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mGluR5 is necessary for maintenance of methamphetamine-induced associative learning

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Abstract

Conditioned place preference (CPP) reflects the significance of contextual cues that are associated with rewarding effects of abused drugs such as methamphetamine (Meth). Glutamate neurotransmission is augmented following exposure to stimulants and associated cues. Activation of group I metabotropic glutamate receptors (mGluR) are critical for the acquisition and expression of stimulant-induced CPP. We hypothesized that the maintenance of Meth-induced CPP would also require activated mGluR, and that the role of mGluR1 *versus* mGluR5 group I subtypes may differ. To test this hypothesis, negative allosteric modulators (NAMs) of these receptors were administered following the development of Meth-induced CPP. NAMs exert their functional effects by displacing agonist from agonist-occupied receptors, thus NAMs selectively target brain regions with glutamate release. Conditioning with Meth every other day for six days resulted in significant preference for the Meth-paired compartment. Two once-daily injections of the mGluR1 NAM, JNJ16259685 (0.3mg/kg, i.p.) or its vehicle on days 13 and 14 after Meth-conditioning did not influence the maintenance of Meth-induced CPP; however, administration of the mGluR5 NAMs MTEP (3mg/kg, i.p.) and MPEP (30mg/kg, i.p.) inhibited maintenance processes necessary for CPP to be expressed. These findings suggest a subtype-specific role of mGluR5 receptors in the maintenance of place preference memory and potential of mGluR5 NAMs as a useful target for Meth addiction therapy.

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Author Disclosure

NIH had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication

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Keywords

conditioned place preference; metabotropic glutamate receptor; mGluR5; mGluR1; rat

Introduction

Methamphetamine (Meth) addiction is a problem of global health concern for which there is no FDA-approved pharmacotherapy. Even after protracted abstinence, Meth-addicted individuals are prone to cue-elicited relapse (Hartz, et al., 2001). One aspect of addiction that makes it such a persistent phenomenon is the strength of learned associations between the rewarding effects of drugs and the context in which drugs are administered (O'Brien, et al., 1992). Drug-induced associative learning can be studied in rodents using conditioned place preference (CPP) (Tzschentke, 2007).

After cessation from stimulant administration, dynamic changes occur within the corticostriatal glutamate transmitter system. After approximately two weeks following repeated stimulant administration glutamate levels are reduced in medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) (Baker, et al., 2003; Lominac and Szumlinski, 2008), and ionotropic and metabotropic glutamate receptors are increased in these brain regions (Ghasemzadeh, et al., 2009b; Ghasemzadeh, et al., 2009a; Boudreau and Wolf, 2005; Ary and Szumlinski, 2007). Re-exposure to stimulants or stimulant-related cues, increases glutamate levels in the NAc, mPFC and ventral pallidum (VP) beyond that seen in rats without a stimulant treatment history (Qi, et al., 2009; Pierce, et al., 1996; Chen, et al., 2001). Following long-term cessation of stimulant use by human stimulant abusers, the frontal cortex becomes hyper-responsive to drug-associated cues (Childress, et al., 1999). Drug cues hinder abstinence in addiction; therefore, normalizing the glutamatergic responses to drug-associated cues at a relevant time frame is of great therapeutic value.

Glutamate acts on both ionotropic and metabotropic receptors. Group I mGluRs include both metabotropic glutamate receptor subtype 1 (mGluR1) and 5 (mGluR5) which are located primarily on post-synaptic elements (Conn and Pin, 1997). Because of the localization of group I mGluRs within the brain systems important for stimulant-mediated behavior including the mPFC, NAc and VP, negative allosteric modulators (NAMs) of mGluR1 and 5 may provide an avenue to normalize the hyper-responsive glutamate system that occurs after stimulant administration (Romano, et al., 1995). Binding remotely from the agonist binding site, allosteric modulators alter the efficacy of endogenous agonists (Wang, et al., 2009). Use of allosteric modulators also avoids the compensatory effects and widespread action that are prevalent with direct acting agonists/antagonists (Wang, et al., 2009). Group I mGluR NAMs have recently been used in rodent models of addiction. The mGluR5 NAM 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) decreases self-administration of Meth, as well as cue- and Meth-primed reinstatement of Meth self-administration (Gass, et al., 2009; Osborne and Olive, 2008). Likewise, the related mGluR5 NAM, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), reduces the development and expression of Meth- and amphetamine-induced associative learning, respectively (Miyatake, et al., 2005; Herzig, et al., 2005). The mGluR1 NAM, JNJ16259685, decreases ethanol self-administration (Besheer, et al., 2008) and another mGluR1 NAM, EMQMCM, reduces cue- and drug-induced reinstatement of nicotine self-administration in rodents (Dravolina, et al., 2007). While negative modulation of mGluR1 or mGluR5 decreases reward-mediated behaviors, these receptor subtypes may play different roles in acquisition, consolidation and retention of memory (Steckler, et al., 2005b; Simonyi, et al., 2007; Salinska, 2006). For example, the mGluR1 receptor is important for the acquisition, while the mGluR5 receptor may be more critical for the retention or maintenance, of spatial memories (Steckler, et al., 2005b). What

remains unknown is the role of these receptors, and potential subtype-specific effects, in the maintenance of stimulant-associated memories.

The maintenance of drug memories underlies relapse; therefore, a better understanding of the role of group I mGluRs in this relationship may aid relapse reduction. We hypothesize that post-conditioning administration of mGluR5 NAMs will disrupt the memory maintenance of a positive association between Meth and context cues in a CPP task. We chose to administer the NAMs 13 and 14 days post-conditioning, based on the following: (i) this is a time frame when extracellular limbic glutamate is increased in the VP following amphetamine (Chen, et al., 2001), (ii) glutamate levels are also elevated in the mPFC following a treatment course of Meth similar to the one used in the current study (Qi, et al., 2009) likely enhancing glutamatergic overflow from the mPFC to the VP, (iii) we observed neuronal changes in the VP at this time subsequent to repeated Meth administration (McDaid, et al., 2006), and (iv) glutamate receptors are up-regulated in the mPFC and NAc following extended withdrawal from repeated cocaine administration (Ghasemzadeh, et al., 2009a; Ghasemzadeh, et al., 2009b). Comparison between the mGluR1 and mGluR5 NAMs will allow us to differentiate between the involvements of the mGluR subtypes in this Meth-mediated behavior.

Experimental Procedures

Ninety-four male, 225–250g, Sprague-Dawley rats were treated in accordance with NIH Guide for the care and use of laboratory animals and the Rush University Institutional Animal Care and Use Committee. Rats were allowed to habituate to the environmentally controlled *vivarium* (23–25°C; 7AM/7PM light dark cycle) at least one week prior to the start of behavioral testing and given food and water *ad libitum*. All studies were conducted during the light phase.

(+)Methamphetamine hydrochloride (Meth, Sigma-Aldrich, St. Louis, MO) in 0.9% NaCl sterile saline was given at a dose of 1mg/kg as the base. Our lab has demonstrated that this dosing regimen of Meth produces robust, persistent CPP (Voigt, et al., 2011; Herrold, et al., 2011). The doses of JNJ1625985 (Tocris Bioscience, Ellisville, MO), MTEP (3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine, Tocris Bioscience), and MPEP (2-methyl-6-(phenyl-ethynyl)-pyridine, a gift from Novartis Institutes for BioMedical Research; Basel, Switzerland) were selected based on the following literature demonstrating brain receptor occupancy, receptor selectivity, and specific behavioral outcomes. The mGluR1 NAM, JNJ16259685 doses 0.3 and 3mg/kg are in within the range of maximum receptor occupancy in the brain following subcutaneous administration and JNJ16259685 has no affinity for AMPA or NMDA receptors, ion channels or transporters (Lavreysen, et al., 2004). Behaviorally, 0.3mg/kg JNJ16259685 reduces ethanol self-administration without reducing the self-administration of natural reinforcers (Besheer, et al., 2008) and 3mg/kg reduces anxiety in rats (Steckler, et al., 2005a). *In vivo* occupancy of mGluR5 receptors by MTEP and MPEP reveals that in the rat brain, receptors are >75% occupied at 3mg/kg MTEP and 10mg/kg MPEP when administered i.p. (Anderson, et al., 2003). MTEP is selective for the mGluR5 compared to mGluR1 and NMDAR (100 and 300 times, respectively) (Cosford, et al., 2003). Behaviorally, 3mg/kg MTEP reduces Meth self-administration (Osborne and Olive, 2008) as well as cue- and drug-induced reinstatement of Meth self-administration without affecting food self-administration (Gass, et al., 2009). MPEP is less potent than MTEP at the mGluR5 receptor but still retains selectivity for the mGluR5 receptor compared to mGluR1 and NMDAR (100 and 10 times more selective, respectively) (Anderson, et al., 2002; Cosford, et al., 2003). Behaviorally, 30mg/kg MPEP reduces the development and expression of morphine-induced CPP (Herzig and Schmidt, 2004) and 50mg/kg, MPEP reduces the expression of amphetamine, but not food,-induced CPP (Herzig, et al., 2005).

All NAMs were dissolved in 10% w/v (2-hydroxypropyl)- γ -cyclodextrin in sterile water solution (termed vehicle, Sigma-Aldrich). All drugs and their vehicles were given *via* intraperitoneal (i.p.) injection in a volume of 1ml/kg.

CPP boxes (Accuscan Instruments, Inc., Columbus, OH) used for the study are described in a previous publication from our laboratory (Voigt, et al., 2011). Briefly, the CPP boxes consisted of two large chambers with distinct, neutral cues separated by sliding Plexiglas doors from a smaller center chamber with a smooth white floor and white sides. Rats were transported to the behavioral testing room at least 30min prior to experimentation. Timeline of the behavioral paradigm is illustrated in Figure 1A. All rats were given a pre-test and as a group, the rats had no significant preference for either chamber (see Results); however, for conditioning, the individual rats were paired with Meth in the chamber in which they spent the least amount of time during the pre-test. Rats were treated with Meth on days 1, 3, and 5, and saline on days 2, 4, and 6 then immediately placed in the appropriate chamber for 45min. A previous report from our laboratory using the same CPP boxes, number of pairings, and Meth dose illustrates that the order of Meth *vs.* saline pairings does not impact CPP (Voigt, et al., 2011). On day 9, untreated rats were tested for chamber preference (CPP Test 1) as in the pre-test. Similar to procedures employed by Paolone and colleagues, (Paolone, et al., 2009), if the difference between pre-test and CPP Test 1 was at least a 10% (>180s), the rats were used for assessing the effects NAMs. This assured a sufficient 'signal' was used to ascertain the antagonism capacity of mGluR1/5 NAMs (70 out of 94 rats met this criterion). On days 10–17, all rats were given once daily vehicle (1ml/kg) injections in their home cage. On days 18 and 19, rats were given in their home cage, a once-daily injection of either vehicle (1ml/kg), JNJ16259685 (0.3mg/kg or 3mg/kg), MTEP (3mg/kg), or MPEP (30mg/kg). On day 22, untreated rats were tested for preference (CPP Test 2) as described previously for CPP Test 1. This delay was imposed to allow for NAMs to be washed out of the system and the behavioral response to be evaluated independent of any direct effects these drugs may have on the system.

Rats were assigned to treatment group based on performance on CPP Test 1. Differences in time spent per chamber between pre-test and CPP Test 1 was determined *via* a paired *t*-test. Preference was determined based on a significant increase in amount of time spent on the Meth- *vs.* saline-paired chamber on CPP Test 1 and 2 *via* a two-way repeated measure (rm) ANOVA with *post hoc* Newman Keuls test. $\alpha=0.05$ for all tests. Statistical outliers for time spent in any of the three chambers during CPP Tests 1 or 2 were removed if data fell outside two standard deviations from the mean. Data are represented as the mean $\pm$ standard error of the mean (SEM).

Results

The time spent in the two large chambers for all rats was not different during the pre-test (749.8 $\pm$ 44.4sec *vs.* 787.5 $\pm$ 38.3sec; $t_{(93)}=0.490$, $p=0.625$). Three days after conditioning, rats demonstrated a preference for the Meth- (961.3 $\pm$ 30.0sec) *vs.* the saline-paired chamber (662.3 $\pm$ 29.6sec, $t_{(93)}=5.042$, $p<0.0001$). This outcome was validated by a significant difference between the amount of time spent in the Meth-paired chamber before (pre-test; 476 $\pm$ 23sec) and after Meth-conditioning (CPP Test 1; 961 $\pm$ 30sec; $t_{(93)}=13.14$, $p<0.0001$). Rats overcame any initial chamber bias or potential anxiety for the chamber where they initially spent the least amount of time to demonstrate a preference for the now salient context associated with the rewarding properties of Meth. Rats that showed more than a 10% change in preference on the pretest *vs.* CPP Test 1 ($n=70$), spent 1071 $\pm$ 28.5sec in the Meth-paired chamber and 562.6 $\pm$ 28.2sec in the saline-paired chamber during CPP Test 1 ($t_{(69)}=9.020$, $p<0.0001$).

Rats given post-conditioning vehicle (Fig. 1B, $n=11$; significant effect of chamber $F_{(1,20)}=23.075$, $p=0.0001$, no effect of test $F_{(1,20)}=0.054$, $p=0.818$, and significant interaction $F_{(1,20)}=9.099$, $p=0.007$) or JNJ16259685 at a dose of 0.3mg/kg (Fig. 1C, $n=12$; significant effect of chamber $F_{(1,22)}=95.531$, $p<0.0001$, no effect of test $F_{(1,22)}=0.0002$, $p=0.987$, and no interaction $F_{(1,22)}=0.911$, $p=0.350$) spent significantly more time in the Meth- vs. saline-paired chamber on both CPP Test 1 and 2. To further validate that the mGluR1 NAM had no effect on the maintenance of Meth-induced CPP, another group of rats were tested and given a higher dose of the mGluR1 NAM. Rats given 3mg/kg of JNJ16259685 spent significantly more time in the Meth- vs. saline-paired chamber on both CPP Test 1 and 2 (Fig. 1D, $n=12$; significant effect of chamber $F_{(1,22)}=35.743$, $p<0.0001$, no effect of test $F_{(1,22)}=0.094$, $p=0.762$, and a significant interaction $F_{(1,22)}=4.816$, $p=0.039$). Thus, the conditioning protocol induced place preference that persisted for at least 16 days and was not diminished by repeated testing or post-conditioning injections of vehicle or the mGluR1 NAM. However, rats treated on days 18 and 19 with the mGluR5 NAMs, MTEP (Fig. 1E, $n=15$; significant effect of chamber $F_{(1,28)}=14.686$, $p=0.001$, no effect of test $F_{(1,28)}=0.088$, $p=0.769$, and significant interaction $F_{(1,28)}=7.048$, $p=0.013$) or MPEP (Fig. 1F, $n=9$; significant effect of chamber $F_{(1,16)}=22.785$, $p=0.0002$, no effect of test $F_{(1,16)}=0.024$, $p=0.879$, and a significant interaction $F_{(1,16)}=14.930$, $p=0.001$), failed to maintain a preference for the Meth-paired chamber on CPP Test 2 (two-way rmANOVA, $p>0.05$). There was a between group difference ($F_{(4)}=2.616$, $p=0.045$) on CPP Test 2 in horizontal beam breaks (vehicle 3800 ± 262 , JNJ16259685 0.3mg/kg 3250 ± 219 , JNJ16259685 3 mg/kg 2936 ± 134 , MTEP 3640 ± 242 , and MPEP 3086 ± 291) but no difference was found with a *post hoc* Newman Keuls test for multiple comparisons. There was no between group difference ($F_{(4)}=1.352$, $p=0.262$) in vertical beam breaks (vehicle 693 ± 82 , JNJ16259685 0.3mg/kg 607 ± 61 , JNJ16259685 3 mg/kg 522 ± 56 , MTEP 545 ± 38 , MPEP 523 ± 74). These data indicate that mGluR1/5 NAM treatment history did not affect spontaneous motor activity on the subsequent CPP test day.

Discussion

Previous studies demonstrate the importance of mGluR1 and 5 in drug-mediated behaviors. For example, mGluR5 positive allosteric modulators facilitate the *extinction* of cocaine-induced CPP (Gass and Olive, 2009); however, our work is the first to determine the role of mGluR5 in the *maintenance* of Meth-induced CPP. Acquisition of spatial learning is impaired by administration of JNJ16259685 prior to training on the Morris water maze (Steckler, et al., 2005b). Yet, mGluR1 NAM treatment after training on the Morris water maze only partially impairs performance on a subsequent test of spatial memory retention (Steckler, et al., 2005b). Retention of passive avoidance learning is also spared following mGluR1 NAM treatment (Gravius, et al., 2005). Though mGluR1 is important for drug reinforcement behaviors, it may not be as critical for the maintenance of spatial memories which play a role in CPP behavior. The current study provided the first evaluation of mGluR1 NAMs on previously acquired drugcontext associations induced by repeated Meth administration. In this paradigm, the mGluR1 NAM JNJ16259685 did not alter subsequent expression of place preference. This outcome may reflect the delayed post-conditioning time of the NAM administration, and it is possible that its administration earlier after place conditioning might result in a disruption of the drug-context association. Supporting this possibility, mGluR1 NAM administration 3 days after repeated cocaine blunted the expression of cocaine-induced motor sensitization (Dravolina, et al., 2006).

Our results suggest that activation of mGluR5 at 13–14 days post-conditioning is necessary for the maintenance of Meth-induced CPP, as rats that were treated with the mGluR5 NAMs MTEP or MPEP failed to demonstrate preference for the Meth-paired context. The positive outcomes from two different mGluR5 NAMs, MTEP and MPEP, and the negative outcomes

with both 0.3 and 3mg/kg doses of the mGluR1 NAM, JNJ16259685, converge to indicate that this may be an mGluR5-specific phenomenon. The post-conditioning time of mGluR5 modulation may also be important, for, pilot data from our lab suggest that an early post-conditioning administration (2 and 3 days after Meth injection) of MPEP does not alter subsequent expression of Meth-induced CPP (i.e., CPP remained statistically significant ($t_{(11)}=3.292$, $p=0.007$) when tested one day after two daily home cage injections of MPEP (30mg/kg, i.p.). However, in Meth self-administering rats that have undergone extinction training, MTEP pre-treatment reduces cue-induced reinstatement (Gass, et al., 2009). Thus, mGluR5 appear to be important for several aspects of Meth reward-mediated behaviors (CPP and self-administration) as well as multiple phases of Meth-induced associative learning (expression and maintenance).

Based on mGluR5 distribution within the rodent brain (Romano, et al., 1995) as well as stimulant-induced effects on glutamatergic signaling allows us to hypothesize that brain regions such as the NAc and VP, may be key mediators in our observed behavioral effects. The NAc is an essential brain region for cue- and Meth-induced reinstatement of drug seeking (Rocha and Kalivas, 2010) which demonstrates enhanced immediate early gene, *c-fos*, activation in response to Meth-associated cues (Rhodes, et al., 2005). NAMs exert functional effects on agonist-bound receptors, and while the literature on glutamate transmitter effects subsequent to Meth administration is limited, increases in NAc basal glutamate have been shown to occur 3 weeks after repeated Meth (Lominac and Szumlinski, 2008). Thus, mGluR5 NAMs administered during the late maintenance period in the current study may have blunted an enhanced glutamatergic transmission leading to a decreased expression of Meth-induced CPP. Another brain substrate that may be involved is the VP, since 14 days after repeated amphetamine, an acute challenge of the drug in the VP increases VP glutamate (Chen, et al., 2001). The VP serves as an important structure for encoding the salience of drug reward cues (Tindell, et al., 2005) and the integration of neuronal signaling to produce motivated motor behavior (Mogenson and Yang, 1991). Our laboratory has shown that cessation from repeated treatment of cocaine results in enhanced response of VP neurons to glutamate (McDaid, et al., 2005), and an up-regulation of mGluR5 expression in the VP 14 days after Meth administration (unpublished results). Thus, administration of mGluR5 NAMs during this time frame may have blunted the enhanced neuronal response in the VP. Future studies, will be necessary to determine the relative contribution of specific brain regions (i.e., NAc vs. VP) in the current behavioral outcomes; however, the current study suggests that mGluR5 system occurred approximately two weeks after the acquisition of Meth-induced associative learning.

The current study provides an important step towards determining the effects of Group I mGluR ligands on the maintenance of stimulant-induced memories. Though, previous studies have determined that the mGluR1/5 ligands used in the current study failed to alter reward-mediated behaviors, including CPP induced by natural rewards (Besheer, et al., 2008; Herzog, et al., 2005; Gass, et al., 2009), it is not known whether these ligands influence the maintenance of CPP. Our findings reveal that mGluR5 is necessary for the *maintenance of CPP that was induced by the psychostimulant, Meth*. Therefore, our study results are selective to the role of mGluR5 specifically in the maintenance of Meth-induced CPP and cannot be generalized to natural rewards. Directions for further characterization of this important and clinically relevant area of research may include the determination of the effect of the mGluR1 NAM JNJ16259685 given earlier in the maintenance period, or for a longer period of time during the maintenance period, and the effects of mGluR1/5 NAMs on the maintenance of CPP induced by other stimulants such as cocaine and nicotine.

Cue-elicited relapse is a significant obstacle to abstinence for Meth addicts (Hartz, et al., 2001); thus, a pharmacotherapy that can inhibit the maintenance of associative processes

should aid in reducing cue evoked drug-seeking. This study has identified a critical time-frame at which negative modulation of mGluR5 receptors is sufficient to disrupt the maintenance of Meth-induced context associations. These novel findings add to current understanding of the neurobiological underpinnings of Meth-associated memories and indicate that mGluR5 NAMs deserve further exploration as potential pharmacotherapy for the Meth-withdrawn human addict.

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Figure 1. The mGluR5 NAMs MTEP and MPEP, but not the mGluR1 NAM JNJ1625985, inhibit the expression of Meth-CPP

A) Timeline of treatment and testing. Ø, no treatment; M, methamphetamine (1mg/kg, i.p.); S, saline (1ml/kg, i.p.); V, vehicle (1ml/kg, i.p.). **B)** Rats treated with vehicle (n=11), **C)** JNJ16259685 at 0.3mg/kg (n=12), or **D)** JNJ16259685 at 3mg/kg (n=12) demonstrated a significant difference in amount of time spent in the Meth- vs. saline-paired chamber during CPP Test 1 and 2. **D)** Rats treated with the mGluR5 NAM MTEP (n=15) demonstrated a significant preference for the Meth-paired chamber during CPP Test 1, but the preference was not observed during CPP Test 2. **E)** Rats treated with MPEP (n=9) did not maintain the significant preference for the Meth-paired chamber after days 17 and 18 intervening NAM

treatments. Data represent mean $\pm$ SEM. Repeated measure ANOVA with *post-hoc* Newman Keuls test for multiple comparisons, ** $p < 0.01$