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Dissociable roles of mGlu5 and dopamine receptors in the rewarding and sensitizing properties of morphine and cocaine

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Abstract

Rationale Drugs of abuse are initially used because of their rewarding properties. As a result of repeated drug exposure, sensitization to certain behavioral effects of drugs occurs, which may facilitate the development of addiction. Recent studies have implicated the metabotropic glutamate receptor 5 (mGlu5 receptor) in drug reward, but its role in sensitization is unclear. Stimulation of dopamine receptors plays an important role in drug reward, but not in the sensitizing properties of cocaine and morphine.

Objective This study aims to evaluate the role of mGlu5 and dopamine receptors in the development of cocaine- and morphine-induced conditioned place preference (CPP) and psychomotor sensitization.

Materials and methods Rats were treated with the mGlu5 receptor antagonist MTEP (0, 1, 3, and 10 mg/kg, i.p.) or the dopamine receptor antagonist α -flupenthixol (0, 0.125, 0.25,

and 0.5 mg/kg, i.p.) during place conditioning with either morphine (3 mg/kg, s.c.) or cocaine (15 mg/kg, i.p.). Furthermore, MTEP (1 mg/kg, i.p.) or α -flupenthixol (0.5 mg/kg, i.p.) was co-administered during cocaine (30 mg/kg, i.p.) or morphine (3.0 mg/kg, s.c.) pretreatment and psychomotor sensitization was tested 3 weeks post-treatment. **Results** MTEP attenuated the development of morphine- but not cocaine-induced CPP. In contrast, MTEP suppressed the development of cocaine- but not morphine-induced psychomotor sensitization. α -Flupenthixol blocked the development of both cocaine- and morphine-induced CPP but did not affect the development of sensitization to either drug.

Conclusion Dopamine receptor stimulation mediates cocaine and morphine reward but not sensitization. In contrast, the role of mGlu5 receptors in reward and sensitization is drug-specific.

Keywords Morphine · Cocaine · Dopamine receptor · Metabotropic glutamate receptor · Locomotor activity · Sensitization · Reward · Conditioned place preference

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Introduction

Over the last two decades, a substantial body of evidence implicating glutamatergic neurotransmission in the development and expression of neuroplastic changes underlying drug addiction has accumulated (Wolf 1998; Vanderschuren and Kalivas 2000; Kalivas 2009; Schmidt and Pierce 2010). Glutamate can bind to two distinct receptor types: the ionotropic glutamate receptors (iGlu receptors) and the metabotropic glutamate receptors (mGlu receptors) (Spooren et al. 2003; Kew and Kemp 2005). Most research

on the role of glutamate in addictive behavior has focused on iGlu receptors, and although studies have shown that iGlu receptors are involved in drug reward and sensitization (Vanderschuren and Kalivas 2000; Wolf 1998; Gass and Olive 2008; Schmidt and Pierce 2010) clinical trials have thus far been unsuccessful in identifying iGlu receptor ligands that effectively treat addiction (Bisaga et al. 2000; Tzschentke 2002; Heidbreder and Hagan 2005).

Recent studies have identified mGlu receptors as potential targets for the treatment of drug addiction. Eight different subtypes of this receptor have been described, of which the metabotropic glutamate 5 receptor (mGlu5 receptor) has been most prominently implicated in addictive behavior (Kenny and Markou 2004; Spooen et al. 2003; Gass and Olive 2008). For instance, the mGlu5 receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) has been shown to block the development of cocaine- and morphine-conditioned place preference (CPP) (Popik and Wrobel 2002; Herzig and Schmidt 2004; Aoki et al. 2004), although in one study the effect of MPEP on drug-induced CPP was specific for cocaine; i.e., morphine, nicotine, amphetamine, and alcohol CPP were not affected (McGeehan and Olive 2003). Furthermore, mGlu5 receptor knockout mice do not self-administer cocaine (Chiamulera et al. 2001) and MPEP or the structurally related mGlu5 receptor antagonist 3-[(2-methyl-1, 3-thiazol-4-yl) ethynyl] pyridine (MTEP) decreased self-administration of different drugs of abuse, including cocaine, metamphetamine, heroin, alcohol, nicotine, and ketamine under fixed-ratio schedules of reinforcement (Paterson et al. 2003; Tessari et al. 2004; Olive et al. 2005; Kenny et al. 2005; Schroeder et al. 2005; van der Kam et al. 2007; Gass et al. 2009; Martin-Fardon et al. 2009). In addition, MPEP and MTEP were also found to reduce breakpoints in animals responding for cocaine, methamphetamine, alcohol, and nicotine under a progressive ratio schedule of reinforcement, whereas the effects on responding for food were inconsistent between studies (Paterson and Markou 2005; Besheer et al. 2008; Gass et al. 2009). Together, these studies suggest that the mGlu5 receptor is critically involved in -drug reinforcement.

The mGlu5 receptor has also been implicated in drug-induced psychomotor hyperactivity. The psychomotor stimulant effect of cocaine is absent in mGlu5 receptor knockout mice (Chiamulera et al. 2001) and MPEP decreases the acute psychomotor effects of cocaine, amphetamine, and nicotine (McGeehan et al. 2004; Herzig and Schmidt 2004; Tessari et al. 2004). The psychomotor stimulant effects of drugs of abuse are well known to persistently increase after repeated drug administration, a phenomenon known as behavioral sensitization (Stewart and Badiani 1993; Robinson and Berridge 1993; Vanderschuren and Kalivas 2000). Since it is thought that behavioral sensitization is an important driving factor in the development of drug addiction

(Robinson and Berridge 1993, 2003; Vanderschuren and Pierce 2010), it is of interest to investigate the involvement of the mGlu5 receptor in psychomotor sensitization. Previous studies have shown that MPEP and MTEP attenuate the expression of morphine-, cocaine-, and nicotine-induced psychomotor sensitization (Tessari et al. 2004; Kotlinska and Bochenski 2007; Kotlinska and Bochenski 2009). However, the role of the mGlu5 receptor in the development of sensitization has remained unexplored. In this regard, it is of interest that mGlu5 receptors have been shown to be involved in the neuroplastic changes underlying learning (Fendt and Schmid 2002; Rodrigues et al. 2002; Gravius et al. 2005; Xu et al. 2009). In view of the mechanistic similarities between drug- and experience-induced behavioral plasticity (Kelley 2004; Hyman et al. 2006), it is possible that mGlu5 receptors are also involved in the development of psychomotor sensitization.

The aim of the present study was to further evaluate the role of the mGlu5 receptor in drug reward and the development of sensitization. To this end, we investigated the effect of the mGlu5 receptor antagonist MTEP and the dopamine receptor antagonist α -flupenthixol on the induction of morphine- and cocaine-induced CPP and psychomotor sensitization. Since the role of dopamine in reward and sensitization is well established, we included the dopamine receptor antagonist in this study for comparison. Mesolimbic dopamine has been widely implicated in the rewarding effects of drugs of abuse (Koob et al. 1998; Wise 2004; Pierce and Kumaresan 2006), but it does not play a critical role in the development of sensitization of the psychomotor stimulant properties of cocaine and morphine (Vanderschuren and Kalivas 2000). Furthermore, it has been shown that mGlu5 receptor stimulation can raise extracellular dopamine in prefrontal cortex and striatum, which can be blocked by, for instance, MPEP or the general mGluR antagonist (+)-MCPG (Bruton et al. 1999; Renoldi et al. 2007). Thus, mGlu5 receptor blockade may reduce the ability of cocaine or morphine to enhance mesolimbic dopamine neurotransmission which may, in turn, attenuate the rewarding effects of these drugs—although cocaine did increase nucleus accumbens dopamine overflow in mGlu5 receptor knockout mice (Chiamulera et al. 2001). We chose to test two types of drug of abuse that differ in their initial actions on the central nervous system. Cocaine inhibits the reuptake of dopamine, serotonin, and noradrenalin into the presynaptic terminal, causing an accumulation of these neurotransmitters in the synaptic cleft and a prolonged receptor stimulation (Heikkila et al. 1975; Ritz et al. 1987), and morphine is an agonist at mu-opioid receptors.

Based on the studies described above, we hypothesized that the mGlu5 receptor is involved in both drug reward and sensitization, while dopamine receptors play a role in reward but not in sensitization. Therefore, we

expected that both α -flupenthixol and MTEP would block the development of cocaine- and morphine-induced CPP and that MTEP but not α -flupenthixol would block the development of cocaine- and morphine-induced psychomotor sensitization.

Materials and methods

Subjects

Male Wistar rats (Charles River, Sulzfeld, Germany) weighing 170 ± 15 g upon arrival in the laboratory were used for all experiments. The animals were housed two per cage (Macrolon cages, $40 \times 26 \times 20$ cm) in climate-controlled rooms (temperature, $21 \pm 2^\circ\text{C}$; 60–65% relative humidity) under a 12-h day/night cycle with lights on at 7 am. Regular chow (SDS, England) and water were available ad libitum. The animals were allowed to habituate to the housing conditions for at least 1 week and were handled three times prior to the experiment. Two days before testing, the rats were moved to the experimental room. The experiments were approved by the Animal Ethics Committee of Utrecht University, the Netherlands, and were conducted in agreement with Dutch laws (Wet op de dierproeven, 1996) and European regulations (Guideline 86/609/EEC).

Place conditioning

Apparatus

The place conditioning apparatus (TSE Systems, Bad Homburg, Germany) consisted of three compartments, and each compartment differed with regard to visual and tactile cues. Two equally sized compartments were used for place conditioning ($30 \times 25 \times 30$ cm, $l \times w \times h$). The first conditioning compartment had black walls, a fine metal mesh floor, and white light (2 W) in the Plexiglas lid to achieve a comparable light intensity in both conditioning compartments, while the other conditioning compartment had walls with black and white stripes, a wide metal mesh floor, and no light in the Plexiglas lid. Pilot studies performed in our laboratory have shown that the rats had no consistent unconditioned preference for one of the compartments, i.e., there was not one particular compartment that was preferred by the majority of animals during the pretest (see below). The third, middle compartment ($10 \times 25 \times 30$ cm) was only used for introducing the animal into the apparatus during the pretest and test sessions. This middle compartment had white walls, a smooth floor, and white light (2 W) in the Plexiglas lid. During the pretest and test sessions, arched gateways gave access to the two adjacent conditioning

compartments, which allowed the animals to freely move around the entire apparatus. During conditioning sessions, the rats were placed in one of the two conditioning compartments and access to the other compartments was blocked by inserting dividers without a gateway between the compartments. All compartments were equipped with photo-sensors which detect the location of the animals, and TSE software was used to calculate the total time spent in each compartment.

Procedure

The experiments consisted of three phases: a pretest (session 1), a conditioning period (session 2–9), and a test phase (session 10). The sessions took place once per day and 5 days per week. During the pretest, that took place under drug-free conditions, the rats were free to explore the entire apparatus for 15 min. At the beginning of the pretest the animals were placed in the middle, neutral compartment and we measured the time they spent in each compartment. The rats that spent more than 500 s in one conditioning compartment were excluded from the experiment (in total, 4% of all rats tested). The remaining animals were divided into four groups according to a counterbalanced design (Tzschentke 2007). Thus, on the basis of their pretest scores (i.e., time spent in the two conditioning compartments during the pretest), the rats were assigned to a compartment in which they would receive drug treatment, so that the baseline preference in each test group for the (to be) drug-paired and (to be) saline-paired compartments approximated 50%. Thus, some rats, based on the pretest scores, would be conditioned in their preferred compartment, but others would be conditioned in their non-preferred compartment. This procedure rules out the possibility that preference shifts are the result of decreased avoidance of the non-preferred compartment. During place conditioning, the rats received four drug-paired sessions (session 2, 4, 6, and 8) and four saline-paired sessions (session 3, 5, 7, and 9). The first experiment was performed in order to determine if the doses of α -flupenthixol or MTEP used would induce CPP or conditioned place aversion (CPA) by themselves. Before the start of drug-paired sessions, the rats were injected with one of the following drugs: α -flupenthixol (0 or 0.5 mg/kg, i.p.), 30 min later followed by a saline (1.0 ml/kg, i.p.) injection; MTEP (0 or 10 mg/kg, i.p.), 20 min later followed by a saline injection (1.0 ml/kg, i.p.). Immediately after the saline injection, the animals were placed into the drug-paired compartment for 40 min. Before the start of saline-paired sessions, the rats were injected twice with saline (1.0 ml/kg, i.p.), 20 (in the MTEP experiment) or 30 min (in the α -flupenthixol experiment) apart. The time points of the injections during the saline sessions matched the time point of the injections during the drug-paired sessions. Session 10

consisted of a 15-min test where animals could freely move around the entire apparatus. This test session was carried out under drug-free conditions. Similar as in the pretest-session, the animals were introduced into the apparatus by placing them in the middle, neutral compartment. Next, we measured the time spent in each compartment. In the second set of experiments, we determined the effect of MTEP and α -flupenthixol on cocaine- and morphine-induced place conditioning. Before the start of drug pairing sessions, the rats were injected with one of the following drug combinations: α -flupenthixol (0, 0.125, 0.25, or 0.5 mg/kg, i.p.) 30 min before a cocaine (15 mg/kg, i.p.) or morphine injection (3 mg/kg, s.c.) or MTEP (0, 1, 3, or 10 mg/kg, i.p.) 20 min before a cocaine (15 mg/kg, i.p.) or morphine injection (3 mg/kg, s.c.). Directly after the second injection (i.e., cocaine or morphine), the animals were placed in the drug-paired compartment for 40 min. Vehicle-paired sessions and the test sessions were carried out as described above. The doses of cocaine and morphine were based on pilot studies. Thus, 15 mg/kg cocaine was the lowest dose that induced robust and reproducible CPP, whereas CPP could be induced with morphine at doses of 1 mg/kg and higher.

Psychomotor sensitization

Apparatus

The locomotor activity of rats was measured in open-field test cages (50×35×40 cm). The horizontal distance traveled was tracked automatically using a video tracking system (Ethovision, Noldus Information Technology BV, Wageningen, Netherlands) which determined the position of the animals five times per second.

Procedure

To determine the effect of MTEP and α -flupenthixol on the induction of cocaine psychomotor sensitization, the rats were pretreated in open-field cages for five consecutive days. During pretreatment sessions, the animals were first allowed to habituate to the open field for 30 min, after which they received an injection of α -flupenthixol (0.5 mg/kg, i.p.), MTEP (1 mg/kg, i.p.), or saline (1 ml/kg, i.p.). At 30 min after the administration of α -flupenthixol or 20 min after the administration of MTEP, the rats were injected with either cocaine (30 mg/kg, i.p.) or saline. The pretreatment dose of cocaine used was based on pilot studies. Thus, we observed robust and reproducible sensitization after repeated treatment with 30 mg/kg (but not 15 mg/kg) cocaine. At 3 weeks after the last pretreatment session, the rats were challenged with cocaine. The challenge session started with a 30-min habituation period. Next, the animals were injected with saline (1 ml/

kg, i.p.), and they were injected with cocaine (10 mg/kg, i.p.) 30 min later. The locomotor activity of the animals during all sessions was monitored from the time of introduction to the open field until 60 min after the cocaine injection. To determine the effect of MTEP and α -flupenthixol on the induction of morphine psychomotor sensitization, the animals were pretreated for ten sessions (five sessions a week). During pretreatment sessions, the animals were allowed to habituate to the open field for 30 min, after which they were injected with α -flupenthixol (0.5 mg/kg, i.p.), MTEP (1.0 mg/kg, i.p.), or saline (1.0 ml/kg, i.p.). At 30 min after the first injection, the rats were injected with either morphine (3.0 mg/kg, s.c.) or saline (1.0 ml/kg, s.c.). The pretreatment dose of morphine used was based on pilot studies. Thus, we observed robust and reproducible sensitization after repeated treatment doses of 1 mg/kg morphine and higher. At 3 weeks after the last pretreatment session, the animals were challenged with morphine (1.0 mg/kg, s.c.). The procedure of the challenge session was similar to the cocaine challenge session described above. During all sessions, locomotor activity was monitored from the time of introduction to the open field until 90 min after the last injection.

Statistics

Place conditioning data are expressed as mean time spent in drug- or vehicle-paired compartments \pm S.E.M. (in seconds). Outliers, identified using Dixon outlier test, were excluded from the analyses (1.6% of all animals). To determine the occurrence of CPP, we analyzed each group using Student's *t*-test for paired samples, comparing the time spent in the drug-paired with the time spent in the saline-paired compartment. For the psychomotor sensitization experiments, horizontal activity is expressed as mean \pm S.E.M. distance traveled (in centimeters). The locomotor responses during the pretreatment sessions are presented as mean \pm S.E.M. distance traveled during 60 min after cocaine or saline injection or as the mean \pm S.E.M. distance traveled during 90 min after morphine or saline injection. Data were analyzed using a three-way repeated-measures ANOVA with sessions as within-subjects factor and the receptor antagonists (MTEP or α -flupenthixol) and the drug used to induce psychomotor sensitization (cocaine or morphine) as two between-subjects factors. During the challenge sessions, the distance traveled was analyzed in 10-min blocks. Data were analyzed using a three-way repeated-measures ANOVA with time blocks as within-subjects factor and receptor antagonists (MTEP or α -flupenthixol) and the drug used to induce psychomotor sensitization (cocaine or morphine) as two between-subjects factors. Post-hoc comparisons were made where appropriate using Student–Newman–Keuls tests. Behavioral data

were analyzed using SPSS 15.0. The criterion for statistically significant differences was set at $p < 0.05$

Drugs

MTEP (3-[(2-methyl-1,3-thiazol-4-yl) ethynyl] pyridine) was a generous gift from Dr. Will Spooren (F. Hoffman-la Roche Ltd, Basel, Switzerland). The MTEP doses used were based on literature (Anderson et al. 2002; Cosford et al. 2003) and pilot studies. MTEP, cocaine-HCl (Bufa BV, Uitgeest, The Netherlands), morphine-HCl (OPG Regilabs bv, Utrecht, The Netherlands), and cis-(Z)- α -flupenthixol dihydrochloride (Sigma, Zwijndrecht, The Netherlands) were dissolved in sterile physiological saline (0.9% NaCl).

Results

Place conditioning effect of MTEP and α -flupenthixol

Figure 1 shows that MTEP and α -flupenthixol, at the highest doses used in this study, did not induce CPP or CPA compared with saline. Moreover, the animals repeatedly treated with saline in both compartments of the place conditioning apparatus did not develop a preference for one compartment or the other, demonstrating that repeated exposure to the apparatus did not induce a preference for one particular set of environmental cues [MTEP: $t(\text{sal})_7 = -1.351$ NS, $t(\text{MTEP})_7 = 0.642$ NS; α -flupenthixol $t(\text{sal})_7 = -0.742$ NS, $t(\alpha\text{-flupenthixol})_7 = -0.258$ NS].

Effect of MTEP and α -flupenthixol on cocaine-induced place conditioning

In animals pretreated with saline, cocaine induced significant preference for the drug-paired compartment in both experiments. The acquisition of cocaine-induced CPP was not affected by MTEP. In this experiment, one rat from the saline, one rat from the 3 mg/kg, and one rat from the 10 mg/kg group were excluded from analysis as outliers. Figure 2a shows that cocaine-induced CPP was present in all groups independent of MTEP treatment [sal: $t_6 = 5.413$ $p < 0.01$; 1 mg/kg MTEP: $t_7 = 4.066$ $p < 0.01$; 3 mg/kg MTEP: $t_6 = 7.554$ $p < 0.001$; 10 mg/kg MTEP: $t_6 = 5.455$ $p < 0.01$]. On the other hand, α -flupenthixol attenuated the acquisition of cocaine-induced CPP. In this experiment, one animal from the 0.125 mg/kg α -flupenthixol group was excluded as an outlier. Figure 2b shows that cocaine no longer induced CPP when 0.25 and 0.5 mg/kg α -flupenthixol was co-administered during conditioning [sal: $t_{15} = 3.134$ $P < 0.01$; 0.125 mg/kg flupenthixol: $t_{13} = 4.569$ $p < 0.001$; 0.25 mg/kg flupenthixol: $t_{14} = 0.546$ NS; 0.5 mg/kg flupenthixol: $t_{14} = 1.590$ NS].

Effect of MTEP and α -flupenthixol on morphine-induced place conditioning

In animals pretreated with saline, morphine induced a significant preference for the drug-paired compartment in both experiments. The acquisition of morphine-induced place preference was suppressed by MTEP. Figure 3a shows that, when 1 and 3 mg/kg MTEP was co-administered with morphine during conditioning, no morphine-induced CPP developed [sal: $t_{14} = 4.240$ $p < 0.05$; 1 mg/kg MTEP: $t_{13} = 1.346$ NS; 3 mg/kg MTEP: $t_{14} = 0.382$ NS]. However, 10 mg/kg MTEP did not attenuate place preference [$t_{14} = 2.381$ $p < 0.05$]. α -Flupenthixol attenuated the acquisition of morphine-induced CPP. Figure 3b shows that the highest dose of α -flupenthixol significantly reduced morphine-induced CPP [sal: $t_{15} = 2.669$ $P < 0.05$; 0.125 mg/kg flupenthixol: $t_{15} = 6.104$ $P < 0.001$; 0.25 mg/kg flupenthixol: $t_{14} = 4.890$ $P < 0.001$; 0.5 mg/kg flupenthixol: $t_{15} = 1.677$ NS].

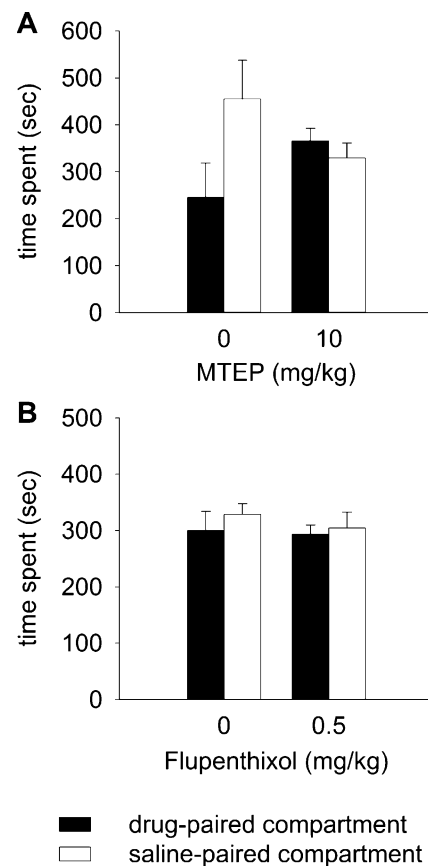


Fig. 1 The effect of MTEP- and α -flupenthixol on place conditioning. **a** Rats were conditioned with saline in both compartments ($n=8$) or with 10 mg/kg MTEP, i.p., in one compartment and saline in the other ($n=8$). **b** Rats were conditioned with saline in both compartments ($n=8$) or with 0.5 mg/kg α -flupenthixol, i.p., in one compartment and saline in the other ($n=8$). Data are presented as mean \pm S.E.M. time spent in drug-paired and saline compartment on test day

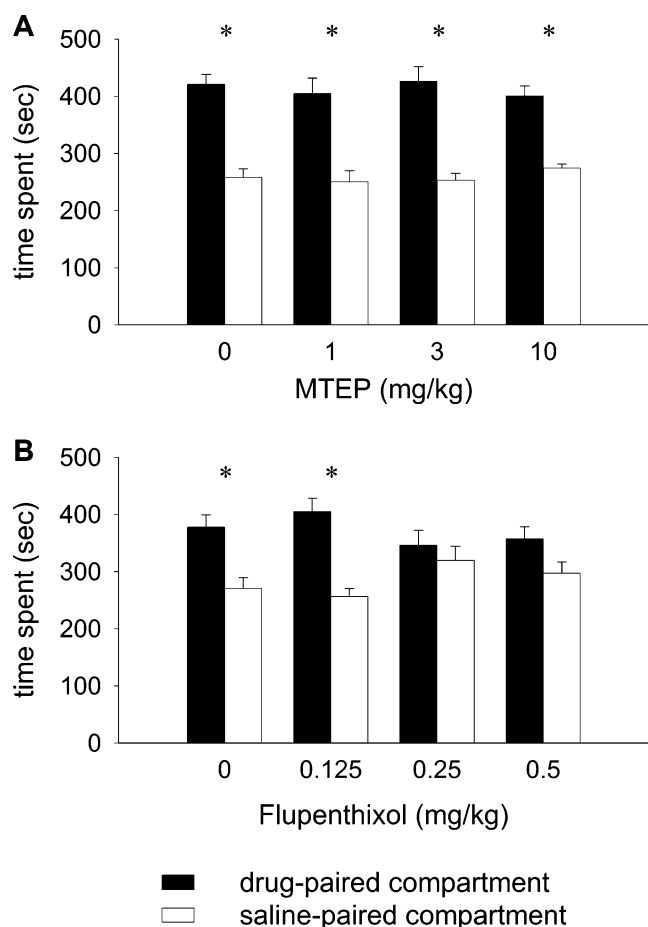


Fig. 2 The effect of MTEP and α -flupenthixol on the development of cocaine-induced CPP. **a** Rats were conditioned with cocaine (15 mg/kg, i.p.) together with saline (0; $n=7$), 1 ($n=8$), 3 ($n=7$), or 10 ($n=7$) mg/kg, i.p., MTEP. **b** Rats were conditioned with cocaine (15 mg/kg, i.p.) together with saline (0; $n=16$), 0.125 ($n=14$), 0.25 ($n=15$), or 0.5 ($n=15$) mg/kg, i.p., α -flupenthixol. Data are presented as mean \pm S.E.M. time spent in drug- and saline-paired compartment on test day. * $p < 0.05$ for difference in time spent in drug- and saline-paired compartment (Student's t -test)

The effects of MTEP and α -flupenthixol on psychomotor activity during cocaine and morphine pretreatment

Figure 4 shows the psychomotor effects of cocaine, MTEP, and α -flupenthixol during the first and last (i.e., fifth) day of pretreatment. Figure 4a shows that cocaine treatment enhanced psychomotor activity during the pretreatment sessions [$F(\text{cocaine})_{1,28}=28.504$ $p < 0.001$], but no sensitization to cocaine was observed during pretreatment [$F(\text{session} \times \text{coc})_{1,28}=0.784$ NS]. MTEP did not alter the cocaine-induced psychomotor response [$F(\text{MTEP} \times \text{cocaine})_{1,28}=2.190$ NS; $F(\text{session} \times \text{MTEP} \times \text{coc})_{1,28}=0.041$ NS], neither did MTEP influence the psychomotor activity by itself [$F(\text{MTEP})_{1,28}=1.486$ NS; $F(\text{session} \times \text{MTEP})_{1,28}=0.240$ NS]. Figure 4b shows that cocaine treatment increased psychomotor activity during pretreatment ses-

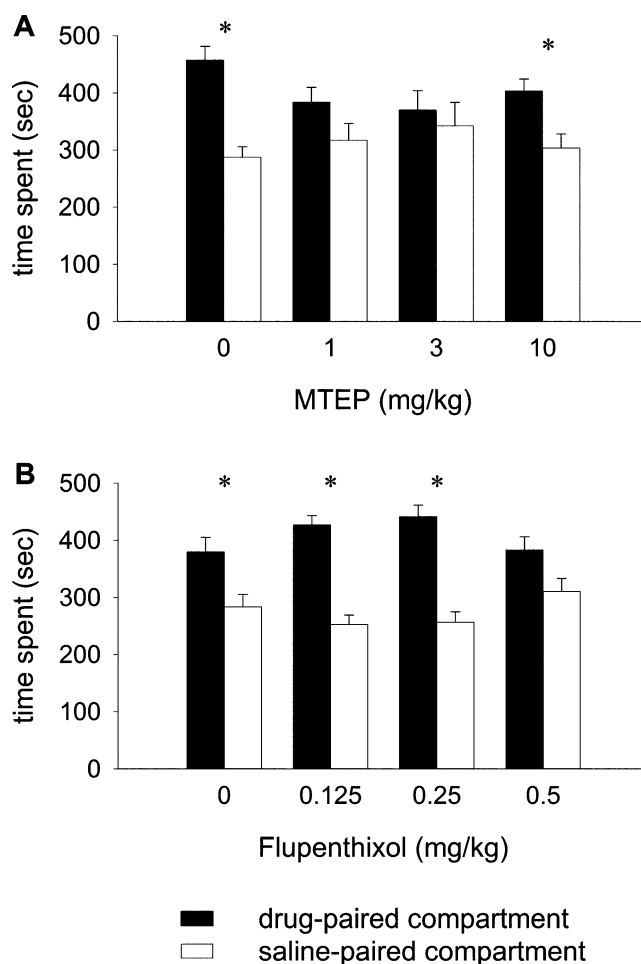


Fig. 3 The effect of MTEP and α -flupenthixol on the development of morphine-induced CPP. **a** Rats were conditioned with morphine (3 mg/kg, s.c.) together with saline (0; $n=15$), or 1 ($n=14$), 3 ($n=15$), or 10 ($n=15$) mg/kg, i.p. MTEP. **b** Rats were conditioned with morphine (3 mg/kg, s.c.) together with saline (0; $n=16$), or 0.125 ($n=16$), 0.25 ($n=15$), or 0.5 ($n=16$) mg/kg, i.p., α -flupenthixol. Data are presented as mean \pm S.E.M. time spent in drug- and saline-paired compartment on test day. * $p < 0.05$ for difference in time spent in drug-paired and saline-paired compartment (Student's t -test)

sions [$F(\text{cocaine})_{1,32}=36.827$ $p < 0.001$], that this effect of cocaine did not sensitize [$F(\text{session} \times \text{cocaine})_{1,32}=0.008$ NS], and that α -flupenthixol did not affect the cocaine-induced psychomotor activity during the pretreatment sessions [$F(\alpha\text{-flupenthixol} \times \text{cocaine})_{1,32}=2.841$ NS; $F(\text{session} \times \alpha\text{-flupenthixol} \times \text{cocaine})_{1,32}=2.841$ NS]. In addition, α -flupenthixol itself did not influence psychomotor activity [$F(\alpha\text{-flupenthixol})_{1,32}=4.052$ NS; $F(\text{session} \times \alpha\text{-flupenthixol})_{1,32}=0.008$ NS].

Figure 5 shows the psychomotor effects of morphine, MTEP, and flupenthixol during the first and last (i.e., tenth) day of pretreatment. Figure 5a shows that MTEP did not affect morphine-induced psychomotor activity during pretreatment. Sensitization to morphine was observed during pretreatment since the morphine-induced psychomotor

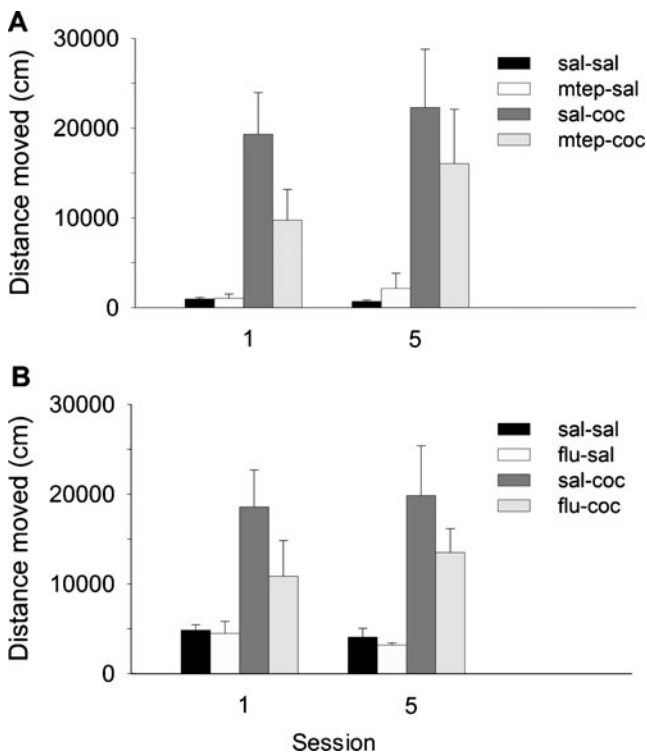


Fig. 4 The effects of MTEP and α -flupenthixol on the locomotor response to cocaine during pretreatment. **a** Locomotor responses to cocaine (*coc*; 30 mg/kg, i.p.) or saline (*sal*) in rats treated 20 min before with MTEP (1.0 mg/kg, i.p.) or saline (*sal*) ($n=8$ per group). **b** Locomotor responses to cocaine (*coc*; 30 mg/kg, i.p.) or saline (*sal*) in rats treated 30 min before with α -flupenthixol (*flu*; 0.5 mg/kg, i.p.) or saline (*sal*) ($n=9$ per group). Locomotor responses were measured on days 1 and 5 of pretreatment. Data are presented as total distance traveled (cm) in 1 h after cocaine or saline, expressed in mean \pm S.E.M.

activity increased over sessions [$F(\text{morphine})_{1,19}=10.296$ $p<0.01$; $F(\text{session} \times \text{morphine})_{1,19}=16.716$ $p=0.001$]. MTEP did not alter the morphine-induced psychomotor activity during these sessions [$F(\text{MTEP} \times \text{morphine})_{1,19}=1.965$ NS; $F(\text{session} \times \text{MTEP} \times \text{morphine})_{1,19}=0.503$ NS] and MTEP did not affect the activity by itself [$F(\text{MTEP})_{1,19}=0.274$ NS; $F(\text{session} \times \text{MTEP})_{1,19}=1.965$ NS]. Figure 5b shows that α -flupenthixol did not affect the morphine-induced psychomotor activity during the pretreatment sessions. During these sessions, morphine did not induce an increase in psychomotor activity [$F(\text{morphine})_{1,17}=2.561$ NS; $F(\text{session} \times \text{morphine})_{1,17}=3.349$ NS]. The absence of morphine sensitization during pretreatment was caused by one control rat showing a highly increased activity only during the tenth pretreatment session. Treatment with α -flupenthixol did not affect the morphine-induced psychomotor activity [$F(\alpha\text{-flupenthixol} \times \text{morphine})_{1,17}=0.007$ NS; $F(\text{session} \times \alpha\text{-flupenthixol} \times \text{morphine})_{1,17}=0.004$ NS] and did not affect activity by itself [$F(\alpha\text{-flupenthixol})_{1,17}=1.709$ NS; $F(\text{session} \times \alpha\text{-flupenthixol})_{1,17}=0.519$ NS].

The effect of MTEP and α -flupenthixol on cocaine- and morphine-induced psychomotor sensitization

Figure 6a shows that, during the habituation phase of the challenge session, there was an effect of cocaine pretreatment [$F(\text{cocaine})_{1,28}=4.714$ $p=0.039$], but no effect of MTEP pretreatment [$F(\text{MTEP})_{1,28}=1.378$ NS; $F(\text{MTEP} \times \text{cocaine})_{1,28}=2.234$ NS]. After the saline injection, there was no effect of cocaine or MTEP pretreatment [$F(\text{cocaine})_{1,28}=0.000$ NS; $F(\text{MTEP})_{1,28}=0.070$ NS], but there was an interaction between cocaine and MTEP [$F(\text{MTEP} \times \text{cocaine})_{1,28}=4.646$ $p<0.05$]. Cocaine pretreatment resulted in a sensitized psychomotor response to a low dose of cocaine [$F(\text{cocaine})_{1,28}=9.282$ $p<0.01$; $F(\text{time blocks} \times \text{cocaine})_{1,28}=16.158$ $p<0.001$], and co-administration of MTEP during pretreatment suppressed this sensitized cocaine-induced psychomotor response [$F(\text{MTEP})_{1,28}=8.506$ $p<0.01$; $F(\text{time blocks} \times \text{MTEP})_{1,28}=1.781$ $p<0.01$; $F(\text{MTEP} \times \text{cocaine})_{1,28}=8.651$ $p<0.01$; $F(\text{time blocks} \times \text{MTEP} \times \text{cocaine})_{1,28}=7.249$ $p<0.01$].

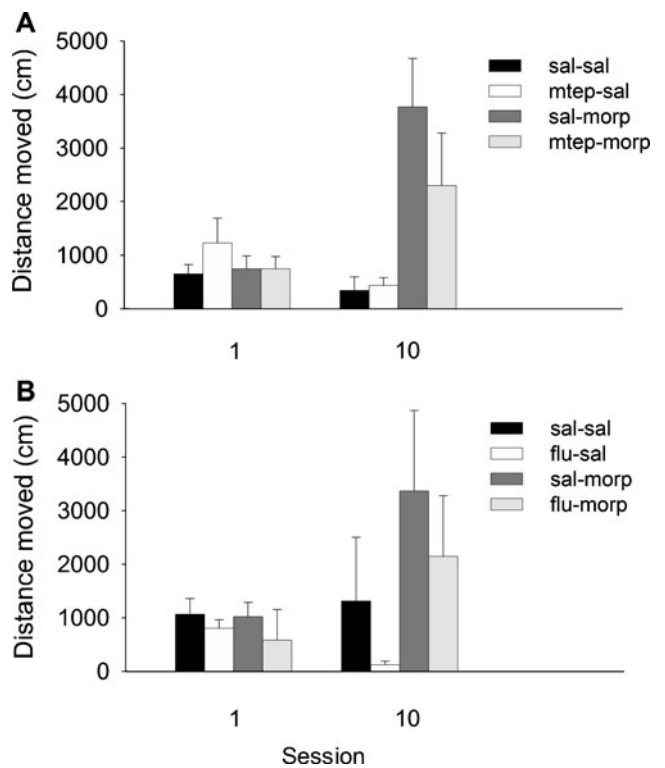


Fig. 5 The effects of MTEP and α -flupenthixol on the locomotor response to morphine during pretreatment. **a** Locomotor responses to morphine (*morp*; 3.0 mg/kg, s.c.) or saline (*sal*) in rats treated 30 min before with MTEP (1.0 mg/kg, i.p.) or saline (*sal*) ($n=8$ per group). **b** Locomotor responses to morphine (*morp*; 3.0 mg/kg, s.c.) or saline (*sal*) in rats treated 30 min before with α -flupenthixol (*flu*; 0.5 mg/kg, i.p.) or saline (*sal*) ($n=9$ per group). Locomotor responses were measured on days 1 and 10 of pretreatment. Data are presented as total distance traveled (cm) in 1 h after morphine or saline, expressed in mean \pm S.E.

Figure 6b shows that cocaine-induced psychomotor sensitization was not altered by α -flupenthixol pretreatment. Neither cocaine nor α -flupenthixol pretreatment affected the locomotor responses during the habituation phase and after the saline challenge [habituation: $F(\text{cocaine})_{1,32}=0.184$ NS; saline: $F(\text{cocaine})_{1,32}=0.049$ NS; habituation: $F(\alpha\text{-flupenthixol})_{1,32}=0.443$ NS; saline: $F(\text{flupenthixol})_{1,32}=0.054$ NS; habituation: $F(\alpha\text{-flupenthixol}\times\text{cocaine})_{1,32}=1.925$ NS; saline: $F(\alpha\text{-flupenthixol}\times\text{cocaine})_{1,32}=1.273$ NS]. After the challenge with cocaine, the animals pretreated with cocaine showed an increased locomotor response [$F(\text{cocaine})_{1,32}=8.863$ $p<0.01$; $F(\text{time blocks}\times\text{cocaine})_{1,32}=11.550$ $p<0.001$]. α -Flupenthixol pretreatment did not influence this sensitized response [$F(\alpha\text{-flupenthixol})_{1,32}=0.266$ NS; $F(\text{time blocks}\times\alpha\text{-flupenthixol})_{1,32}=0.669$ NS; $F(\alpha\text{-flupen-$

thixol \times cocaine) $_{1,32}=1.195$ NS; $F(\text{time blocks}\times\alpha\text{-flupenthixol}\times\text{cocaine})_{1,32}=0.921$ NS].

Figure 7a shows that morphine-induced locomotor sensitization during the challenge session was not altered by MTEP pretreatment. During the habituation phases and the 30 min after the saline injections, neither morphine nor MTEP pretreatment affected the locomotor responses [habituation: $F(\text{morphine})_{1,19}=1.155$ NS; $F(\text{MTEP})_{1,19}=0.330$ NS; $F(\text{MTEP}\times\text{morphine})_{1,19}=0.161$ NS; saline: $F(\text{morphine})_{1,19}=2.747$ NS; $F(\text{MTEP})_{1,19}=0.057$ NS; $F(\text{MTEP}\times\text{morphine})_{1,19}=0.803$ NS]. After the challenge with morphine, a sensitized locomotor response was observed in morphine-pretreated animals [$F(\text{morphine})_{1,19}=16.373$ $p=0.001$; $F(\text{time blocks}\times\text{morphine})_{1,19}=2.591$ NS]. MTEP pretreatment did not alter morphine sensitization [$F(\text{MTEP})_{1,19}=0.845$ NS; $F(\text{time blocks}\times\text{MTEP})_{1,19}=0.408$ NS; $F(\text{morphine}\times\text{MTEP})_{1,19}=0.633$ NS; $F(\text{session}\times\text{MTEP}\times\text{morphine})_{1,19}=0.669$ NS].

Figure 7b shows that morphine-induced locomotor sensitization during the challenge session was not altered by α -flupenthixol pretreatment. Neither morphine nor α -flupenthixol pretreatment influenced the locomotor responses of the animals during the habituation phase and after the saline injection of the challenge session [habituation: $F(\text{morphine})_{1,17}=0.013$ NS; $F(\alpha\text{-flupenthixol})_{1,17}=3.189$ NS; $F(\alpha\text{-flupenthixol}\times\text{morphine})_{1,17}=0.278$ NS; saline: $F(\text{morphine})_{1,17}=0.302$ NS; $F(\alpha\text{-flupenthixol})_{1,17}=0.845$ NS; $F(\alpha\text{-flupenthixol}\times\text{morphine})_{1,17}=1.085$ NS]. The morphine challenge induced an increased locomotor response in animals that were pretreated with morphine [$F(\text{morphine})_{1,17}=22.686$ $p<0.001$; $F(\text{time blocks}\times\text{morphine})_{1,17}=2.775$ $p<0.05$], but α -flupenthixol had no influence on this response [$F(\alpha\text{-flupenthixol})_{1,17}=2.257$ NS; $F(\text{time blocks}\times\alpha\text{-flupenthixol})_{1,17}=0.460$ NS; $F(\text{morphine}\times\alpha\text{-flupenthixol})_{1,17}=1.110$ NS; $F(\text{session}\times\alpha\text{-flupenthixol}\times\text{morphine})_{1,17}=0.372$ NS].

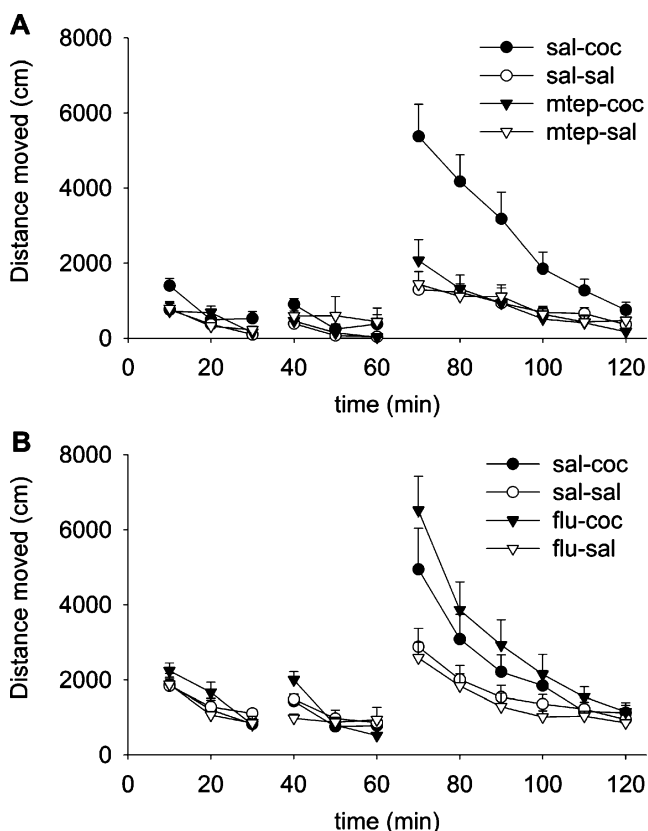


Fig. 6 **a** Locomotor responses to cocaine (10 mg/kg, i.p.), in animals pretreated for 5 days with: saline plus saline (*sal-sal*; $n=8$), saline plus 30 mg/kg cocaine, i.p. (*sal-coc*; $n=8$), 1.0 mg/kg MTEP, i.p., plus saline (*mtep-sal*; $n=8$) or 1.0 mg/kg MTEP, i.p., plus 30 mg/kg cocaine, i.p. (*mtep-coc*; $n=8$) 3 weeks post-treatment. **b** Locomotor responses to cocaine (10 mg/kg, i.p.) in animals pretreated for 5 days with: saline plus saline (*sal-sal*; $n=9$), saline plus 30 mg/kg cocaine, i.p. (*sal-coc*; $n=9$), 0.5 mg/kg α -flupenthixol, i.p., plus saline (*flu-sal*; $n=9$), or 0.5 mg/kg α -flupenthixol, i.p., plus 30 mg/kg cocaine, i.p. (*flu-coc*; $n=9$), 3 weeks post-treatment. Data are presented as mean \pm S.E.M. distance traveled (in cm) per 10 min during habituation to the test cages (10–30 min), after a saline injection (40–60 min), and after the cocaine challenge (10 mg/kg, i.p., 70–120 min)

Discussion

In the present study, we investigated the role of mGlu5 and dopamine receptors in the rewarding and sensitizing properties of cocaine and morphine. To that aim, we administered the mGlu5 receptor antagonist MTEP and the dopamine receptor antagonist α -flupenthixol during the development of cocaine and morphine CPP and psychomotor sensitization. In agreement with our hypotheses, co-administration of α -flupenthixol during place conditioning with morphine and cocaine attenuated CPP, but α -flupenthixol did not affect the development of cocaine- and morphine-induced psychomotor sensitization.

However, the results with MTEP only partially confirmed our hypotheses. Co-administration of MTEP during

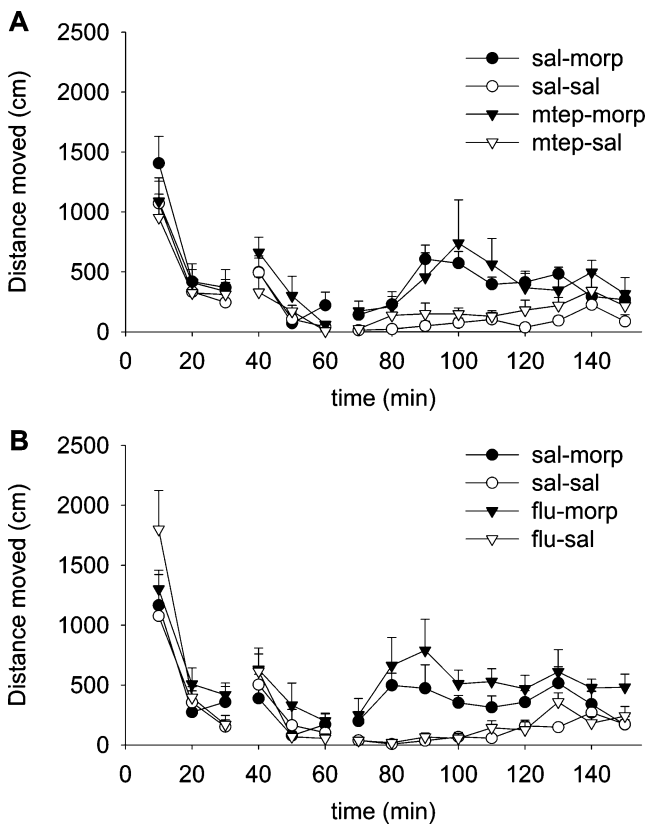


Fig. 7 **a** Locomotor responses to morphine (1.0 mg/kg, s.c.) in animals pretreated for 5 days with: saline plus saline (*sal-sal*; $n=6$), saline plus 3.0 mg/kg morphine, s.c., (*sal-morp*; $n=5$), 1.0 mg/kg MTEP, i.p., plus saline (*mtep-sal*; $n=6$) or 1.0 mg/kg MTEP, i.p., plus 3.0 mg/kg morphine, s.c. (*mtep-morp*; $n=6$), 3 weeks post-treatment. **b** Locomotor responses to morphine (1.0 mg/kg, s.c.) in animals pretreated for 5 days with: saline plus saline (*sal-sal*; $n=5$), saline plus 3.0 mg/kg morphine, s.c. (*sal-morp*; $n=5$), 0.5 mg/kg α -flupenthixol, i.p., plus saline (*flu-sal*; $n=5$) or 0.5 mg/kg α -flupenthixol, i.p., plus 3.0 mg/kg morphine, s.c. (*flu-morp*; $n=6$), 3 weeks post-treatment. Data are presented as mean \pm S.E.M. distance traveled (in cm) per 10 min during habituation to the test cages (10–30 min), after a saline injection (40–60 min), and after the morphine challenge (1.0 mg/kg, s.c., 70–150 min)

place conditioning with morphine attenuated morphine-induced CPP, whereas MTEP treatment during cocaine conditioning did not affect the development of cocaine-induced CPP. MTEP blocked the development of psychomotor sensitization to cocaine, but not morphine.

Place conditioning

MTEP attenuated morphine-induced CPP when 1 or 3 mg/kg, but not when 10 mg/kg was co-administered during conditioning. This suggests that mGlu5 receptors play a role in mediating morphine reward. These results are in agreement with other studies in which MPEP attenuated the development of morphine-induced CPP (Popik and Wrobel 2002; Aoki et al. 2004; Herzig and Schmidt 2004).

However, other studies have shown that MPEP had no effect on morphine CPP (McGeehan and Olive 2003) and actually potentiated heroin-induced CPP (van der Kam et al. 2009a). Because MTEP and MPEP can cause deficits in spatial learning (Naie and Manahan-Vaughan 2004; Gravius et al. 2008; Bikbaev et al. 2008), it is possible that MTEP impaired learning, i.e., the establishment of an association between the environmental cues in the morphine-paired compartment and the rewarding properties of the drug (see also Fendt and Schmid 2002; Rodrigues et al. 2002; Gravius et al. 2005; Xu et al. 2009), without effectively influencing the rewarding effects of morphine. However, MTEP did not suppress cocaine-induced CPP, which suggests that learning of an environment–reward association was intact in MTEP-treated animals. It is therefore unlikely that the effect of MTEP on morphine CPP is the result of impairment in learning. We do not have a straightforward explanation for the finding that 10 mg/kg MTEP did not influence morphine CPP. It might be that an off-target effect of MTEP is responsible for this lack of effect. In vitro essays have shown that high concentrations of MTEP inhibit monoamine oxidase A and NR1a/2B-containing NMDA receptors, but it is unlikely that the dose of 10 mg/kg, i.p., MTEP resulted in brain concentrations high enough to elicit these effects (Cosford et al. 2003; Nagel et al. 2007). Alternatively, the repeated injection of 10 mg/kg MTEP may have evoked tolerance to the effects of the drug. Indeed, the repeated administration of MTEP can lead to tolerance into its analgesic and anxiolytic effects (Busse et al. 2004; Sevostianova and Danysz 2006).

In the present study, MTEP did not affect cocaine-induced CPP. This suggests that stimulation of mGlu5 receptors is not critical for cocaine reward. This finding stands in contrast to studies showing that MPEP blocks the development of cocaine CPP (Herzig and Schmidt 2004; McGeehan and Olive 2003). Interestingly, recent studies have shown that MPEP potentiates the development of CPP induced by subeffective doses of cocaine, nicotine, ketamine, and heroin (van der Kam et al. 2009a; Rutten et al. 2010). Since effective doses of cocaine and morphine were used in the present study, a potentiation of the development of CPP by MTEP was not likely to be detected. However, the MPEP that was used in these previous studies is a less selective mGlu5 receptor antagonist than MTEP, since it can also bind to NMDA receptors (O'Leary et al. 2000; Cosford et al. 2003). It is well known that NMDA receptor antagonists block the development of cocaine and morphine CPP (Cervo and Samanin 1995; Maldonado et al. 2007; Tzschentke and Schmidt 1995; Tzschentke and Schmidt 1997) but can also potentiate the reinforcing effects of drugs and have reinforcing effects themselves (Vanderschuren et al. 1998). It is therefore possible that the earlier observed effects with MPEP on the development of CPP were the result of NMDA

receptor blockade. Future studies must reveal whether MTEP can augment the development of CPP induced by subeffective doses of drugs.

The results of the present study are consistent with the well-established role of dopamine receptor stimulation in the rewarding properties of cocaine and morphine (Koob et al. 1998; van Ree et al. 1999; Wise 2004; Pierce and Kumaresan 2006; but see Spyraiki et al. 1982; Mackey and van der Kooy 1985). We used the non-selective dopamine receptor antagonist α -flupenthixol that targets both dopamine D1 and D2 receptors. The dopamine D1 receptor has widely been implicated in drug reward. Multiple studies have shown that the D1 receptor antagonist SCH23390 blocks the development of both cocaine- and morphine-induced CPP (cocaine: Cervo and Samanin 1995; Shippenberg and Heidbreder 1995; Baker et al. 1998; Nazarian et al. 2004; morphine: Leone and Di Chiara 1987; Shippenberg and Herz 1988; Acquas et al. 1989; Acquas and Di Chiara 1994; Manzanedo et al. 2001). In contrast to dopamine D1 receptors, dopamine D2 receptors do not seem to be critical for the development of cocaine-induced CPP (Cervo and Samanin 1995; Shippenberg and Heidbreder 1995; Nazarian et al. 2004). With regard to morphine-induced CPP, there have been reports that dopamine D2 receptor antagonists block the development of morphine-induced CPP (Leone and Di Chiara 1987; Manzanedo et al. 2001), while others have reported no effect (Shippenberg and Herz 1988).

In the **Introduction** we mentioned that mGlu5 receptors may be involved in drug reward via downstream modulation of mesolimbic dopamine activity. However, our results, showing partially divergent effects of MTEP and α -flupenthixol on drug-induced CPP, do not support this possibility. Thus, whereas α -flupenthixol blocked the development of both cocaine- and morphine-induced CPP, MTEP attenuated only the development of morphine-induced CPP. The rewarding properties of cocaine depend more strongly on dopaminergic neurotransmission than morphine reward (van Ree et al. 1999; Pierce and Kumaresan 2006). Therefore, the finding that MTEP only attenuated the process least dependent on dopaminergic neurotransmission indicates that MTEP influences drug reward through mechanisms that are relatively dopamine-independent. The exact mechanism of action of MTEP on morphine-induced CPP remains to be elucidated. Interestingly, stimulation of nucleus accumbens mGlu5 receptors has been shown to enhance endocannabinoid activity (Robbe et al. 2002), and unlike cocaine reward the rewarding properties of opiates strongly depend on endocannabinoid signaling (e.g., Cossu et al. 2001; De Vries et al. 2003; for reviews see Maldonado et al. 2006; Solinas et al. 2008). One intriguing possibility is therefore that blockade of nucleus accumbens mGlu5 receptors reduces opioid-induced endocannabinoid activity, which diminishes the rewarding properties of morphine.

Indeed, enhanced nucleus accumbens endocannabinoid activity plays a prominent role in heroin but not cocaine self-administration, independent of nucleus accumbens dopamine activity (Caille and Parsons 2003, 2006; Caille et al. 2007).

It can be excluded that MTEP or α -flupenthixol affected place conditioning because of any aversive or rewarding properties of the antagonists themselves. When MTEP or α -flupenthixol was administered during place conditioning in the absence of cocaine or morphine, neither substance induced a preference or aversion for the antagonist-paired compartment.

Taken together, the present study suggests that dopamine receptors are critically involved in cocaine and morphine reward and that mGlu5 receptors play an important role in morphine but not cocaine reward.

Psychomotor sensitization

In the present study, α -flupenthixol was unable to alter the development of cocaine- and morphine-induced locomotor sensitization. This supports the notion that dopaminergic neurotransmission is not critical for the induction of cocaine and morphine sensitization (Vanderschuren and Kalivas 2000). Similar findings have been reported with both D1 and D2 receptor antagonists, i.e., SCH 23390, sulpride, eticlopride, and YM-09151-2 (cocaine: Mattingly et al. 1994; Kuribara 1995; White et al. 1998; morphine: Vezina and Stewart 1989; Jeziorski and White 1995). It is unlikely that the dose of 0.5 mg/kg α -flupenthixol was too low to affect the development of psychomotor sensitization. Even though α -flupenthixol did not alter locomotor activity during pretreatment sessions, this dose of α -flupenthixol was sufficient to block the rewarding effects of cocaine in the place conditioning experiment. Furthermore, it has been repeatedly shown that doses of dopaminergic drugs that do reduce the psychomotor stimulant effects of cocaine and morphine do not block the development of sensitization (Vezina and Stewart 1989; Mattingly et al. 1994; Jeziorski and White 1995; Kuribara 1995; White et al. 1998).

MTEP blocked the development of cocaine-induced psychomotor sensitization without affecting the acute psychomotor responses to cocaine. Consistent with the latter observation, Herzig and Schmidt (2004) have shown that MPEP does not affect cocaine- and morphine-induced psychomotor activity. However, they did not challenge their animals with cocaine or morphine in the absence of MPEP after a period of abstinence, which left the question on whether mGlu5 receptors are involved in the development of locomotor sensitization open. Previously, Ghasemzadeh et al. (1999, 2009) have shown an increase in mGlu5 receptor mRNA level in the nucleus accumbens shell and dorsolateral striatum and an augmented mGlu5 receptor protein level in the synaptosomal membrane of the nucleus

accumbens shell and core in cocaine-sensitized animals. This suggests a link between the development of cocaine sensitization and mGlu5 receptors, but ours is the first pharmacological intervention study that demonstrates a critical role for mGlu5 receptors in the development of cocaine-induced psychomotor sensitization. In contrast, even though repeated morphine treatment has been shown to result in an increase in mGlu5 protein level in the nucleus accumbens (Aoki et al. 2004), MTEP did not attenuate morphine psychomotor sensitization.

The explanation for why mGlu5 receptors are involved in the development of psychomotor sensitization to cocaine but not to morphine might lie in the differential interactions of these drugs with glutamatergic neurotransmission. For instance, cocaine increases extracellular glutamate levels in various brain regions of drug-naïve animals (Smith et al. 1995; Reid et al. 1997; McKee and Meshul 2005) and repeated cocaine administration results in the sensitization of cocaine-induced extracellular glutamate levels in the nucleus accumbens and ventral tegmental area (Pierce et al. 1996; Reid and Berger 1996; Kalivas and Duffy 1998; Bell et al. 2000). In contrast, morphine administration initially results in decreases in extracellular glutamate levels in various brain regions, including the nucleus accumbens and dorsal striatum (Sepulveda et al. 1998; Desole et al. 1996; Enrico et al. 1998). With repeated treatment, tolerance develops to this effect of morphine on extracellular glutamate levels (Sepulveda et al. 1998; Desole et al. 1996). Together, brain glutamate release responds more strongly to cocaine than to morphine, which makes it more likely that mGlu5 receptors become activated by repeated cocaine administration than by morphine. In this regard, the dissociable role of mGlu5 receptors in the development of cocaine and morphine psychomotor sensitization is reminiscent of the role of NMDA receptors in these processes. It is well established that NMDA receptors are involved in the development of cocaine-induced locomotor sensitization (Scheggi et al. 2002; Vanderschuren and Kalivas 2000; Wolf and Jeziorski 1993), but the evidence that NMDA receptors are important for the development of morphine sensitization is inconsistent (Jeziorski et al. 1994; Tzschentke and Schmidt 1996; Vanderschuren et al. 1997; Ranaldi et al. 2000; Scheggi et al. 2002). Alternatively, since morphine pretreatment lasted for 10 days, compared to 5 days of cocaine pretreatment, the possibility that tolerance to the effect of MTEP developed over repeated dosing cannot be excluded. Thus, it might be that tolerance to the effect of MTEP, although this has thus far only been demonstrated for doses of 3 mg/kg and higher (Busse et al. 2004; Sevostianova and Danysz 2006), explains the lack of effect of MTEP on the development of morphine sensitization.

Conclusions

The present study shows that the role of mGlu5 receptors in reward and sensitization is distinct for morphine and cocaine. Although mGlu5 receptor antagonists have been proposed to hold promise for the treatment of drug addiction, recent studies have shown that the role of the mGlu5 receptor in addictive behavior is not as straightforward as initially assumed (van der Kam et al. 2009a; 2009b; Hao et al. 2010; Rutten et al. 2010). Therefore, caution should be taken not to overgeneralize the anti-addictive properties of mGlu5 receptor ligands.

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