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AMN082, a metabotropic glutamate receptor 7 allosteric agonist, attenuates locomotor sensitization and cross-sensitization induced by cocaine and morphine in mice

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ABSTRACT

Previous studies have indicated that metabotropic glutamate receptors 7 (mGluR7s) are involved in drug addiction. However, the role of these receptors in drug-induced behavioral sensitization is unknown. The aim of the present study was to determine whether systemic injection of AMN082, a selective mGluR7 allosteric agonist, reduces the cocaine- and morphine-induced hyperactivity and the development and expression of locomotor sensitization, and also affects the reciprocal cross-sensitization to the stimulant effect of cocaine and morphine in mice. AMN082 (1.25–10.0 mg/kg, i.p.) did not have an impact on locomotion of naive mice and did not affect the acute cocaine- or morphine-induced hyperactivity, except the dose of 10 mg/kg that suppressed the locomotor effect of both drugs. Repeated exposure to cocaine or morphine (10 mg/kg, 5× every 3 days) gradually increased locomotion during induction of sensitization and after 4 (cocaine) or 7 day (morphine) withdrawal phase when challenged with cocaine (10 mg/kg, i.p.) or morphine (10 mg/kg, i.p.) on day 17 or 20, respectively. Pretreatment of animals with the lower doses of AMN082 (1.25–5.0 mg/kg, i.p.), 30 min before every cocaine or morphine injection during repeated drug administration or before cocaine or morphine challenge, dose-dependently attenuated the development, as well as the expression of cocaine or morphine locomotor sensitization. AMN082 also inhibited the reciprocal cross-sensitization between these drugs. Prior to administration of MMPIP (10 mg/kg, i.p.), a selective mGluR7 antagonist reversed the inhibitory effect of AMN082 on the development or expression of cocaine or morphine sensitization. These data indicate that AMN082 attenuated the development and expression of cocaine and morphine sensitization, and the reciprocal cross-sensitization via a mechanism that involves mGluR7s. Thus, AMN082 might have therapeutic implications not only in the treatment of cocaine or opioid addiction but also in the treatment of cocaine/opioid polydrug-abusers.

1. Introduction

Repeated, intermittent exposure to drugs of abuse, including psychostimulants and opioids, produces persistent increase in their psychomotor activating effects and their incentive motivational properties, a phenomenon termed behavioral sensitization (Shippenberg and Heidbreder, 1995; Steketee and Kalivas, 2011; Vanderschuren and Kalivas, 2000). Behavioral sensitization is a long-lasting phenomenon and can persist for some time after cessation of drug administration (Paulson et al., 1991). Neuronal changes underlying this phenomenon are thought to contribute to the development of compulsive drug seeking and craving — factors that characterize addiction (Morgan and Roberts, 2004; Robinson and Berridge, 2000). Cross-sensitization has been observed between drugs from different pharmacological classes and may play a role in the escalation of drug use in the polydrug-abuse populations (Smith et al., 2009).

Psychostimulants and opiates are often abused together, specifically cocaine with heroin or morphine (Hoffman et al., 1998). It is likely that combined use of these drugs produces effects greater than either drug alone (Trujillo et al., 2011). Preclinical studies have shown that cross-sensitization can develop between opioid agonists and cocaine to enhance their locomotor and rewarding effects. For instance, cocaine-treated rats exhibit cross-sensitization to the locomotor (McDaid et al., 2005) and conditioned rewarding (Shippenberg et al., 1998) effects of morphine. Likewise, heroin-treated rats exhibit cross-sensitization to the locomotor effects of cocaine (Leri et al., 2003), and morphine-treated rats exhibit cross-sensitization to both the locomotor (Cunningham et al., 1997; Lett, 1989; Velazquez et al., 2010) and

Abbreviations: ANOVA, analysis of variance; GABA, γ-aminobutyric acid; SEM, standard error of the mean; iGluR, ionotropic glutamate receptors; mGluR, metabotropic glutamate receptors; VTA, ventral tegmental area; NAc, nucleus accumbens; mPFC, medial prefrontal cortex; VP, ventral pallidum; ip, intraperitoneal injection.

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conditioned rewarding (Shippenberg et al., 1998) effects of cocaine. These data suggest that common neurobiological substrates contribute to sensitization induced by repeated, intermittent treatment with opioids and cocaine.

Psychostimulants and opiates mainly affect the central nervous system brain sites known as the reward circuit. The reward circuit includes the ventral tegmental area (VTA), nucleus accumbens (NAc), the medial prefrontal cortex (mPFC), the ventral pallidum (VP) and other sites, which are collectively termed the "motive circuit" (Pierce and Kalivas, 1997). These structures are believed to be involved in the induction and expression of behavioral sensitization. A large body of evidence indicates that the midbrain dopamine system is strongly involved in the drug reward and development of behavioral sensitization (Chen et al., 2009; Dalley and Everitt, 2009; Serrano et al., 2002; Volkow et al., 2002). Moreover, considerable evidence suggests that the glutamate system not only modulates these dopamine-related pathways and behavioral responses to addictive drugs, involving locomotion, but also is involved in the induction and expression of behavioral sensitization (Vanderschuren and Kalivas, 2000; Vezina and Kim, 1999; Wolf, 1998).

Indeed, modulation of glutamate receptor functions by: (1) ionotropic glutamate receptor (iGluR) antagonists (e.g. Jeziorski et al., 1994; Karler et al., 1994; Mendez and Trujillo, 2008), (2) group I metabotropic glutamate receptor (mGluR) antagonists (Kotlinska and Bochenski, 2007, 2011; Timmer and Steketee, 2012; Veeneman et al., 2011) or (3) group II mGluR agonists (Xie and Steketee, 2009) reduced cocaine- and/or morphine-induced sensitization. Such results may suggest that these receptors comprise important targets in medication development for the treatment of cocaine or morphine addiction. However, not all evidence supports this suggestion (Atalla and Kuschinsky, 2006; Dravolina et al., 2006; Tzschentke and Schmidt, 1996). Furthermore, the side effects or poor bioavailability of antagonists or agonists of these receptors restrict their potential therapeutic use (Moldrich et al., 2003; Olive, 2009).

In contrast to mGluR group I (mGluR1/5) and group II (mGluR2/3), the role of mGluR group III (mGluR4/6/7/8) in cocaine and morphine sensitization is largely unknown, due to the lack of systematically active, subtype-selective agents. Published data indicate that auto- and heteroreceptors of mGluR4/7/8 reside predominantly on the nerve terminals of glutamatergic corticostriatal and GABA-ergic, striatopallidal pathways, respectively. These presynaptic receptors regulate basal and/or phasic release of respective transmitters to maintain basal ganglia homeostasis (see Mao et al., 2013).

With the recent development of AMN082, a selective mGluR7 allosteric agonist (Mitsukawa et al., 2005), it has been reported that activation of mGluR7 by AMN082 dose-dependently inhibited intravenous cocaine or oral alcohol self-administration and cocaine-enhanced electrical brain-stimulation reward (Li et al., 2009; Salling et al., 2008). Furthermore, AMN082 inhibited reinstatement of cocaine seeking in a rat relapse model (Li et al., 2010). Similar to cocaine studies, activation of mGluR7 by AMN082 inhibited the rewarding and motivational effects of heroin (Li et al., 2013). Therefore, the aim of this study was to examine whether AMN082 was capable of preventing (i) the acute cocaine- and morphine-induced hyperactivity or (ii) the development and expression of sensitization and (iii) reciprocal cross-sensitization to the locomotor stimulant effect of cocaine and morphine in mice. To clarify the role of mGluR7 activation in the action of AMN082, the selective allosteric antagonist of the mGluR7s, MMPIP (Suzuki et al., 2007) was used.

2. Methods

2.1. Animals

Male Swiss mice (HZL, Warsaw, Poland) weighing between 20 and 25 g upon delivery were used. Animals were housed at five mice per cage in a constant temperature and humidity-controlled environment, and were habituated for 1 week prior experimentation. The mice had ad libitum access to food (Bacutil, Motycz, Poland) and tap water, except during experimental sessions. Lighting was maintained under a 12 hour light–dark cycle (lights on at 6:00 AM–6:00 PM). In all experiments, each animal was used only once. All experimental procedures were performed according to the National Institute of Health Guidelines for the Care and Use of Laboratory Animals, and the European Council Directive of 24 November 1986 for Care and Use of Laboratory Animals (86/609/EEC), and approved by the Local Ethics Committee.

2.2. Drugs

Cocaine HCl (Tocris Bioscience, Bistrol, United Kingdom) and morphine HCl (Polfa, Kutno, Poland) were dissolved in saline (0.9% NaCl) and administered intraperitoneally (i.p.). N,N′-dibenzhydrylethane-1,2-diamine dihydrochloride (AMN082) and 6-(4-methoxyphenyl)-5-methyl-3-(4-pyridinyl)-isoxazolo[4,5-c]pyridin-4(5H)-one hydrochloride (MMPIP) were purchased from Tocris Bioscience (Bistrol, United Kingdom). For i.p. injection, AMN082 and MMPIP were suspended in 0.5% methylcellulose, which was used as a vehicle. Both compounds were administered in a volume of 10 ml/kg (0.01 ml/g body weight). Fresh drug solutions were prepared on each day of the experiments. Drug injection times were determined based upon pilot studies and literature reports.

2.3. Apparatus

The locomotor (ambulatory) activity measurements were performed between 10:00 AM and 5:00 PM using 10 activity chambers (round Plexiglas cage, 30 cm in diameter, Multiserv, Lublin, Poland). The animals were individually placed into cages, which were situated in a sound-attenuated room. The cages were equipped with one row of four infrared light-sensitive photocells located 1 cm above the floor. Locomotor activity was defined as the number of interruptions of a beam during the observation period.

2.4. Effect of AMN082 treatment on the acute cocaine- or morphine-induced hyperlocomotion and basal locomotor activity

Mice ($n = 6–10$) were pretreated with a single injection of AMN082 (1.25, 2.5, 5.0 or 10 mg/kg, i.p.) or vehicle 30 min before injection of cocaine (10 mg/kg, i.p.) or morphine (10 mg/kg, i.p.). Locomotor activity was recorded for 30 or 60 min, respectively, immediately after cocaine/morphine administration. Furthermore, an influence of AMN082 (1.25, 2.5, 5.0 and 10 mg/kg, i.p.) alone on the locomotor activity of naive mice was examined.

2.5. Induction of cocaine and morphine sensitization

The induction of sensitization to cocaine-induced hyperactivity was based on the method described by Kuribara (1994). Thus, mice received five i.p. injections of cocaine at a dose of 10 mg/kg, with 3 day intervals (on the 1st, 4th, 7th, 10th and 13th days). Control animals received saline (0.9% NaCl). Four days after the last treatment (17th day of experiment) the mice received the challenge dose of cocaine (10 mg/kg i.p.) or saline. Immediately after the acute cocaine/saline challenge dose, the animals' ambulatory activity was measured for 30 min (expression of sensitization).

The induction of sensitization to morphine was based on the method described by Kuribara (1997) with minor modifications. According to this method, mice received five i.p. injections of morphine at a dose of 10 mg/kg, once daily, every 3 days (on the 1st, 4th, 7th, 10th and 13th days). Control animals received saline. Seven days after the last treatment (20th day of experiment), the mice treated with either saline or morphine received a challenge dose of morphine (10 mg/kg i.p.) or saline. Immediately after the acute morphine/saline challenge dose,

the animals' ambulatory activity was measured for 60 min (expression of sensitization).

2.5.1. Effect of co-administration of AMN082 on the development of sensitization to the locomotor stimulant effect of cocaine and morphine. Influence of MMPIP on the AMN082 effect

To investigate the influence of AMN082 on the development of sensitization to the locomotor stimulant effect of cocaine, the mice (n = 7–9) were pretreated with AMN082 (1.2, 2.5 or 5.0 mg/kg, i.p.) or vehicle, 30 min before cocaine (10 mg/kg, i.p.) or saline (control group) injection on the first day (day 1) of the experiment. The mice were directly placed in the test apparatus and locomotor activity was measured for the following 30 min. The administration procedure was repeated on days 4, 7, 10, and 13, and locomotor activity measurements were performed as described above. To determine whether mGluR7s are involved in the AMN082 effect on the development of cocaine sensitization, the cocaine-treated group was pretreated with MMPIP (10 mg/kg, i.p.), an allosteric mGluR7-selective antagonist, 30 min prior to AMN082 (5.0 mg/kg, i.p.) injection. Control mice were injected with saline and vehicle. Following a withdrawal period of 4 days (day 17), all groups of mice were challenged with cocaine (10 mg/kg, i.p.) without AMN082 and/or MMPIP administration and the locomotor activity was measured for 30 min.

To investigate the influence of AMN082 on the development of sensitization to the locomotor stimulant effect of morphine, the mice (n = 6–10) were pretreated with AMN082 (1.25, 2.5 or 5.0 mg/kg, i.p.) or vehicle, 30 min before each morphine (10 mg/kg, i.p.) or saline (control group) injection every 3 days, for five times (on the 1st, 4th, 7th, 10th and 13th days). Immediately after morphine administration, locomotor activity was measured for 60 min. To determine whether the mGluR7s are involved in the AMN082 effect on the induction of morphine locomotor sensitization, the morphine-treated group was pretreated with MMPIP (10 mg/kg, i.p.), 30 min prior to AMN082 (5.0 mg/kg, i.p.) injection. Control mice were injected with saline and vehicle. Following a withdrawal period of 7 days (day 20), all groups of mice received a challenge dose of morphine (10 mg/kg, i.p.) without AMN082 and/or MMPIP administration and locomotor activity was measured for 60 min.

2.5.2. Effect of AMN082 treatment on the expression of sensitization to the locomotor stimulant effect of cocaine and morphine. Influence of MMPIP on the AMN082 effect

In order to test the effect of AMN082 on the expression of sensitization to the locomotor stimulant effect of cocaine, separate groups of mice (n = 8–10) were sensitized to cocaine as described above. On the test day (17th day of experiment), mice were treated with AMN082 (1.25, 2.5 or 5.0 mg/kg i.p.) or vehicle 30 min before the cocaine challenge (10 mg/kg, i.p.), and the locomotor activity was measured for 30 min. To determine whether mGluR7s are involved in this AMN082 effect on the expression of cocaine sensitization, the cocaine-sensitized mice, before cocaine challenge (10 mg/kg, i.p.), were pretreated with MMPIP (10 mg/kg, i.p.), 30 min prior to AMN082 (5.0 mg/kg, i.p.) injection. Immediately after cocaine challenge, locomotor activity was measured for 30 min.

To evaluate an influence of the mGluR7 agonist on the expression of morphine-induced locomotor sensitization, separate groups of mice (n = 8–10) were sensitized to morphine, as described above. On the test day (20th day of experiment), 30 min prior to the challenge dose of morphine (10 mg/kg, i.p.) mice were treated with AMN082 (1.25, 2.5 or 5.0 mg/kg, i.p.) or vehicle and locomotor activity was recorded for 60 min. To determine whether the mGluR7s are involved in the effect of AMN082 on the expression of morphine sensitization, the morphine sensitized mice, before morphine challenge (10 mg/kg, i.p.), were pretreated with MMPIP (10 mg/kg, i.p.), 30 min before AMN082 (5.0 mg/kg) injection. Immediately after morphine challenge, locomotor activity was measured for 60 min.

2.5.3. Effect of AMN082 on the expression of reciprocal locomotor cross-sensitization between cocaine and morphine

The induction of cocaine sensitization was performed according to the method described above. Following a period of 4 days without treatment (17th day of experiment), the cocaine-sensitized and saline-treated mice (n = 7–10) were pretreated with AMN082 (2.5 or 5.0 mg/kg, i.p.) or vehicle, 30 min before the challenge with morphine (10 mg/kg, i.p.). Locomotor activity was measured for 30 min, immediately after morphine challenge.

The induction of morphine sensitization was performed according to the method described above. Following a period of 7 days without treatment (20th day of experiment) the morphine-sensitized and saline-treated mice (n = 9–10) were pretreated with AMN082 (2.5 or 5.0 mg/kg, i.p.) or vehicle, 30 min before the challenge with cocaine (10 mg/kg, i.p.). Locomotor activity was measured for 60 min, immediately after the cocaine challenge.

2.6. Statistical analysis

All statistical analyses were performed using Prism 5.0, GraphPad Software and R 3.0.0 for Windows. The data from experiment 1 were analyzed by a two-way (group and treatment) analysis of variance (ANOVA) (Fig. 1). Experiment 2 (Figs. 2–3) was analyzed by a two-way (treatment group, day) ANOVA (induction of sensitization) (A, C panels), a two-way ANOVA (expression of sensitization) (treatment, non-sensitized/sensitized group) (B panel) and a three way ANOVA (treatment, AMN082, MMPIP) (D panel). Data from experiment 3 (Fig. 4) were analyzed by a two-way ANOVA (treatment, non-sensitized/sensitized group) (A, C panels) and by a three way ANOVA (group, AMN082, MMPIP) (B, D panels). Data from experiment 4 (Fig. 5) were analyzed by a two-way ANOVA (challenge, non-sensitized/sensitized group) (A, C panels) and a one-way ANOVA (AMN082) (B, D panels). Subsequent comparisons were performed by Bonferroni's post-hoc test for two- and three-way ANOVAs, and Tukey's post hoc multiple comparison test for one-way ANOVA. All data were expressed as means (±S.E.M.). $P < 0.05$ was considered statistically significant in all cases.

3. Results

3.1. Effect of AMN082 treatment on the acute cocaine- or morphine-induced hyperlocomotion and basal locomotor activity

Two-way ANOVA indicated statistically significant differences between groups (saline and cocaine): [$F(1,79) = 109.7$; $P < 0.0001$]; treatment [$F(4,79) = 3.771$; $P = 0.0074$]; and group × treatment interaction [$F(4,79) = 3.494$; $P = 0.0111$]. Post-hoc Bonferroni's test showed that acute injection of cocaine at a dose of 10 mg/kg, i.p. elevated spontaneous locomotion of mice in comparison with the control group ($P < 0.01$). AMN082 significantly reduced the locomotor hyperactivity induced by cocaine only at a dose of 10 mg/kg, i.p. ($P < 0.05$). This effect was not observed in mice treated with a lower dose of AMN082, i.e. 1.25, 2.5 and 5.0 mg/kg, i.p. (Fig. 1A).

Two-way ANOVA detected statistically significant differences between the groups (saline, morphine): [$F(1,70) = 28.2$; $P = 0.0001$]; treatment [$F(4,70) = 2.622$; $P < 0.05$]; and group × treatment interaction [$F(4,70) = 1.773$; $P = 0.144$]. Post-hoc Bonferroni's test showed that acute injection of morphine at a dose of 10 mg/kg, i.p. elevated spontaneous locomotion of mice in comparison with the control group ($P < 0.01$). AMN082 significantly reduced the locomotor hyperactivity induced by morphine only at a dose of 10 mg/kg, i.p. ($P < 0.05$). This effect was not observed in mice treated with a lower dose of AMN082, i.e. 1.25, 2.5, and 5.0 mg/kg, i.p. ($P > 0.05$) (Fig. 1B).

In both experiments, AMN082 (1.25–10 mg/kg, i.p.) given alone did not change the locomotor effect of mice. Because AMN082 at the dose of 10 mg/kg reduced acute hyperactivity induced by cocaine or morphine,

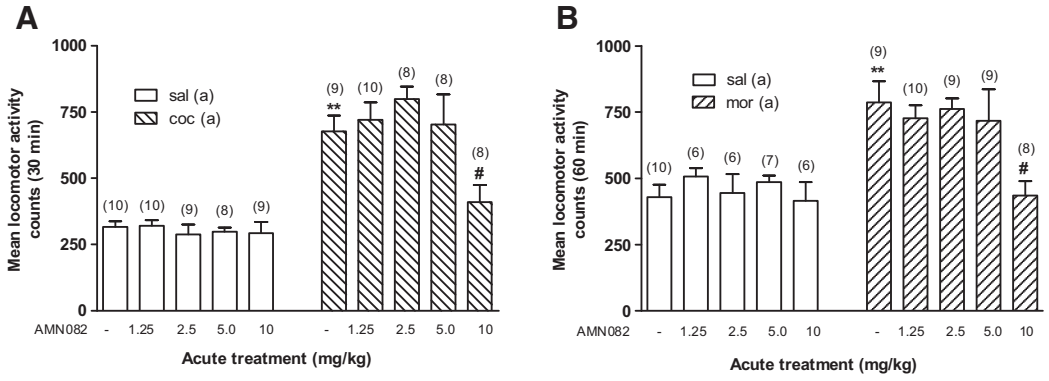

Fig. 1. The effect of single AMN082 administration on the acute cocaine- (A) or morphine- (B) induced hyperactivity in mice. The mice were administered with vehicle or AMN082 (1.25, 2.5, 5.0 and 10 mg/kg), 30 min prior to the acute administration of saline or cocaine (10 mg/kg)/morphine (10 mg/kg). After the second injection, the locomotor activity of mice was measured for 30 min (cocaine) or 60 min (morphine) in the activity chambers. The results are expressed as mean ± S.E.M. Numbers in parentheses indicate the number of animals used (n = 6–10 animals per group). $^{**}P < 0.01$ vs. saline/vehicle group; $^{\#}P < 0.05$ vs. cocaine/vehicle (or morphine/vehicle) group. sal, saline; coc, cocaine; mor, morphine; a; acute.

we preferred to use ineffective doses (1.25–5.0 mg/kg, i.p.) of AMN082 for sensitization experiments.

3.2. Effect of co-administration of AMN082 on the development of sensitization to the locomotor stimulant effect of cocaine and morphine. Influence of MMPIP on the AMN082 effect

Fig. 2A shows the effect of i.p. injection of AMN082 (1.25, 2.5, 5.0 mg/kg, i.p.) with or without cocaine (10 mg/kg, i.p.) on the induction of locomotor sensitization. Two-way ANOVA, followed by Bonferroni's test [treatment: $F(7,280) = 98.36$, $P < 0.0001$; day: $F(4,280) = 5.063$; $P < 0.0001$; treatment × day: $F(28,280) = 2.609$, $P < 0.0001$] indicated that pretreatment with AMN082 dose-dependently attenuated the induction of cocaine-induced sensitization. On the 17th day (expression), cocaine challenge (10 mg/kg, i.p.) produced significantly different responses among the groups [treatment: $F(3,55) = 7.67$; $P = 0.0002$; non-sensitized or sensitized group: $F(1,55) = 31.19$; $P < 0.0001$; treatment × non-sensitized or sensitized group $F(3,55) =$

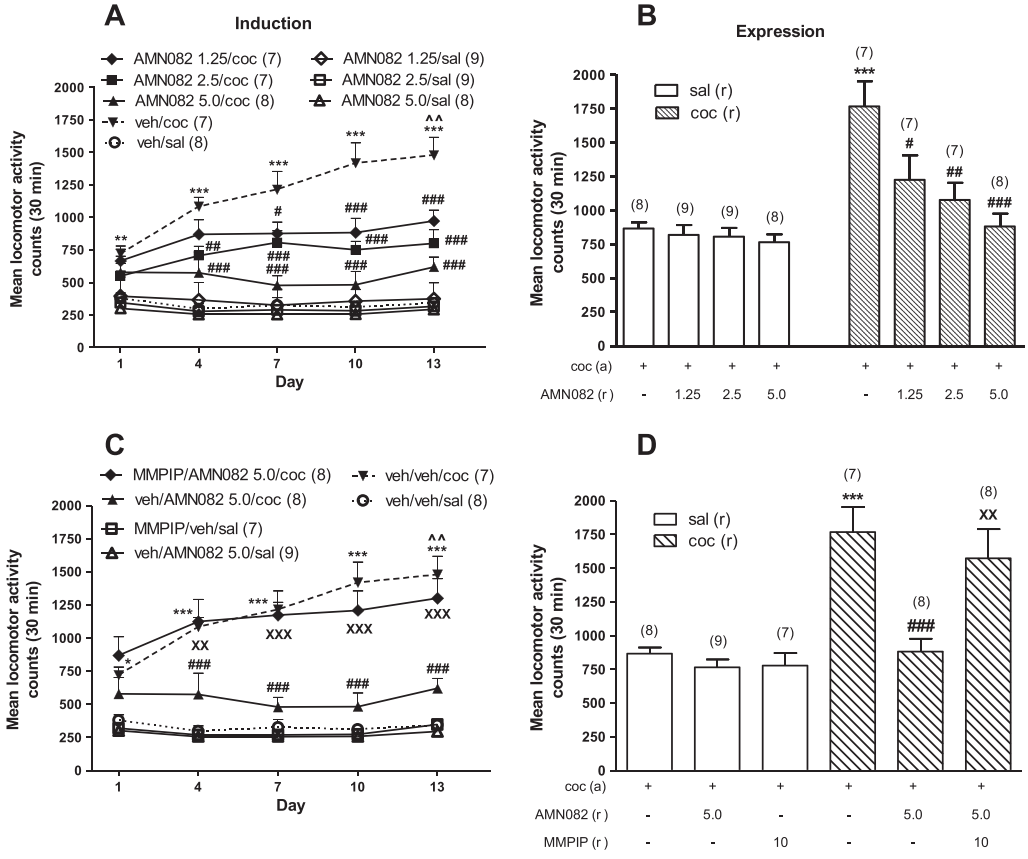

Fig. 2. The effect of AMN082 on the development (induction and expression) of sensitization to the locomotor stimulant effect of cocaine in mice. The influence of MMPIP pretreatment on the AMN082 effect. AMN082 (1.25, 2.5 and/or 5.0 mg/kg) was given 30 min before cocaine injection during induction of sensitization (A, C). MMPIP (10 mg/kg) was given 30 min prior to AMN082 (5 mg/kg) treatment (C). After a 4-day drug-free period, on day 17 (expression) the mice were challenged with cocaine (10 mg/kg) without AMN082 or MMPIP pretreatment and locomotor activity was measured for 30 min (B, D). The results are expressed as mean ± S.E.M. Numbers in parentheses indicate the number of animals used (n = 7–9 animals per group). $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ vs. the vehicle/saline group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$ vs. the vehicle/cocaine group; $^{xx}P < 0.01$ and $^{xxx}P < 0.001$ vs. the AMN082/cocaine group; $^{\wedge\wedge}P < 0.01$ vs. cocaine given on the 1st day of the development of sensitization. veh, vehicle; sal, saline; coc, cocaine; a, acute; r, repeated (five) injections of cocaine/saline and/or AMN082 5.0/MMPIP during the induction of sensitization.

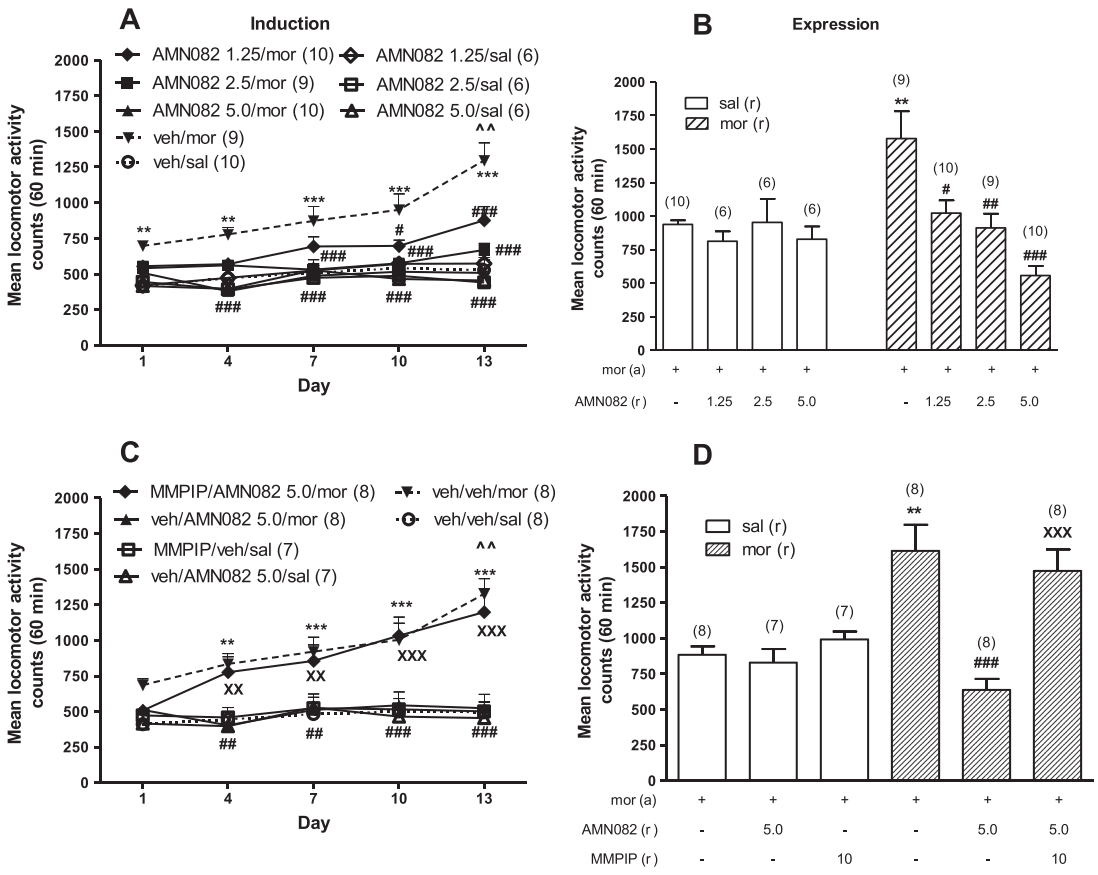

Fig. 3. The effect of AMN082 on the development (induction and expression) of sensitization to the locomotor stimulant effect of morphine in mice. The influence of MMPIP pretreatment on the AMN082 effect. AMN082 (1.25, 2.5 and/or 5.0 mg/kg) was given 30 min before morphine injection during induction of sensitization (A, C). MMPIP (10 mg/kg) was given 30 min prior to AMN082 (5 mg/kg) treatment (C). After a 7-day drug-free period, on day 20 (expression) the mice were challenged with morphine (10 mg/kg) without AMN082 or MMPIP pretreatment and locomotor activity was measured for 60 min (B, D). The results are expressed as mean ± S.E.M. Numbers in parentheses indicate the number of animals used (n = 6–10 animals per group). $^{*}P<0.05$, $^{**}P<0.01$ and $^{***}P<0.001$ vs. the vehicle/saline group; $^{\#}P<0.05$, $^{\#\#}P<0.01$ and $^{\#\#\#}P<0.001$ vs. the vehicle/morphine group; $^{xx}P<0.01$ and $^{xxx}P<0.001$ vs. the veh/AMN082 5.0/morphine groups; $^{\wedge\wedge}P<0.01$ vs. morphine given on the 1st day of the development of sensitization. veh, vehicle; sal, saline; mor, morphine; a, acute, r, repeated (five) injections of morphine/saline and/or AMN082 5.0/MMPIP during the induction of sensitization.

4.943; $P = 0.0041$] (Fig. 2B). Cocaine challenge (expression of sensitization) produced significantly higher locomotor activity in the cocaine-pretreated group compared to the saline-pretreated control ($P < 0.001$). AMN082 at the doses of 1.25 mg/kg ($P < 0.05$), 2.5 mg/kg ($P < 0.01$) or 5.0 mg/kg ($P < 0.001$) respectively, was effective in attenuating the development of cocaine sensitization, compared to cocaine-pretreated and cocaine-challenged mice. No differences in locomotor activity between saline- and AMN082 (1.25, 2.5, 5.0 mg/kg)-pretreated groups after cocaine challenge were observed (Fig. 2B).

Using the same experimental setup, the two-way ANOVA, followed by Bonferroni's test [treatment: $F(5,215) = 127.5$, $P < 0.0001$; day: $F(4,215) = 7.818$, $P < 0.0001$; treatment × day interaction: $F(20,215) = 2.296$, $P < 0.0001$], showed that MMPIP blocked the inhibitory effect of AMN082 (5.0 mg/kg, i.p.) on the induction of cocaine sensitization (Fig. 2C). Three-way ANOVA [cocaine $F = (1,43) = 38.7$; $P < 0.0001$; AMN082 $F(1,43) = 6.71$, $P = 0.012$; MMPIP $F(1,43) = 0.68$, $P = 0.41$; cocaine × AMN082 $F(1,43) = 9.94$; $P = 0.002$; cocaine × MMPIP $F(1,43) = 9.07$; $P = 0.004$], followed by Bonferroni's post-hoc comparisons test indicated that MMPIP (10 mg/kg, i.p.) pretreatment during the induction of cocaine-induced sensitization, significantly blocked the inhibitory effect of AMN082 (5.0 mg/kg i.p.) on the expression of cocaine sensitization ($P < 0.01$) (Fig. 2D).

Fig. 3A shows the effect of i.p. injection of AMN082 (1.25, 2.5, 5.0 mg/kg) with or without morphine (10 mg/kg, i.p.), on the induction of locomotor sensitization. Two-way ANOVA, followed by Bonferroni's test [treatment: $F(7,288) = 31.47$; $P < 0.0001$; day: $F(4,288) = 6.716$; $P < 0.0001$] indicated that pretreatment with AMN082 attenuated the induction of morphine-induced sensitization. On the 20th day (expression of sensitization), morphine challenge (10 mg/kg, i.p.) produced significantly different responses among the groups [treatment: $F(3,57) = 8.899$, $P < 0.0001$; treatment × non-sensitized or sensitized group interaction: $F(3,57) = 6.139$; $P = 0.0011$] (Fig. 3B). The post hoc analysis indicated that morphine challenge produced significantly higher locomotor activity in the morphine-pretreated group compared to the saline-pretreated control ($P < 0.01$). AMN082 at the doses 1.25 mg/kg ($P < 0.05$), 2.5 mg/kg ($P < 0.01$) or 5.0 mg/kg ($P < 0.001$) respectively, was effective in attenuating the development of morphine sensitization compared to morphine-pretreated and morphine-challenged mice. No differences in locomotor activity between saline- and AMN082 (1.25, 2.5, 5.0 mg/kg) pretreated groups were observed after cocaine challenge.

Using the same experimental setup, two-way ANOVA, followed by Bonferroni's test [treatment: $F(5,205) = 37.61$, $P < 0.0001$; day: $F(4,205) = 8.086$; $P < 0.0001$; treatment × day interaction: $F(20,205) = 2.216$; $P = 0.0029$] showed that MMPIP blocked the inhibitory effect of AMN082 (5.0 mg/kg, i.p.) on the induction of morphine sensitization (Fig. 3C). Three-way ANOVA [morphine $F(1,44) = 12.2$, $P = 0.001$; AMN082 $F(1,44) = 11.54$, $P = 0.001$; MMPIP $F(1,44) = 7.16$, $P = 0.01$; morphine × AMN082 $F(1,44) = 15.03$, $P = 0.0003$; morphine × MMPIP $F(1,44) = 9.38$. $P = 0.003$], followed by Bonferroni's post-hoc comparisons test indicated that MMPIP (10 mg/kg, i.p.) pretreatment during the development of morphine-induced sensitization, significantly blocked the inhibitory effect of

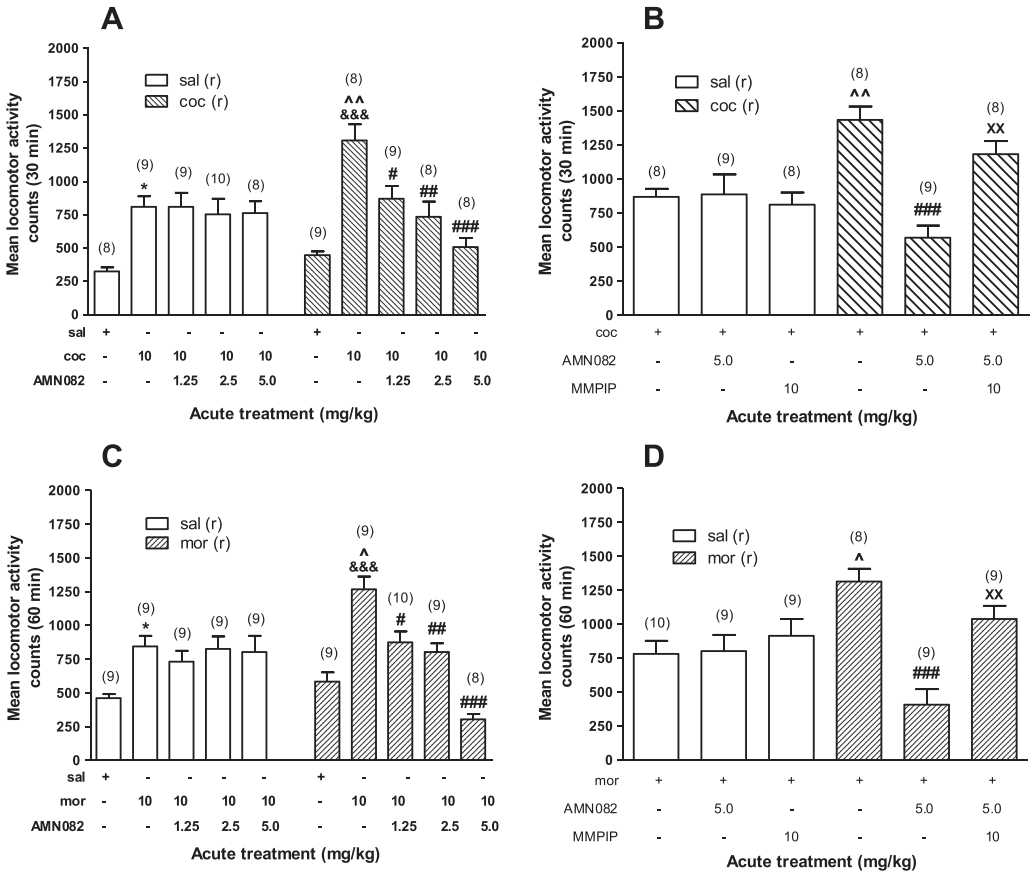

Fig. 4. The effect of single administration of AMN082 on the expression of cocaine- or morphine-induced sensitization to the locomotor stimulant effect of cocaine (A) or morphine (C) in mice. Influence of MMPIP on the AMN082 effect on the expression of cocaine (B) and morphine (D) sensitization. AMN082 (1.25, 2.5, 5.0 mg/kg) was given 30 min prior to cocaine (10 mg/kg) or morphine (10 mg/kg) challenge on day 17 or 20, respectively. MMPIP (10 mg/kg) was given 30 min before AMN082 (5 mg/kg) administration. The mice were then tested for the locomotor activity for 30 (cocaine) or 60 min (morphine). The results are expressed as ± S.E.M. Numbers in parentheses indicate the number of animals used (n = 8–10 animals per group). $^{*}P < 0.05$ vs. the vehicle/saline group; $^{\&\&\&}P < 0.001$ vs. the cocaine/saline (or morphine/saline) group; $^{\wedge}P < 0.05$ and $^{\wedge\wedge}P < 0.01$ vs. the saline/cocaine (or saline/morphine) group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$ vs. the cocaine/cocaine (or morphine/morphine) group; $^{xx}P < 0.01$ vs. the AMN082/cocaine (or AMN082/morphine) group. sal, saline; coc, cocaine; mor, morphine; r, repeated (five) injections of cocaine (or morphine) during the induction of sensitization.

AMN082 (5.0 mg/kg, i.p.) on the expression of morphine sensitization ($P < 0.001$) (Fig. 3D).

3.3. Effect of AMN082 treatment on the expression of sensitization to the locomotor stimulant effect of cocaine and morphine. Influence of MMPIP on the AMN082 effect

Fig. 4A shows the effects of acute AMN082 (1.25, 2.5, 5.0 mg/kg, i.p.) administration on the expression of sensitization in saline- and cocaine-sensitized mice. Two-way ANOVA followed by Bonferroni's test [treatment: $F(4,76) = 14.51$, $P < 0.0001$; non-sensitized or sensitized group: $F(1,76) = 1.947$; $P = 0.167$; treatment × non-sensitized or sensitized group interaction: $F(4, 76) = 4.275$; $P = 0.0036$], indicated that AMN082 significantly attenuated the expression of cocaine-induced locomotor sensitization. Additionally, AMN082 (1.25, 2.5, 5.0 mg/kg, i.p.) had no effect on the locomotor activity of saline-treated mice challenged with cocaine (Fig. 4A). Three-way ANOVA [cocaine $F(1,46) = 5.38$, $P = 0.024$; AMN082 $F(1,46) = 7.63$, $P = 0.008$; MMPIP $F(1,46) = 0.51$, $P = 0.47$; cocaine × AMN082 $F(1,46) = 19.31$, $P < 0.001$; cocaine × MMPIP $F(1,46) = 10.87$, $P = 0.001$], followed by Bonferroni's post-hoc comparisons test shows that acute administration of MMPIP (10 mg/kg, i.p.), 30 min before AMN082 (5.0 mg/kg, i.p.), significantly reversed AMN082-induced reduction of expression of cocaine sensitization ($P < 0.01$) (Fig. 4B).

Fig. 4C shows the effects of acute AMN082 (1.25, 2.5, 5.0 mg/kg, i.p.) on the expression of sensitization in saline- and morphine-sensitized mice. Two-way ANOVA, followed by Bonferroni's test [treatment: $F(4,80) = 14.52$; $P < 0.0001$; non-sensitized or sensitized group: $F(1,80) = 0.4194$; $P = 0.5191$; treatment × non-sensitized or sensitized group interaction: $F(4,80) = 8.515$; $P < 0.0001$], indicated that AMN082 significantly attenuated the expression of morphine-induced locomotor sensitization. Additionally, AMN082 (1.25, 2.5, 5.0 mg/kg, i.p.) alone had no effect on the locomotor activity of saline-treated mice challenged with morphine (Fig. 4C). Three-way ANOVA [morphine $F(1,48) = 0.7$, $P = 0.40$; AMN082 $F(1,48) = 10.3$, $P = 0.002$; MMPIP $F(1,48) = 2.91$, $P = 0.094$; morphine × AMN082 $F(1,48) = 17.79$, $P = 0.0001$; morphine × MMPIP $F(1,48) = 5.48$, $P = 0.02$] followed by Bonferroni's post-hoc comparisons test shows that acute administration of MMPIP (10 mg/kg, i.p.), 30 min before AMN082 (5.0 mg/kg, i.p.), significantly reversed AMN082-induced reduction of expression of cocaine sensitization ($P < 0.01$) (Fig. 4D).

3.4. Effect of AMN082 treatment on the expression of reciprocal locomotor cross-sensitization between cocaine and morphine

In the separate groups of animals, saline-, and cocaine-treated mice were challenged with morphine (10 mg/kg, i.p.) on the 17th day of experiment (expression of sensitization). Two-way ANOVA, followed by Bonferroni's test [non-sensitized or sensitized group: $F(1,28) = 18.9$, $P = 0.0002$; challenge (saline, morphine) $F(1,28) = 41.38$, $P < 0.0001$; non-sensitized or sensitized group × challenge interaction [$F(1,28) = 4.896$; $P = 0.0352$], indicated that the challenge doses of morphine significantly increased locomotor activity in the cocaine-sensitized mice, in comparison with the cocaine-treated animals challenged with saline

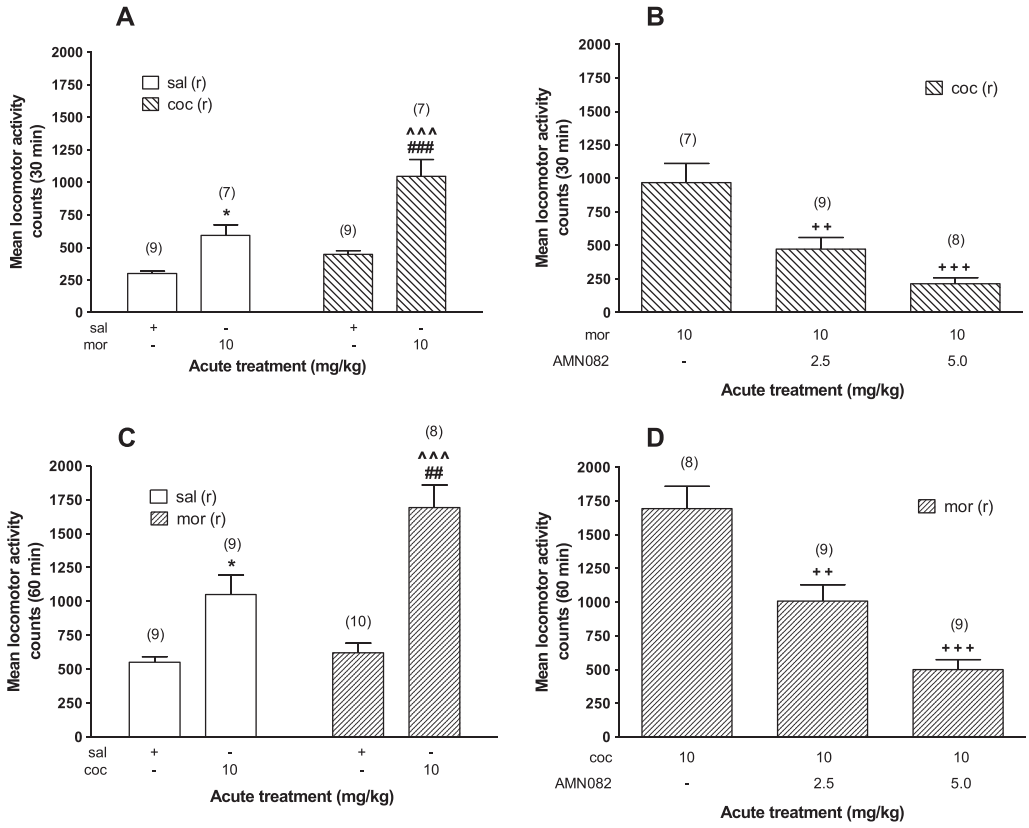

Fig. 5. The reciprocal cross-sensitization between cocaine and morphine to their locomotor effects (A, C). Influence of AMN082 on the expression of locomotor cross-sensitization between cocaine and morphine (B) or between morphine and cocaine (D) to their locomotor effects in mice. After a 4- (cocaine) or 7- (morphine) day drug-free period, the saline-, cocaine-, or morphine-sensitized mice were challenged with morphine (10 mg/kg) or cocaine (10 mg/kg), and locomotor activity of mice was measured for 60 or 30 min, respectively. AMN082 (2.5 or 5.0 mg/kg) was given 30 min before cocaine or morphine challenge injection. The results are expressed as means ± S.E.M. Numbers in parentheses indicate the number of animals used (n = 7–10 animals per group).*$P < 0.05$ vs. the saline/saline group; $^{##}P < 0.01$ and $^{###}P < 0.001$ vs. the saline/cocaine (or saline/morphine) group; $^{\wedge\wedge\wedge}P < 0.001$ vs. the cocaine/saline (or morphine/saline) groups; $^{++}P < 0.01$ and $^{+++}P < 0.001$ vs. the cocaine/morphine (or morphine/cocaine) group. sal, saline; coc, cocaine; mor, morphine; r, repeated (five) injections of cocaine (or morphine) during the induction of sensitization.

($P < 0.001$) or in comparison with the acute morphine injection (10 mg/kg, i.p.) ($P < 0.001$) to the saline-treated mice (Fig. 5A). These results confirm the expression of cross-sensitization between cocaine and morphine. The one-way ANOVA indicated that injection of AMN082 (2.5 and 5.0 mg/kg, i.p.), 30 min before morphine challenge (10 mg/kg, i.p.) significantly inhibited [$F(2,21) = 15.11$; $P < 0.0001$] the expression of cross-sensitization. The post hoc Tukey's test showed that AMN082 at doses of 2.5 ($P < 0.01$) and 5.0 mg/kg i.p. ($P < 0.001$), decreased the effect of morphine challenge dose (Fig. 5B).

In the separate groups of animals, saline-, and morphine-treated mice were challenged with cocaine (10 mg/kg, i.p.) on the 20th day of experiment (expression of sensitization). Two-way ANOVA, followed by Bonferroni's test [non-sensitized or sensitized groups: $F(1.32) = 9.986$; $P = 0.0034$; challenge (saline, cocaine): $F(1.32) = 48.96$; $P < 0.0001$; non-sensitized or sensitized groups × challenge interaction [$F(1,32) = 6.467$; $P = 0.016$], indicated that the challenge doses of cocaine increased locomotor activity in the morphine-sensitized mice, in comparison with the morphine-treated animals challenged with saline ($P < 0.001$), or in comparison with the acute cocaine injection (10 mg/kg, i.p.) ($P < 0.01$) to the saline-treated mice (Fig. 5C). These results confirm the expression of cross-sensitization between morphine and cocaine. The one-way ANOVA indicated that AMN082 (2.5 and 5.0 mg/kg, i.p.) administration, 30 min before cocaine challenge (10 mg/kg, i.p.), significantly inhibited [$F(2,23) = 23.42$; $P < 0.0001$] the expression of cross-sensitization. The post hoc Tukey's test showed that AMN082 at doses of 2.5 ($P < 0.01$) and 5.0 mg/kg, i.p. ($P < 0.001$) decreased the effect of cocaine challenge dose (Fig. 5D).

4. Discussion

The present study indicated that AMN082 (1.25–10 mg/kg), a selective mGluR7 allosteric agonist, did not alter basal locomotor activity, neither influenced the acute cocaine- and morphine-induced locomotor activity in mice, except the dose of 10 mg/kg, which inhibited cocaine and morphine-induced locomotion. However, AMN082 attenuated the development and expression of cocaine- and morphine-induced sensitization and the reciprocal cross-sensitization at the low doses that did not disturb the acute locomotor hyperactivity induced by these drugs. These effects of AMN082 were reversed by MMPIP, an allosteric mGluR7-selective antagonist suggesting that mGluR7 is critically involved in cocaine- and morphine locomotor sensitization.

4.1. Effects of AMN082 on acute locomotor hyperactivity induced by cocaine and morphine and basal locomotor activity

Interactions between glutamate and midbrain dopamine pathways in the basal ganglia contribute importantly to the generation of motor behaviors (Vezina and Kim, 1999). Cocaine acts as an indirect dopamine receptor agonist (Ritz et al., 1987) but morphine increases dopamine level principally via activation of mu opioid receptors (Johnson and North, 1992). Group III mGluR (mGluR4/6/7/8) modulates locomotor activity induced by dopamine agonists in the NAc (David and Abraini, 2002; Rouillon et al., 2008). Previous studies have shown that intracerebral administration of L-AP4, a non-selective and non-systemically active group III mGluR agonist (Schoepp et al., 1999), significantly

decreased extracellular dopamine and glutamate levels in the NAc (Hu et al., 1999; Xi et al., 2003), and attenuated cocaine- and amphetamine-induced hyperactivity and striatal dopamine levels (David and Abraini, 2003; Mao et al., 2000). However, these effects of L-AP4 could be dependent not only on the stimulation of mGluR7, but also on stimulation of mGluR4 and mGluR8 (Yang, 2005). Among the group III mGluRs, particularly mGluR7 is highly expressed in the basal ganglia circuit, suggesting that it may display a fundamental role in the control of normal and abnormal motor activities (Kinoshita et al., 1998; Kosinski et al., 1999). It has been recently shown that AMN082, a potent (EC_{50} = 64–290 nM) and selective mGluR7 allosteric agonist (Mitsukawa et al., 2005), in contrast to L-AP4, does not alter accumbal dopamine levels (Li et al., 2008). In our study, acute administration of AMN082 (1.25–10.0 mg/kg) did not induce changes in locomotor activity of naive mice. Furthermore, pretreatment with low doses of AMN082 (1.25–5.0 mg/kg) had no effect on the acute cocaine- and morphine-induced locomotor hyperactivity. However, published data on the effects of AMN082 on locomotor activity are controversial. Some reports indicated that AMN082 (1–20 mg/kg) does not alter either basal or cocaine-enhanced locomotor activity in mice and rats (Bahi et al., 2012; Li et al., 2009) but others indicated that AMN082 at a dose of 10 mg/kg decreases locomotor activity of mGluR7 knockout and wild-type mice, demonstrating mGluR7-unrelated effects (Palucha et al., 2007; Salling et al., 2008). In our study, AMN082 at a dose of 10.0 mg/kg also reduced the acute locomotor stimulation induced by cocaine or morphine in mice. Because AMN082 effects at higher doses (>10 mg/kg) were off-target and independent on mGluR7 in various pharmacological tests (see Greco et al., 2010), lower doses of AMN082 (1.25–5.0 mg/kg) were selected for the sensitization study in mice.

4.2. AMN082 effects on the development of cocaine and morphine sensitization

The published data indicated that systemic or local administration of the selective mGluR7 agonist, AMN082, into the NAc, dose-dependently decreases extracellular GABA and increases extracellular glutamate, but has no effect on extracellular dopamine in the NAc (Li et al., 2008). Furthermore, an increase in extracellular glutamate in the NAc is secondary to a reduction in NAc GABA release (Li et al., 2008). The inhibition of medium spiny GABA-ergic output neurons in the NAc, predominantly projecting to the ventral pallidum (VP) (Bennett and Bolam, 1994; Groenewegen et al., 1996), serves as one of the final common pathways mediating psychostimulants' reward. However, the VP is necessary not only for the motivational (Hiroi and White, 1993; McFarland and Kalivas, 2001; Smith et al., 2009), but also for the motor properties of psychomotor stimulants and opiates (Gong et al., 1996; Napier, 1992). Interestingly, the VP is critically involved in the development (Johnson and Napier, 2000; Mickiewicz et al., 2009) and expression of morphine sensitization (Mickiewicz et al., 2009). Johnson and Napier (2000) argued that morphine-induced stimulation of mu-opioid receptors suppresses GABA-ergic activity in the VP and increases dopamine cell firing in the VTA, a structure involved in the induction of morphine sensitization. This hypothesis is supported by microdialysis studies showing that intra-VP morphine application increases meso-accumbal dopamine activity (Anagnostakis and Spyraki, 1994). Recently published data revealed that VP is involved in locomotor cross-sensitization to morphine in the cocaine-sensitized rats. The cross-sensitization to morphine was observed 3 days after discontinuation of five, once daily, i.p. injections of cocaine (McDaid et al., 2005). In our study, similar withdrawal period was applied (4-days) for cross-sensitization to morphine in the cocaine-sensitized mice. The existence of a cross-sensitization to the stimulant effect of cocaine and morphine has been reported earlier (Cunningham et al., 1997; Lett, 1989; McDaid et al., 2005; Velazquez et al., 2010). Our study extends those reports and demonstrates, for the first time, that AMN082 (1.25–5.0 mg/kg) was able to inhibit the reciprocal cross-sensitization between the locomotor stimulant effects of cocaine and morphine in mice. Because the effects of morphine in the VP may be mediated by GABA (Chrobak and Napier, 1993), there is a possibility that GABA-ergic transmission is also altered in the VP of the cocaine-pretreated animals. Indeed, cocaine-induced sensitization is associated with an overall decrease in pre- and postsynaptical GABA transmission in the striatum (Jung et al., 1999) and acute cocaine decreases extracellular GABA levels in the VP (Bennett and Bolam, 1994; Li et al., 2009; Torregrossa et al., 2008). Thus, it has been suggested that AMN082-induced increase in extracellular glutamate in the NAc may functionally antagonize cocaine- or dopamine-induced reduction in NAc-VP GABA transmission (Li et al., 2009, 2013; Xi and Gardner, 2008), and therefore, may antagonize the primary rewarding, reward-enhancing, and motivational effects of cocaine and heroin. Taking into account that the neurocircuitry and neuronal substrates that underlie behavioral sensitization and rewarding effects of these drugs are similar, we hypothesize that an increase in extracellular glutamate in the NAc that is secondary to reduction in NAc GABA release appears to play a central role in the inhibitory effects of AMN082 on the development of cocaine- or morphine-induced sensitization.

4.3. AMN082 effects on expression of cocaine and morphine sensitization

Published data indicated that extinction or withdrawal from repeated cocaine (Baker et al., 2003; McFarland et al., 2003; Pierce et al., 1996) but not heroin (LaLumiere and Kalivas, 2008) is associated with reduced basal levels of glutamate in the NAc. In contrast, cocaine challenge (Pierce et al., 1996; Reid and Berger, 1996) or priming injections of cocaine and heroin, that have been shown to be related to reinstatement of the drug-seeking behavior, induce a significant increase in extracellular glutamate in this region (Cornish and Kalivas, 2000; Knackstedt and Kalivas, 2009; LaLumiere and Kalivas, 2008). Basal extracellular levels of glutamate in the NAc are primarily maintained by cysteine–glutamate exchange (Baker et al., 2002) and provide a tone on presynaptic group II mGluRs (mGluR2/3) that are involved in modulation synaptic glutamate release (Baker et al., 2002; Xi et al., 2002). *N*-acetylcysteine, a compound that enhances cysteine–glutamate exchange and increases basal levels of glutamate in the NAc, blocks drug-induced reinstatement of cocaine (Baker et al., 2003; Moran et al., 2005) and heroin (Zhou and Kalivas, 2008) seeking in rats. Thus, increased glutamate availability in the NAc appears to be effective after exposure to these drugs, in spite of the fact that the basal levels of extracellular glutamate were not significantly altered after heroin withdrawal (LaLumiere and Kalivas, 2008), in contrast to the withdrawal from cocaine (Baker et al., 2003; Pierce et al., 1996). Because an increase in NAc glutamate, after AMN082 administration, leads to an increased binding to presynaptic mGluR2/3 autoreceptors, it is hypothesized that such mGluR2/3-mediated inhibition of glutamate release underlie the antagonism of cocaine-triggered reinstatement by AMN082 of drug-seeking behavior (Li et al., 2010, 2013). This finding is supported by the evidence demonstrating that the mGluR2/3 agonist and MMPIP, a selective mGluR7 antagonist, blocked the inhibitory effect of AMN082 on cocaine priming-induced increases in extracellular glutamate in the NAc and reinstatement of cocaine seeking. This is consistent with the recent finding demonstrating that mGluR2/3 agonists inhibit cocaine- (Baptista et al., 2004), heroin- (Bossert et al., 2004), alcohol- (Zhao et al., 2006) and nicotine-triggered relapse (Liechti et al., 2007) in rats. Furthermore, administration of the mGluR2/3 agonist has been shown to block the expression of sensitized responding to amphetamine (Kim and Vezina, 2002). Thus, in our study, AMN082 may attenuate the expression of cocaine and morphine-induced sensitization by increasing basal levels of glutamate in the NAc, which would decrease the effectiveness of cocaine and morphine challenge. It has been indicated that chronic treatment with the drug during cocaine withdrawal period, which increased basal levels of glutamate in the NAc, greatly reduced the expression of locomotor sensitization to cocaine (Placenza et al., 2008).

Published data indicated that AMN082 did not affect extracellular glutamate or GABA release in the VP in cocaine-abstinent rats (Li et al., 2010), suggesting that glutamate and GABA-ergic transmission is not involved in AMN082-induced inhibition of cocaine-primed relapse. This suggests that different mechanisms appear to underlie antagonism by AMN082 of intravenous cocaine self-administration (by VP GABA-ergic mechanism) and of cocaine-induced reinstatement of drug-seeking behavior (by NAc glutamate mechanism). However, it has been indicated that the VP is involved in the expression of morphine locomotor sensitization after long- (3 weeks) but not short-term (3 days) of morphine withdrawal (Mickiewicz et al., 2009). Thus, more studies are required to fully explicate the manner, in which AMN082 inhibits cocaine and morphine sensitization.

5. Conclusions

The present study demonstrates, for the first time, that the selective mGluR7 allosteric agonist AMN082 inhibits the development and expression of cocaine- and morphine-induced sensitization and cross-sensitization between these drugs at low doses that did not disturb the acute locomotor hyperactivity induced by these drugs. These findings suggest an important role of mGluR7 in the sensitization phenomenon because MMPIP, an allosteric mGluR7-selective antagonist, blocked these effects of AMN082. Thus, our studies suggest that mGluR7s are involved in neuroadaptive processes associated with cocaine and morphine addiction. Finally, our findings indicate that mGluR7 agonists can be effective in preventing cocaine/morphine-dependent individuals from relapsing to these drugs.

Acknowledgments

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