locomotor activity was observed with the higher systemic dose of MK 801 but not following the intra-core administration of the antagonist. Summing up, MK 801 alone might modify the behavior, although, when it is coadministered with drugs or stress, it prevents their effects, suggesting that different mechanisms are involved.

Although our current results focus on the role of NMDA-dependent neurotransmission in stress-induced reinstatement of extinguished cocaine-CPP, there is evidence to suggest that other types of glutamatergic receptors may be involved in the reinstatement of drug-seeking behavior. Thus, previous data demonstrated that both groups of metabotropic glutamate receptors, mGlu I and mGlu II, are involved in cocaine priming-induced reinstatement of extinguished cocaine seeking [39,21,33] and it is also well established that mGlu I and mGlu II receptors are highly expressed in the Nac core [43,50]. However, the role of mGlu I and mGlu II in stress-induced reinstatement is not yet demonstrated. Unpublished preliminary results from our lab suggest that both mGu I and mGlu II receptors may be involved in restraint stress-induced reinstatement of extinguished cocaine-CPP.

5. Conclusions

This study provides clear evidence of the participation of NMDA receptors within the NAc core but not in the shell, in restraint stress-induced reinstatement of extinguished cocaine-CPP. Indeed, intra-core MK 801 administration blocked the restraint stress-induced reinstatement of cocaine-CPP responses, while intra-shell MK 801 administration exerted no influence on this, supporting previous reports of a dissociable glutamate role for the NAc core and the shell, underpinning the proactive influence of stress on sensitization to psychostimulant effects of cocaine [17].

Competing financial interest

The authors declare no competing financial interest.

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