Glucocorticoid receptor antagonism disrupts the reconsolidation of social reward-related memories in rats

E.J. Marijke Achterberg[a], Viviana Trezza[b,c] and Louk J.M.J. Vanderschuren[a,b]

Reconsolidation is the process whereby consolidated memories are destabilized upon retrieval and restabilized to persist for later use. Although the neurobiology of the reconsolidation of both appetitive and aversive memories has been intensively investigated, reconsolidation of memories of physiologically relevant social rewards has received little attention. Social play, the most characteristic social behaviour displayed by young mammals, is highly rewarding, illustrated by the fact that it can induce conditioned place preference (CPP). Here, we investigated the role of signalling mechanisms implicated in memory processes, including reconsolidation, namely glucocorticoid, mineralocorticoid, NMDA glutamatergic and CB1 cannabinoid receptors, in the reconsolidation of social play-induced CPP in rats. Systemic treatment with the glucocorticoid receptor antagonist mifepristone before, but not immediately after, retrieval disrupted the reconsolidation of social play-induced CPP. Mifepristone did not affect social play-induced CPP in the absence of memory retrieval. Treatment with the NMDA receptor antagonist MK-801 modestly affected the reconsolidation of social play-induced CPP. However, the reconsolidation of social play-induced CPP was not affected by treatment with the mineralocorticoid and CB1 cannabinoid receptor antagonists spironolactone and rimonabant, respectively. We conclude that glucocorticoid neurotransmission mediates the reconsolidation of social reward-related memories in rats. These data indicate that the neural mechanisms of the reconsolidation of social reward-related memories only partially overlap with those underlying the reconsolidation of other reward-related memories. ***Behavioural Pharmacology*** **25:216–225 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Reconsolidation is the process whereby a retrieved memory enters a destabilized state and is subsequently restabilized (Nader *et al.*, 2000). It has been suggested that this process provides an opportunity for updating or strengthening existing memory traces (Lee, 2009; Inda *et al.*, 2011). Over the last decade, an extensive body of literature has emerged on the neural mechanisms underlying the reconsolidation of aversive memory traces and also appetitive food and drug memories. However, the reconsolidation of memories of physiologically relevant natural rewards, such as social behaviour, has received little attention (Perrin *et al.*, 2007).

To address this issue, we have recently demonstrated a long-term impairing effect of the β-adrenoceptor antagonist propranolol on the reconsolidation of social reward-related memory using social play behaviour-induced conditioned place preference (CPP) (Achterberg *et al.*, 2012). Social play, the most characteristic social behaviour in juvenile and adolescent mammals, serves to facilitate social, physical and cognitive development (Panksepp *et al.*, 1984; Vanderschuren *et al.*, 1997; Špinka *et al.*, 2001; Pellis and Pellis, 2009; Baarendse *et al.*, 2013). Social play is highly rewarding (Vanderschuren *et al.*, 1997; Trezza *et al.*, 2010, 2011a), as is apparent from the observations that it can induce CPP (Calcagnetti and Schechter, 1992; Crowder and Hutto, 1992; Thiel *et al.*, 2008; Trezza *et al.*, 2009, 2011b). Because place conditioning relies on an associative mechanism, it can be used to study the dynamics of emotionally charged memories (Bernardi *et al.*, 2006; Fricks-Gleason and Marshall, 2008).

Studies on the neural underpinnings of the reconsolidation process have identified a number of signalling mechanisms involved, including β-noradrenergic, *N*-methyl-D-aspartate (NMDA), cannabinoid 1 (CB1) and glucocorticoid receptors in several paradigms and species (for reviews, see Tronson and Taylor, 2007; Besnard *et al.*, 2012). There is a large body of literature showing that glucocorticoid hormones, such as corticosterone, strengthen memory of emotionally arousing experiences (De Quervain *et al.*, 1998, 2009; Roozendaal *et al.*, 2008). These hormones bind to glucocorticoid and mineralocorticoid receptors in brain areas involved in learning and memory, such as the hippocampus, the amygdala and the prefrontal cortex (De Kloet *et al.*, 2005). Blocking glucocorticoid receptors has been found to impair the reconsolidation of aversive events (Jin *et al.*, 2007; Wang *et al.*, 2008; Taubenfeld *et al.*, 2009; Nikzad *et al.*, 2011; Pitman *et al.*, 2011), whereas blocking mineralocorticoid receptors

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was found to interfere with the retrieval of fear memory in mice (Zhou *et al.*, 2011). Interestingly, there is substantial evidence that the release of glucocorticoids is initiated not only in response to aversive stimuli but also in response to rewarding stimuli such as food, drugs of abuse, sex and social play (Piazza and Le Moal, 1997; Gordon *et al.*, 2002; Koolhaas *et al.*, 2011; Buwalda *et al.*, 2012). Indeed, increased glucocorticoid levels have been shown to improve the acquisition and consolidation of appetitive memories (Micheau *et al.*, 1981, 1985; Zorawski and Killcross, 2002; Wichmann *et al.*, 2012).

Glutamatergic NMDA receptors have been implicated widely in the acquisition, (re)consolidation and extinction of both aversive and appetitive memory traces (Przybyslawski and Sara, 1997; Suzuki *et al.*, 2004; Lee *et al.*, 2006a; Lee and Everitt, 2008). In particular, blockade of NMDA receptors was found to interfere with the reconsolidation of drug-induced CPP (Kelley *et al.*, 2007; Sadler *et al.*, 2007; Zhai *et al.*, 2008; Wu *et al.*, 2012). Cannabinoid CB1 receptors are expressed in brain regions involved in memory processing, including the hippocampus, the amygdala and the prefrontal cortex (Katona *et al.*, 2001; Wilson and Nicoll, 2002; Li *et al.*, 2008), and treatment with the CB1 receptor antagonist rimonabant has been shown to impair the reconsolidation process for both aversive and appetitive memories (Bucherelli *et al.*, 2006; Yu *et al.*, 2009; Fang *et al.*, 2011). To the best of our knowledge, however, the effect of blocking glucocorticoid, mineralocorticoid, NMDA or CB1 receptors has not been investigated with respect to the reconsolidation of social reward-related memories.

In the present study, we therefore investigated whether retrieved social reward-related memories in a social play-induced CPP paradigm could be disrupted by administration of the glucocorticoid receptor antagonist mifepristone, the mineralocorticoid receptor antagonist spironolactone, the NMDA receptor antagonist MK-801 or the CB1 receptor antagonist rimonabant, in rats. We hypothesized that when social reward-related memories reconsolidate after memory retrieval, mifepristone, spironolactone, MK-801 and rimonabant would attenuate CPP on a subsequent test by persistently disrupting the memory trace. We predicted that this would also prevent reinstatement of CPP after extinction and retraining.

Methods

Ethics statement

All experiments were approved by the Animal Ethics Committee of Utrecht University and were in agreement with Dutch laws (Wet op Dierproeven 1996) and European regulations (Guideline 86/609/EEC).

Subjects

Male Wistar rats (Charles River, Sulzfeld, Germany) arrived in our animal facility at 21 days of age and were housed in groups of three or four in $40 \times 26 \times 20$-cm ($l \times w \times h$) Makrolon cages under controlled conditions (i.e. temperature 20–24°C, 60–65% relative humidity and 12/12 h light cycle with lights on at 07:00 h). Upon arrival, the animals were allowed at least 5 days of acclimatization to the facility and were handled for 3 days before the start of the experiment. Food and water were freely available. All animals were experimentally naive and were used only once.

Apparatus

Place conditioning was performed as described previously (Trezza *et al.*, 2009, 2011b; Achterberg *et al.*, 2012). The place-conditioning set up (TSE System, Bad Homburg, Germany) comprised eight boxes, each consisting of three compartments with removable Plexiglas lids; two equal-sized large conditioning compartments ($30 \times 25 \times 30$ cm; $l \times w \times h$) separated by a smaller, neutral compartment ($10 \times 25 \times 30$ cm; $l \times w \times h$). The two conditioning compartments had different visual and tactile cues, which also differed from the cues in the middle compartment. The position of the animal in the apparatus was monitored by an array of photobeam sensors located 2.5 cm above the floor. A computer recorded the time (ms) the animals spent in each compartment. All place-conditioning experiments were performed in a sound-attenuated and dimly lit room.

Experimental procedures

Effects of preretrieval or postretrieval mifepristone on social play-induced CPP

The aim of this experiment was to investigate the effect of preretrieval or postretrieval mifepristone treatment on the reconsolidation and the reinstatement of social play-induced CPP. At 26 days of age (day 1), each rat was placed in the middle compartment of the CPP apparatus, and preconditioning side preference was determined by allowing the rats to move freely around the three compartments of the apparatus for 15 min (Pretest). On the basis of their Pretest scores, rats were assigned to a treatment group and to the compartment in which they would be allowed social interaction during conditioning. We used a counterbalanced place-conditioning design (Tzschentke, 2007; Veeneman *et al.*, 2011), meaning that the preconditioning preference in each experimental group for the to be social-paired or non-social-paired compartment $\sim$50%. As a result, on the basis of their Pretest performance, half of the rats in each experimental group were conditioned in their preferred compartment and half were conditioned in their non-preferred compartment. This procedure rules out the possibility that preference shifts are the result of decreased avoidance of the nonpreferred compartment. After the Pretest, rats were individually housed throughout the conditioning period to increase their motivation for social interaction and to facilitate the development of social play-induced CPP (Trezza *et al.*, 2009).

Place conditioning began on day 2. Rats underwent 8 consecutive days of conditioning, with two conditioning

sessions per day. On days 2, 4, 6 and 8 of the experiment, rats were placed for 30 min in one compartment with an initially unfamiliar partner (social session) in the morning, and were placed alone in the other compartment (nonsocial session) in the afternoon. The composition of the pairs of rats during the social sessions was changed daily. As a result, the animals interacted with the same partner on every third conditioning session, to prevent the development of a dominance/subordination relationship within a test pair. All animals were used for analysis of CPP, that is, no neutral 'stimulus animals' were used. On days 3, 5, 7 and 9, the order of sessions was reversed, that is rats were placed alone in one side of the CPP apparatus during the morning session, and were placed in the other compartment with the social partner in the afternoon session. Social and nonsocial conditioning sessions were separated by at least 1 h. On day 10, rats were placed in the middle compartment, where they were allowed to explore the entire apparatus for 15 min [retrieval (RETR)]. The time spent in each compartment was recorded. The animals were treated with vehicle or mifepristone (30 mg/kg, subcutaneously) either 30 min before (preretrieval treatment) or immediately after the retrieval session (postretrieval treatment). The next day, the animals were placed in the middle compartment again and were again allowed to move freely in the apparatus for 15 min to investigate the effect of mifepristone treatment (TEST); this test is also considered the first extinction session. This procedure was repeated once a day for the following days to extinguish place preference, until the mean difference between the time spent in the social-paired and the non-social-paired compartments was no longer statistically significant for four consecutive days in all the experimental groups. This took between 5 and 10 extinction sessions. Twenty-four hours after the last extinction session, the rats received a reconditioning session. Each rat was placed in the social compartment with a social partner for 30 min (social session), and at least 1 h later, it was placed in the nonsocial compartment alone for 30 min (nonsocial session). The next day, the animals were exposed to the whole apparatus for 15 min, and the preference was determined again [reinstatement (REIN)]. As the preretrieval and the postretrieval vehicle groups did not differ significantly in the time they spent in each compartment, the data of these groups were collapsed.

We also investigated whether memory retrieval is necessary for mifepristone to affect the reconsolidation of social play-induced CPP. To that aim, the animals were conditioned as described above. On day 10, instead of a memory retrieval session, animals were treated with mifepristone or vehicle in their home cage. The next day, both groups were tested (TEST) as above.

Effects of preretrieval or postretrieval spironolactone on social play-induced CPP

This experiment was designed to investigate the effect of administration of the mineralocorticoid receptor antagonist spironolactone (50 mg/kg, subcutaneously) on the retrieval and the reconsolidation of memory for social play-induced CPP. The animals were treated with vehicle or spironolactone either 30 min before (preretrieval treatment) or immediately after the retrieval session (postretrieval treatment). Animals were trained and tested for retrieval (RETR), reconsolidation (TEST) and reinstatement (REIN) as in experiment 1.

Effects of preretrieval or postretrieval MK-801 on social play-induced CPP

This experiment was designed to investigate the effect of treatment with the NMDA receptor antagonist MK-801 (0.1 or 0.2 mg/kg, intraperitoneally) on the retrieval and the reconsolidation of memory for social play-induced CPP. The animals were treated with vehicle or MK-801 either 30 min before (preretrieval treatment) or immediately after the retrieval session (postretrieval treatment). The 0.2 mg/kg dose was used only after retrieval because of its disruptive effect on behaviour, which could interfere with memory processing and with the expression of CPP. Animals were trained and tested for retrieval (RETR), reconsolidation (TEST) and reinstatement (REIN) as in experiment 1.

Effects of preretrieval or postretrieval rimonabant on social play-induced CPP

This experiment was designed to investigate the effect of treatment with the cannabinoid CB1 receptor antagonist rimonabant (1.0 mg/kg, intraperitoneally) on the retrieval and the reconsolidation of memory for social play-induced CPP. The animals were treated with vehicle or rimonabant either 30 min before (preretrieval treatment) or immediately after the retrieval session (postretrieval treatment). Animals were trained and tested for retrieval (RETR), reconsolidation (TEST) and reinstatement (REIN) as in experiment 1. Because rimonabant is known to have pruritic effects (Cook *et al.*, 1998; Rubino *et al.*, 2000; Vickers *et al.*, 2003; Tallett *et al.*, 2007), which may interfere with the expression of memory retrieval, scratching behaviour was scored for the animals that received rimonabant before retrieval.

Drugs

The glucocorticoid receptor antagonist mifepristone (RU38486; Tocris Bioscience, Bristol, UK) and the mineralocorticoid receptor antagonist spironolactone (Tocris Bioscience) were dissolved in propylene glycol (Sigma-Aldrich, Schnelldorf, Germany) and administered subcutaneously (mifepristone, 30 mg/kg; spironolactone, 50 mg/kg). The noncompetitive NMDA receptor antagonist (+)-5-methyl-10,11-dihydro-SH-dibenzo[*a*,d]cyclohepten-5,10-imine maleate (MK-801, Tocris Bioscience) was dissolved in saline and administered intraperitoneally (0.1 or 0.2 mg/kg). The CB1 cannabinoid receptor antagonist rimonabant (SR141716A; National Institute of Mental

Health's Chemical Synthesis and Drug Supply Program, National Institutes of Health, Bethesda, Maryland, USA) was dissolved in 5% Tween 80, 5% polyethylene glycol/saline, and administered intraperitoneally (1.0 mg/kg). In all the experiments, the injection volume was 2 ml/kg. Drug doses are based on literature about memory processing in rats (Lee *et al.*, 2006b; Brown *et al.*, 2008; Yu *et al.*, 2009; Pitman *et al.*, 2011; Vafaei *et al.*, 2011).

Statistical analysis

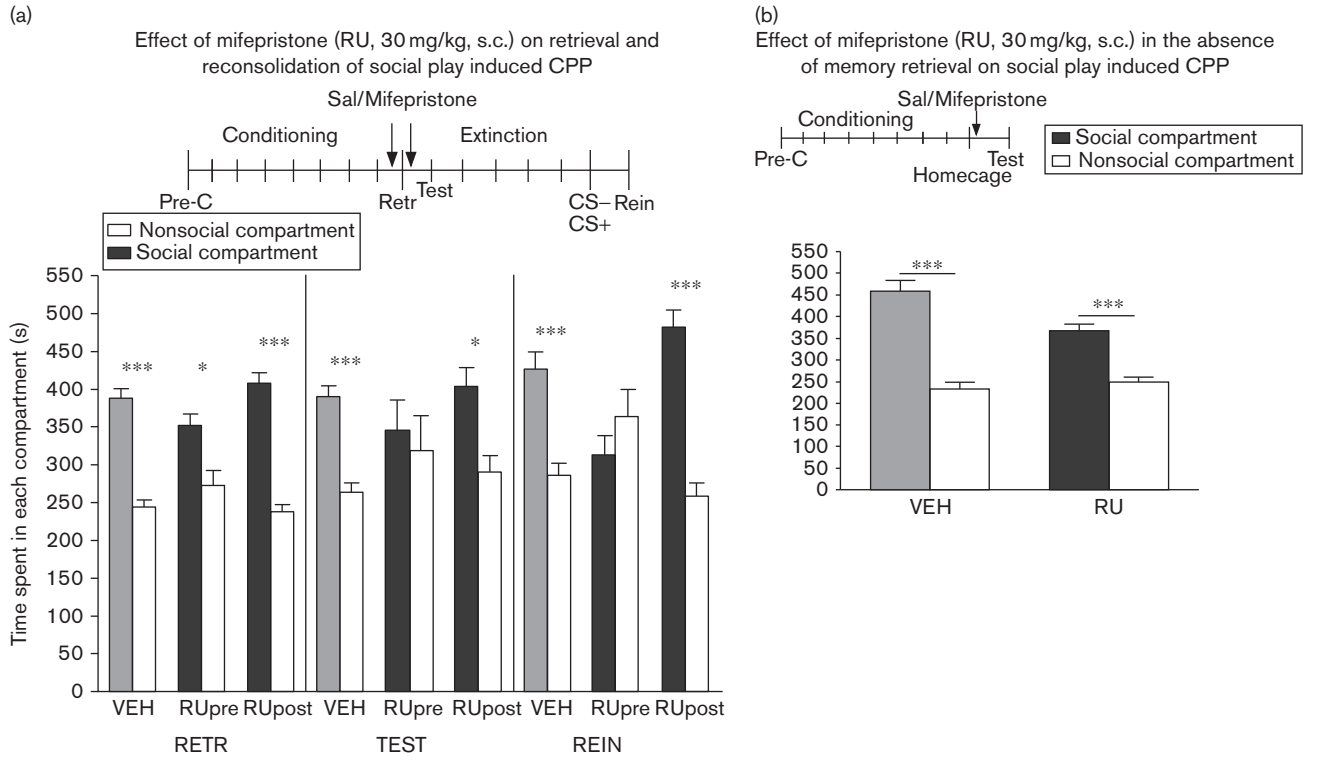
Data were analysed using SPSS software, 15.0 for Windows (Armonk, New York, USA). For each experiment, the time spent in the social paired and the non-social-paired compartments was expressed as mean ± SEM. Data were analysed using analysis of variance (ANOVA) (mixed-model or two-way, depending on the experiment), using compartment (social or nonsocial) and treatment (mifepristone/spironolactone/MK-801/rimonabant or vehicle) as a between-subjects factor and test day as a repeated-measures factor. ANOVA was followed by the Student paired *t*-tests when appropriate, to investigate differences between the time spent in the social and the nonsocial compartments. Differences in the time spent scratching were analysed by an independent-samples *t*-test.

Results

Preretrieval treatment with the glucocorticoid receptor antagonist mifepristone disrupted the reconsolidation, but not the retrieval of social reward-related memories

The mixed-model ANOVA revealed significant effects of the test day ($F_{2,248} = 5.07$, $P = 0.01$) and the compartment ($F_{1,124} = 78.38$, $P < 0.001$) and significant compartment × treatment ($F_{2,124} = 10.39$, $P < 0.001$) and test day × compartment × treatment ($F_{4,248} = 2.96$, $P < 0.02$) interactions. There was no significant main effect of treatment ($F_{2,124} = 0.88$, NS) or other interaction effects (test day × compartment: $F_{2,248} = 1.57$, NS; and test day × treatment: $F_{4,248} = 0.23$, NS; Fig. 1a). A post-hoc analysis revealed that on day 10, all groups showed a significant social play-induced CPP [RETR: veh: $t(31) = 7.41$, $P < 0.001$, $n = 32$; pre:

Fig. 1



(a) Effects of preretrieval and postretrieval mifepristone (RU486; RU) on social play-induced conditioned place preference (CPP). The experimental protocol is depicted above the graph (Pre-C: preconditioning test; CS+: conditioning session with a play partner; CS−: conditioning session alone). Data represent the mean time (s ± SEM) spent in the social compartment (grey and black bars) and the nonsocial compartment (white bars) during 15-min retrieval (RETR), test (TEST) and reinstatement (REIN) sessions: vehicle-treated animals (VEH: 2 ml/kg, subcutaneously, $n = 32$) and mifepristone-treated animals (30 mg/kg, subcutaneously, treatment preretrieval: RUpre, $n = 9$; treatment postretrieval: RUpost: $n = 24$). (b) Effects of mifepristone on social play-induced CPP in the absence of memory retrieval: vehicle-treated animals (VEH: 2 ml/kg, intraperitoneally, $n = 6$) and mifepristone-treated animals (RU: 30 mg/kg, intraperitoneally, $n = 10$). Post-hoc Student's paired *t*-tests for the difference in time spent in the social and the nonsocial compartment; $^*P < 0.05$, $^{***}P < 0.001$.

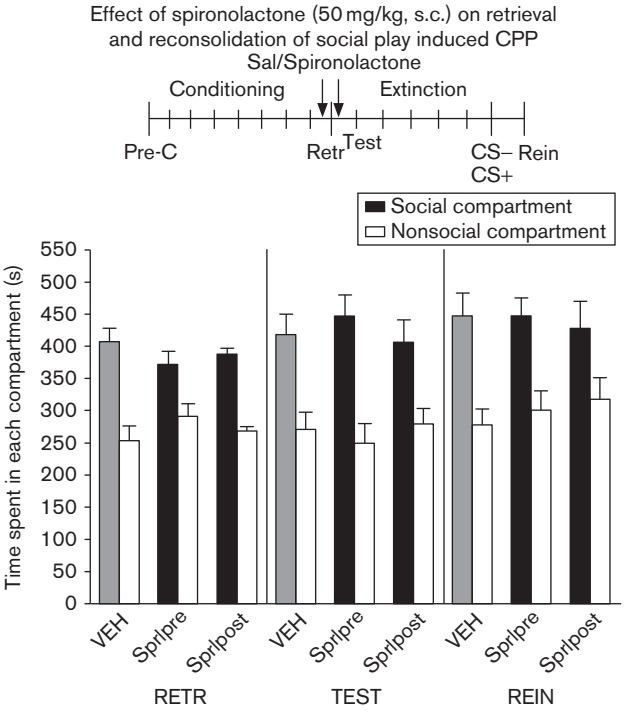
$t(8) = 2.40$, $P < 0.05$, $n = 9$; post: $t(23) = 8.40$, $P < 0.001$, $n = 24$], indicating that mifepristone treatment did not affect the retrieval of social play-induced CPP. Twenty-four hours later (TEST), the vehicle-treated and the postretrieval mifepristone-treated animals still showed a significant preference for the play-paired compartment [veh: $t(31) = 4.81$, $P < 0.001$, post: $t(24) = 2.55$, $P < 0.001$], whereas the preretrieval mifepristone-treated animals no longer showed a preference [pre: $t(8) = 0.32$, NS.]. After the reconditioning session, both the vehicle-treated and the postretrieval mifepristone-treated animals showed a significant social play-induced CPP (REIN: veh: $t(31) = 3.88$, $P < 0.001$, post: $t(24) = 5.65$, $P < 0.001$), whereas no significant reinstatement of CPP was found in the animals treated with mifepristone before retrieval [pre: $t(8) = 0.88$, NS]. These findings indicate that the glucocorticoid receptor antagonist mifepristone disrupts the reconsolidation of social reward-related memory when administered before, but not when administered immediately after, a retrieval session.

Treatment with mifepristone did not affect the reconsolidation of social reward-related memories in the absence of memory retrieval (Fig. 1b). Twenty-four hours after the administration of mifepristone in the home cage (i.e. without a retrieval session), both the vehicle-treated and the mifepristone-treated rats showed a significant preference for the social compartment. The two-way ANOVA revealed significant effects of compartment ($F_{1,28} = 120.25$, $P < 0.001$) and treatment ($F_{1,28} = 8.45$, $P < 0.01$) and a significant compartment × treatment interaction ($F_{1,28} = 14.02$, $P = 0.001$). Post-hoc analysis showed that both the vehicle-treated and the mifepristone-treated animals showed a significant preference for the social-paired compartment [veh: $t(5) = 6.98$, $P < 0.001$, $n = 6$; mifepristone: $t(9) = 5.06$, $P < 0.001$, $n = 10$]. These results indicate that mifepristone treatment without a retrieval session does not affect the reconsolidation of social play-induced CPP.

The mineralocorticoid receptor antagonist spironolactone did not affect the retrieval or the reconsolidation of social reward-related memories

The mixed-model ANOVA showed significant effects of the compartment ($F_{1,52} = 69.92$, $P < 0.001$) and the test day ($F_{2,104} = 3.70$, $P < 0.05$). No other significant main or interaction effects were found (treatment: $F_{2,52} = 0.04$; compartment × treatment: $F_{2,52} = 0.43$; test day × compartment: $F_{2,104} = 0.89$; test day × treatment: $F_{4,104} = 0.05$; test day × treatment × compartment: $F_{4,104} = 1.01$, all NS). All the treatment groups showed a significant preference for the play-paired compartment at RETR and TEST and reinstatement of social play-induced CPP (Fig. 2; vehicle: $n = 12$; preretrieval spironolactone: $n = 10$; postretrieval spironolactone: $n = 7$). These results indicate that administering spironolactone either 30 min before or immediately after a retrieval session does not affect the retrieval or the reconsolidation of social play-induced CPP (Fig. 2).

Fig. 2



Effects of preretrieval and postretrieval spironolactone on social play-induced conditioned place preference (CPP). The experimental protocol is depicted above the graph (Pre-C: preconditioning test; CS+: conditioning session with a play partner; CS–: conditioning session alone). Data represent the mean time (s ± SEM) spent in the social compartment (grey and black bars) and the nonsocial compartment (white bars) during 15-min retrieval (RETR), test (TEST) and reinstatement (REIN) sessions: vehicle-treated animals (VEH: 2 ml/kg, subcutaneously, $n = 12$) and spironolactone-treated animals (30 mg/kg, subcutaneously, treatment preretrieval: Sprlpre: $n = 10$; treatment postretrieval: Sprlpost: $n = 7$).

The effect of the NMDA receptor antagonist MK-801 on the retrieval and the reconsolidation of social reward-related memories

In the experiment where the effect of 0.1 mg/kg MK-801 was tested, the mixed-model ANOVA revealed significant effects of the compartment ($F_{1,172} = 146.53$, $P < 0.001$) and the test day ($F_{2,344} = 4.42$, $P < 0.02$), and significant compartment × treatment ($F_{2,178} = 10.33$, $P < 0.001$), test day × compartment ($F_{2,344} = 6.83$, $P < 0.002$) and test day × compartment × treatment ($F_{4,344} = 3.36$, $P < 0.02$) interactions. There was no significant main effect of the treatment ($F_{2,172} = 1.16$, NS) or the test day × treatment interaction ($F_{4,344} = 0.56$, NS; Fig. 3a). A post-hoc analysis revealed that at RETR and TEST, all groups showed a significant preference for the play-paired compartment [RETR: veh: $t(39) = 9.12$, $P < 0.001$, $n = 40$; pre: $t(28) = 2.48$, $P < 0.02$, $n = 29$; post: $t(20) = 7.21$, $P < 0.001$, $n = 19$; TEST: veh: $t(39) = 6.83$, $P < 0.001$; pre: $t(28) = 2.19$, $P < 0.05$; post: $t(19) = 2.31$, $P < 0.05$]. The vehicle-treated and the postretrieval MK-801-treated animals showed significant reinstatement of social play-induced CPP [REIN: veh: $t(39) = 2.27$, $P < 0.05$,

post: $t(20) = 3.21$, $P < 0.01$], whereas the preretrieval MK-801-treated animals did not [REIN: pre: $t(28) = 0.79$, NS].

In the experiment where the effect of 0.2 mg/kg MK-801 was tested, the mixed-model ANOVA revealed a significant effect of the compartment ($F_{1,28} = 53.00$, $P < 0.001$). No other significant main or interaction effects were found (test day: $F_{2,56} = 1.20$; treatment: $F_{1,28} = 0.08$; test day × compartment: $F_{2,56} = 1.02$; test day × treatment: $F_{2,56} = 0.21$; test day × compartment × treatment: $F_{2,56} = 0.02$, all NS; Fig. 3b). All groups showed a significant preference for the social-paired compartment at RETR, TEST and REIN (Fig. 3b; vehicle: $n = 8$, postretrieval MK-801: $n = 8$). These results indicate that treatment with 0.2 mg/kg MK-801 immediately after a retrieval session does not affect the reconsolidation of social play-induced CPP.

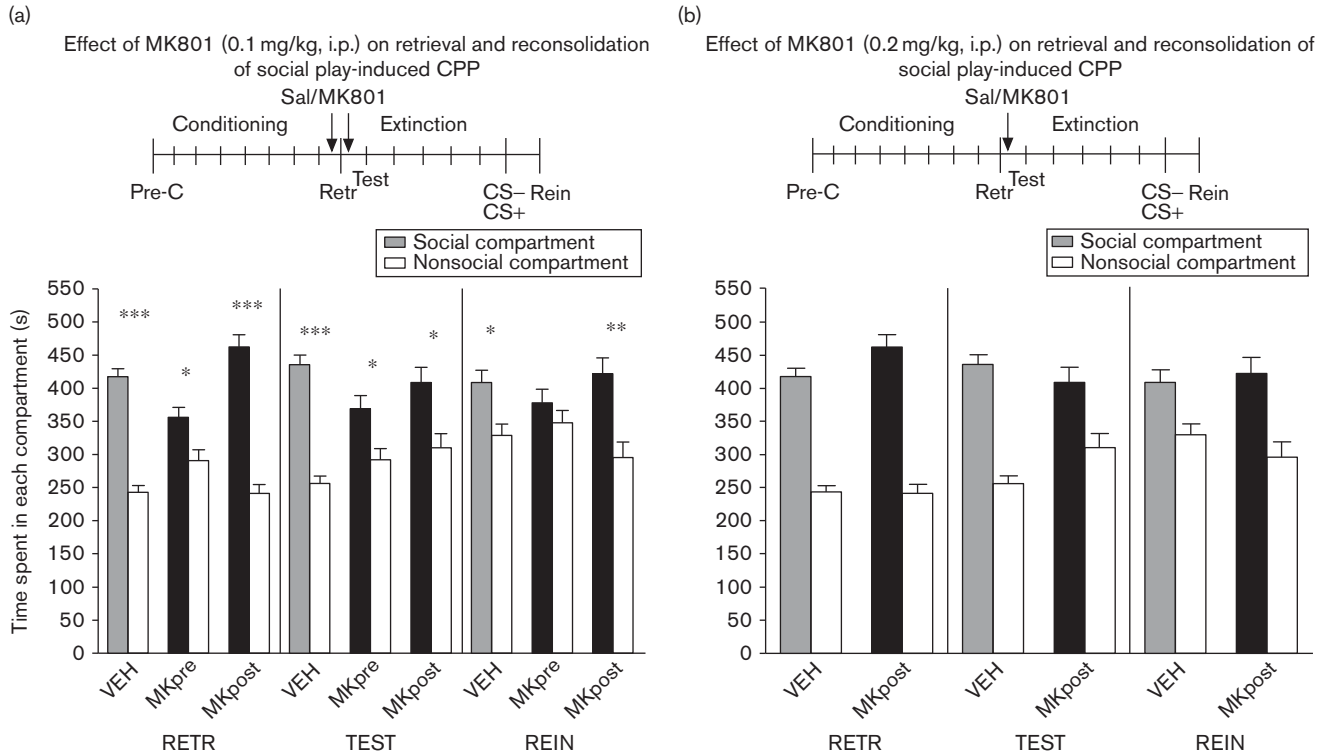
The cannabinoid receptor antagonist rimonabant did not affect the retrieval or the reconsolidation of social reward-related memories

The mixed-model ANOVA revealed a significant effect of the compartment ($F_{1,68} = 55.59$, $P < 0.001$) but no other significant main or interaction effects (test day: $F_{2,136} = 1.16$; treatment: $F_{2,68} = 0.23$; treatment × compartment: $F_{2,68} = 1.19$; test day × compartment: $F_{2,136} = 0.27$; test day × treatment: $F_{4,136} = 0.85$; test day × compartment × treatment: $F_{4,136} = 0.17$, NS). All groups showed a significant preference for the social-paired compartment at RETR, TEST and REIN (Fig. 4a; vehicle: $n = 19$; preretrieval rimonabant: $n = 10$, postretrieval rimonabant: $n = 8$). These results show that treatment with rimonabant (1.0 mg/kg) either 30 min before or immediately after a retrieval session does not affect the retrieval, the reconsolidation or the reinstatement of social play-induced CPP. We also found that rimonabant-pretreated animals spent significantly more time scratching during the 15-min test compared with vehicle-treated animals [$t(12.87) = -2.52$, $P < 0.05$; Fig. 4b].

Discussion

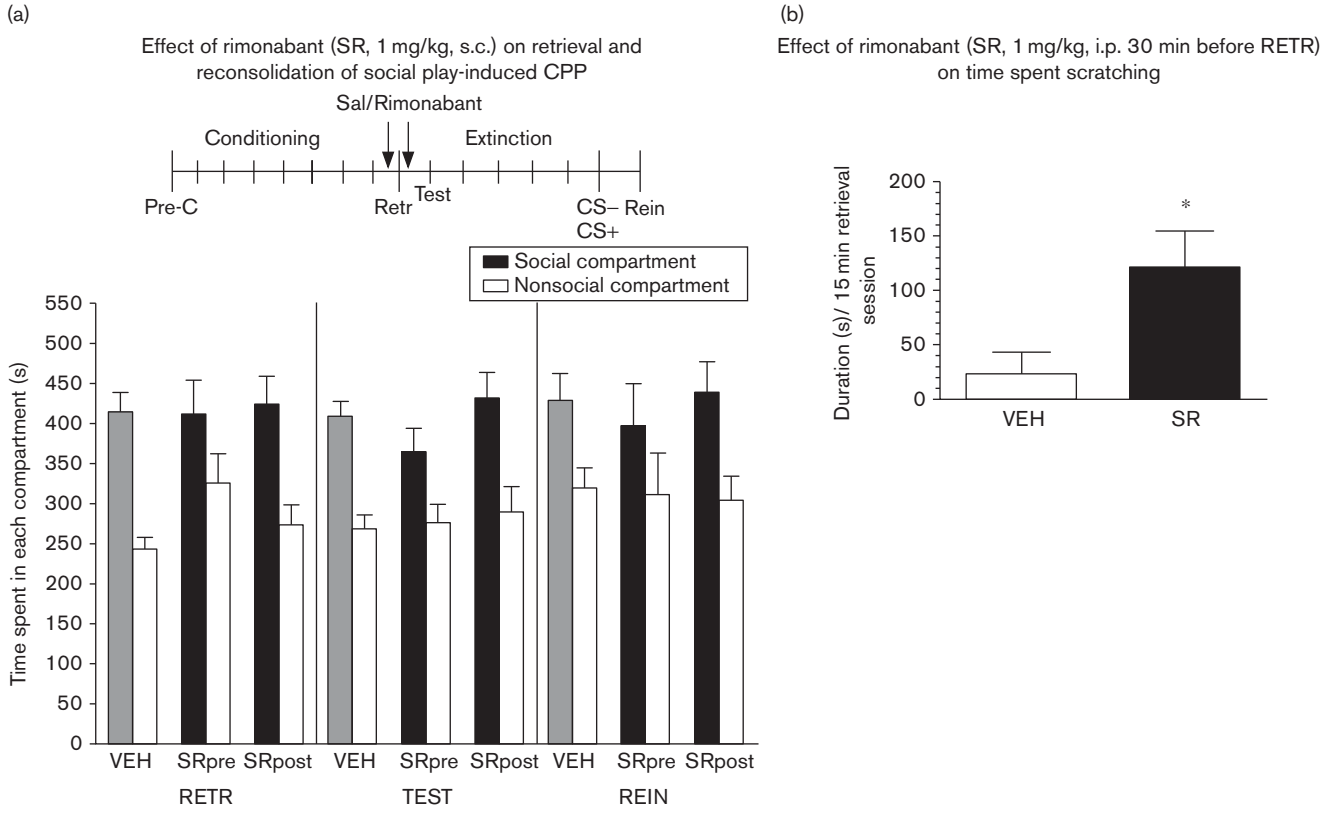
In this study, we investigated the involvement of glucocorticoid, mineralocorticoid, NMDA and cannabinoid CB1 receptors in the retrieval and the reconsolidation of social reward-related memories in rats. Our hypothesis was that

Fig. 3



Effects of MK-801 treatment on social play-induced conditioned place preference (CPP). The experimental protocol is depicted above the graph (Pre-C: preconditioning test; CS+: conditioning session with a play partner; CS−: conditioning session alone). Data represent the mean time (s ± SEM) spent in the social compartment (grey and black bars) and the nonsocial compartment (white bars) during 15-min retrieval (RETR), test (TEST) and reinstatement (REIN) sessions. (a) Effects of preretrieval and postretrieval MK-801 (0.1 mg/kg): vehicle-treated animals (VEH: 2 ml/kg, subcutaneously, $n = 40$) and MK-801-treated animals (0.1 mg/kg, intraperitoneally, treatment preretrieval: MKpre: $n = 29$; treatment postretrieval: MKpost: $n = 19$). Post-hoc Student's paired *t*-tests for the difference in time spent in the social and the nonsocial compartments; $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. (b) Effects of postretrieval MK-801 (0.2 mg/kg): vehicle-treated animals (VEH: 2 ml/kg, intraperitoneally, $n = 8$) and MK-801-treated animals (0.2 mg/kg, intraperitoneally, MKpost: $n = 8$).

Fig. 4



(a) Effects of preretrieval and postretrieval rimonabant (SR141716; SR) on social play-induced conditioned place preference (CPP). The experimental protocol is depicted above the graph (Pre-C: preconditioning test; CS+: conditioning session with a play partner; CS−: conditioning session alone). Data represent the mean time (s ± SEM) spent in the social compartment (grey and black bars) and the nonsocial compartment (white bars) during 15-min retrieval (RETR), test (TEST) and reinstatement (REIN) sessions: vehicle-treated animals (VEH: 2 ml/kg, intraperitoneally, $n=19$) and rimonabant-treated animals (1.0 mg/kg, intraperitoneally, treatment preretrieval: SRpre: $n=10$; treatment postretrieval: SRpost: $n=8$). (b) Time spent scratching during the 15-min test in preretrieval rimonabant-treated animals. Independent samples *t*-test; $^*P<0.05$.

blocking these receptors would disrupt the reconsolidation of social play-induced CPP. We showed that (a) the glucocorticoid receptor antagonist mifepristone disrupts reconsolidation of social play-induced CPP when administered before a retrieval session, and that (b) neither the mineralocorticoid receptor antagonist spironolactone nor the CB1 cannabinoid receptor antagonist rimonabant affected the retrieval or the reconsolidation of social play-induced CPP, whereas preretrieval treatment with the NMDA receptor antagonist MK-801 modestly affected social play-induced CPP. Together, our data show that glucocorticoid neurotransmission mediates the reconsolidation of social play-induced CPP without affecting the retrieval process, whereas mineralocorticoid, NMDA and CB1 cannabinoid receptors are not primarily involved in the dynamics of social reward-related memories.

In the first experiment, vehicle-treated and postretrieval mifepristone-treated animals showed a preference for the social-paired compartment 24 h after retrieval, whereas preretrieval mifepristone-treated animals did not. This effect of mifepristone was not the result of a nonspecific memory impairment, because mifepristone treatment in the absence of retrieval did not alter social play-induced CPP (Jin *et al.*, 2007; Tronel and Alberini, 2007; Taubenfeld *et al.*, 2009; Nikzad *et al.*, 2011; Pitman *et al.*, 2011). Furthermore, after the extinction of CPP, vehicle-treated and postretrieval mifepristone-treated animals showed reinstatement of CPP 24 h after a reconditioning session, whereas preretrieval mifepristone-treated animals did not. The inability to reinstate social play-induced CPP in the preretrieval mifepristone-treated group suggests that acute preretrieval mifepristone persistently disrupted the social play-CPP memory trace, rather than inducing a retrieval deficit or facilitating extinction learning (for a discussion, see Achterberg *et al.*, 2012). Our findings are consistent with previous reports showing that mifepristone treatment (either systemic or intra-amygdala/hippocampus) blocks the reconsolidation of fear memories, while sparing retrieval (Jin *et al.*, 2007; Tronel and Alberini, 2007; Taubenfeld *et al.*, 2009; Nikzad *et al.*, 2011; Pitman *et al.*, 2011), although it should be noted that most of these

previous studies used postretrieval mifepristone treatment, which was ineffective in our study. One likely explanation for this apparent discrepancy is that we used a relatively long retrieval session, because, in our experience, the expression of CPP is difficult to detect using shorter retrieval sessions. In this scenario, postretrieval mifepristone is less effective in interfering with reconsolidation as glucocorticoid receptor-dependent processes involved in the reconsolidation process may take less than 15 min. Interestingly, all the above studies that showed glucocorticoid receptor involvement in reconsolidation were conducted in fear-learning paradigms. Therefore, the present study extends the involvement of glucocorticoid receptors to the reconsolidation of appetitive memories. Pleasurable stimuli such as food, drugs of abuse or sex are known to cause an increase in corticosterone levels (Piazza and Le Moal, 1997; Koolhaas *et al.*, 2011; Buwalda *et al.*, 2012). Indeed, an episode of social play also evokes an increase in corticosterone levels in rats (Gordon *et al.*, 2002). Moreover, increasing glucocorticoid levels improves acquisition and consolidation of appetitive memory (Micheau *et al.*, 1981, 1985; Zorawski and Killcross, 2002; Wichmann *et al.*, 2012) suggesting a role for glucocorticoid receptors in the initial stages of appetitive memory formation. Our data add to this by demonstrating that reconsolidation of reward-related memory can be disrupted by antagonizing glucocorticoid receptors. Whether other reward-related memories, such as drug-reward memory, are affected by antagonizing glucocorticoid receptors remains to be elucidated. The mineralocorticoid receptor antagonist spironolactone did not interfere with the retrieval or the reconsolidation of social reward-related memories. Consistent with our findings, Vafaei *et al.* (2011) found no effect of spironolactone (either systemically and intrahippocampus) on the reconsolidation of inhibitory avoidance memory. In contrast, in a fear-conditioning paradigm, blocking the mineralocorticoid receptors with spironolactone before a brief context retrieval session, but not a cue-tone retrieval session, disrupted subsequent expression of fear, although postretrieval treatment with spironolactone was ineffective (Zhou *et al.*, 2011). Thus, mineralocorticoid receptors may be involved in the reconsolidation of certain aversive rather than appetitive memories. However, the contribution of other factors to the discrepancies between the studies (i.e. reliance on cues vs. contextual information, and species and age differences of the animals tested) can not be ruled out at this point, as the literature on the role of the mineralocorticoid receptor in reconsolidation is very limited.

Treatment with MK-801 modestly affected the reconsolidation of social play-induced CPP. Thus, postretrieval treatment with MK-801 did not alter the expression of social play-induced CPP during the tests for reconsolidation and reinstatement. After preretrieval treatment with 0.1 mg/kg MK-801, there was significant CPP during retrieval and the test for reconsolidation, albeit of a lesser magnitude than seen in the vehicle-treated rats. Interestingly, after reconditioning, there was no reinstatement of CPP in the animals treated with 0.1 mg/kg MK-801 preretrieval. This suggests that preretrieval NMDA receptor blockade impaired the integrity of the memory trace to some extent. Previously, systemic blockade of NMDA receptors has been found to block reconsolidation of aversive (Suzuki *et al.*, 2004; Lee *et al.*, 2006b) as well as drug-reward and food-reward memories (Kelley *et al.*, 2007; Sadler *et al.*, 2007; Brown *et al.*, 2008; Itzhak, 2008; Lee and Everitt, 2008; Milton *et al.*, 2008). There are several explanations for our findings that MK-801 treatment did not profoundly disrupt reconsolidation of social play-induced CPP in the present study. Thus, Ben Mamou *et al.* (2006) and Milton *et al.* (2013) have shown a role for different subtypes of NMDA receptors in the destabilization and the reconsolidation of memory. Blocking NR2B-containing NMDA receptors in the basolateral amygdala prevents the reactivation of a conditioned fear memory, whereas NR2A-containing NMDA receptors are specifically implicated in the reconsolidation of fear memory. It is therefore possible that preretrieval MK-801 administration inhibited the reactivation of the social play-CPP memory trace. As a result, reconsolidation could not be completely blocked because the memory trace was not in a fully active state. This retrieval-inhibition explanation is consistent with the reduced magnitude of CPP after preretrieval MK-801 treatment. Furthermore, treatment with NMDA receptor antagonists disrupts extinction learning (Suzuki *et al.*, 2004; Lee *et al.*, 2006b; Chan and McNally, 2009). According to Suzuki *et al.* (2004), there is a brief time window for reconsolidation after retrieval ($\sim$3 min), whereas extinction occurs only after prolonged exposure (30 min). As explained above, we used a 15-min reactivation session, which may result in competing reconsolidation and extinction processes, whereby MK-801 administration could affect both, so that the social play-CPP memory trace would remain relatively intact.

Neither the retrieval nor the reconsolidation of social play-induced CPP was disrupted by the administration of the CB1 receptor antagonist rimonabant. There is no consensus in the literature on the effect of CB1 antagonists on aversive memory, as disruption (Bucherelli *et al.*, 2006), facilitation (De Oliveira Alvares *et al.*, 2008) and lack of an effect (Suzuki *et al.*, 2008) on reconsolidation have been found. Interestingly, systemic treatment with rimonabant has been shown to disrupt the reconsolidation of nicotine-induced and methamphetamine-induced CPP (Yu *et al.*, 2009; Fang *et al.*, 2011). However, these studies used a higher dose of rimonabant (3.0 mg/kg), which leaves the possibility open that this reconsolidation blockade occurred through a non-CB1 receptor-dependent mechanism of action of rimonabant. Moreover, rimonabant is known to be pruritogenic (Cook *et al.*, 1998; Rubino *et al.*, 2000; Vickers *et al.*, 2003; Tallett *et al.*, 2007). Indeed, we found a significant increase in

scratching in rimonabant-treated animals. We therefore did not test the 3.0-mg/kg dose of rimonabant, as scratching disrupts behaviour severely, which may interfere with memory processing in the CPP box. Treatment with CB1 receptor antagonists has been shown to disrupt extinction learning in aversive paradigms (Marsicano *et al.*, 2002; Suzuki *et al.*, 2004; Niyuhire *et al.*, 2007), but their role in the extinction of appetitive memories is not clear (Manwell *et al.*, 2009; Hernandez and Cheer, 2011). This makes it unlikely that the lack of effect of rimonabant on social play-induced CPP is the result of interference with reconsolidation and extinction at the same time. However, CB1 receptors are thought to be required for memory destabilization (Suzuki *et al.*, 2004, 2008). Our data do not, therefore, support a role for CB1 receptors in the reconsolidation of social reward memories, but the contribution of a destabilization blockade in our findings can as yet not be excluded.

In conclusion, the present study extends our knowledge about the reconsolidation of social reward-related memories in rats, showing that this type of reward memory is subject to the impairing effects of glucocorticoid receptor antagonism. However, our data do not support a primary role for mineralocorticoid, NMDA or CB1 receptors in the reconsolidation of social reward-related memories in rats.

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Conflicts of interest

There are no conflicts of interest.

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