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Effect of novel allosteric modulators of metabotropic glutamate receptors on drug self-administration and relapse: a review of preclinical studies and their clinical implications

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Abstract

Results from preclinical rodent studies during the last 20 years have implicated glutamate neurotransmission in different brain regions in drug self-administration and rodent models of relapse. These results, along with evidence for drug-induced neuroadaptations in glutamatergic neurons and receptors, suggest that addiction might be treatable by medications that inhibit glutamatergic responses to drugs of abuse, drug-associated cues, and stressors. This idea is supported by findings that drug self-administration and relapse, in rodent and primate models, are reduced by systemic injections of antagonists of ionotropic glutamate receptors or metabotropic glutamate receptors (mGluRs) or orthosteric agonists of mGluR2/3 receptors. However, these compounds have not advanced to clinical use because of potential side effects and other factors. This state-of-affairs has led to the development of positive and negative allosteric modulators (PAMs and NAMs) of mGluRs. PAMs and NAMs of mGluRs, either of which can inhibit evoked glutamate release, may be suitable for testing in humans. Here, we review results from recent studies of systemically injected PAMs and NAMs of mGluRs in rodents and monkeys, focusing on whether they reduce drug self-administration, reinstatement of drug seeking, and incubation of drug craving. We also review results from rat studies in which PAMs or NAMs of mGluRs were injected intracranially to reduce drug self-administration and reinstatement. We conclude that PAMs and NAMs of mGluRs should be considered for clinical trials.

Keywords

Glutamate; positive and negative allosteric modulators; PAMs and NAMs; addiction; relapse; self-administration

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Introduction

In 1989, Karler et al. (1) published a paper entitled *Blockade of “reverse tolerance” to cocaine and amphetamine by MK-801.* They reported that, in mice, daily pretreatment with the NMDA receptor antagonist MK-801 prior to daily amphetamine or cocaine injections prevents development of locomotor sensitization. They also reported that, in rats, MK-801 pretreatment prevents development of sensitization to cocaine-induced stereotypy and convulsions. Those and similar findings (2–4) inspired many studies during the 1990s on glutamate’s role in regions of the *mesocorticolimbic dopamine system* (Supplementary Online Material Box S1 glossary of terms) in the development and expression of *psychomotor sensitization* to psychostimulants and opioids (5–7).

The next major development in that line of research was studies by groups led by Kalivas and Pierce in the late 1990s-early 2000s (8, 9). In these studies, site-specific injections of ionotropic AMPA and NMDA receptor agonists and antagonists were combined with *in vivo* microdialysis to demonstrate a role of glutamate transmission in drug-priming-induced *relapse* to cocaine-seeking (9–13), as assessed in the *reinstatement model* (14). The sites implicated were ventral tegmental area (VTA), medial prefrontal cortex (mPFC), and nucleus accumbens (NAc). During this time, the Everitt group also showed a role for glutamate in NAc in cue-induced cocaine seeking, using a second-order reinforcement schedule (15, 16). These and other studies in the 1990s-early 2000s, showing that exposure to psychostimulants and opioids affected glutamate-mediated *neuroadaptations* and *synaptic plasticity* within VTA and NAc (5, 17–22), led to many publications showing that pharmacological targeting of ionotropic and metabotropic glutamate receptors decreases *drug self-administration*, reinstatement of drug seeking, and *incubation of drug craving* (23–29). These studies suggest that behavioral aspects of addiction are mediated by drug-induced neuroadaptations and synaptic plasticity at glutamatergic neurons and receptors in the mesocorticolimbic dopamine system. It is beyond the scope of this review to cover this extensive literature; we refer readers to reviews (18, 25, 26, 30, 31).

Here, we review preclinical studies on inhibition of drug self-administration and relapse by a newer type of glutamatergic drugs called *positive and negative allosteric modulators* (PAMs and NAMs) of mGluRs (32, 33) (Fig. 1). Allosteric modulators bind to mGluRs within the heptahelical transmembrane domain, in contrast to orthosteric ligands, which bind within the extracellular N-terminal region. Allosteric modulators induce conformational changes within receptors’ protein structure, which modify the receptors’ interactions with *orthosteric* ligands and/or recruitment of downstream effector systems. NAMs indirectly decrease activation of mGluRs by glutamate, while PAMs indirectly increase it. The effect of glutamate on mGluRs occupied by allosteric modulators depend on chemical and physical properties of the allosteric modulator and surrounding cellular environment (32) (Fig. 1C; Box S1).

Allosteric ligands are preferable to orthosteric ligands for several reasons, including: (1) higher selectivity for mGluRs’ subtypes, (2) greater structural diversity, (3) pharmacological action within normal physiological range, (4) minimal pure-agonist-like activity, (5) fewer adverse effects associated with receptor sensitization or desensitization, and (6) favorable

pharmacokinetic profiles (34–36). Our review is limited to rodent and nonhuman-primate studies on the effects of systemic (Table 1) and intracranial injections (Table 2 and Fig. 2) of mGluR PAMs and NAMs on drug self-administration, reinstatement of drug seeking after *extinction* of the drug-reinforced responding, and incubation of drug craving. The drugs used in the reviewed studies are nicotine, methamphetamine, cocaine, and alcohol. Due to space limitations, we do not discuss data on psychomotor sensitization, conditioned place preference (CPP), drug discrimination, or homecage alcohol-drinking. In Box 1 we provide a glossary of terms (*italic font*).

Review of neuropharmacological studies using PAMs and NAMs of mGluRs

There are 8 subtypes of mGluRs, more broadly classified into three groups. Selective PAMs and NAMs have been developed for these subtypes; we discuss each in turn.

Group I metabotropic glutamate receptors

Group I mGluRs includes mGluR1 and mGluR5 (Fig. 1). Both of those subtypes are coupled to $G\alpha_q/11$ and are predominantly postsynaptic (37). They have overlapping but distinct anatomical distributions in the brain (38). Both have been extensively studied in terms of behavioral effects of PAMs or NAMs in animal models of drug addiction (29, 39, 40).

mGluR1

Drug self-administration

NAMs of mGluR1 were found to decrease alcohol self-administration in some studies but not others. Two studies used the NAM JNJ16259685 (41) in alcohol-preferring P rats (42) trained to self-administer alcohol versus water on a concurrent fixed-ratio 1 (FR1)-FR1 reinforcement schedule (43, 44). JNJ16259685 injections decreased responding under the FR1 and progressive ratio (PR) schedules (43, 44), but also decreased locomotor activity and lever-pressing for sucrose, suggesting nonspecific motor effects. That interpretation is supported by findings from Schroeder et al. (45) and Hodge et al. (46), neither of whom could detect an effect of the NAM CPCCOEt (47) on alcohol self-administration in P-rats or C57BL/6J mice. In contrast, Lominac et al. (48), using the same mouse strain, found that CPCCOEt injections did decrease alcohol self-administration at doses that do not influence locomotion. The reasons for the different effects of JNJ16259685 (no specific inhibition of alcohol self-administration) versus CPCCOEt (specific inhibition in one study) are unknown and may reflect differences in either their pharmacodynamics or pharmacokinetics.

Finally, results from one study indicate that mGluR1-mediated glutamate transmission contribute to psychostimulant self-administration in monkeys. Achat-Mendes et al. (49) reported that systemic injections of JNJ16259685 decreased cocaine or methamphetamine under a second-order reinforcement schedule of reinforcement (FI5-FR10). At the doses tested, JNJ16259685 had no effect on food-reinforced responding, though it did reduce species-typical locomotion.

Reinstatement

There is consistent evidence that NAMs of mGluR1 decrease reinstatement of drug seeking. For example, Achat-Mendes et al. (49) reported that JNJ16259685 decreases drug-priming-induced reinstatement of cocaine-seeking in monkeys. Two studies showed that intracranial injections of JNJ16259685 decrease context-induced reinstatement of cocaine-seeking after extinction (50, 51). The effective sites were nucleus accumbens (NAc) core (50) or dorsal hippocampus (51), not NAc shell, ventral caudate-putamen, or somatosensory cortex. The effects seem behaviorally specific: JNJ16259685 injections into NAc core or dorsal hippocampus had no effect on extinction responding in the non-drug context, locomotion, or food self-administration. One study showed that intracranial injections of another mGluR1 NAM, YM298198 (52), decreases cocaine-priming-induced reinstatement of cocaine-seeking in rats (53). Again, the NAM was effective when injected into NAc core, not NAc shell, and the effects seemed specific, with no change in sucrose-priming-induced reinstatement of sucrose-seeking.

Finally, one study assessed the effect of the mGluR1 NAM EMQMCM (54) on reinstatement of nicotine-seeking. In rats, EMQMCM injections decreased cue- and nicotine priming-induced reinstatement at doses that have no effect on cue-induced reinstatement of food-seeking (55).

Incubation of drug craving

There is evidence that PAMs of mGluR1 decreases incubation of drug craving. Two studies have documented this with the selective mGluR1 PAM SYN119 (56), using either cocaine or methamphetamine (57, 58). Loweth et al. (57) reported that either acute pretreatment (systemic or into NAc) with SYN119 just prior to a late abstinence (day 45) relapse test or repeated systemic SYN119 injections for 3 weeks during abstinence decreases 'incubated' cocaine-seeking. Scheyer et al. (58) reported that systemic SYN119 injections decrease 'incubated' methamphetamine-seeking after 40+ abstinence days. A mechanistic finding from both studies is that activation of mGluR1 by SYN119 caused mGluR1-mediated synaptic depression, which caused the removal of calcium permeable (CP)-AMPA receptors from NAc synapses; the time-dependent incorporation of high conductance CP-AMPA receptors into NAc synapse is a cellular mechanism critical for incubation of cocaine and methamphetamine craving (26).

Consistent with the PAM findings, Halbout et al. (59) found that incubation of cocaine craving in mice is enhanced by systemic injections of an mGluR1 NAM, A-841720 (60). This enhancement, induced by A-841720 injections during the first 7 days of abstinence from a single day of cocaine self-administration, was observed on abstinence day 43 and was accompanied by suppression of mGluR1 mRNA expression in NAc during both early (day 9) and late abstinence (day 43).

Finally, in rats, Ben-Shahar et al. (61) found that JNJ16259685 had no effect on non-incubated early abstinence (day 3) cocaine-seeking when injected into ventral or dorsal mPFC just prior to a relapse test under extinction conditions. However, one day later, JNJ16259685 injections either prior to or immediately after the relapse (extinction) test

increased resistance to extinction. Additionally, ventral mPFC injections of an mGluR1/5 agonist, MHPG, prior to the relapse test on abstinence day 30, had no effect on drug-seeking on test day, but decreased resistance to extinction on the subsequent relapse (extinction) test a day later. This study suggests that ventral mPFC mGluR1s do not directly modulate the expression of incubation of craving but play a role in extinction learning.

Summary of mGluR1 data

The alcohol studies suggest that under certain conditions inhibition of mGluR1 decreases alcohol self-administration in mice, but not rats. Results from one study in monkeys suggests a role of mGluR1 in cocaine self-administration. The inhibitory effects of NAMs of mGluR1 on reinstatement after extinction are different from results with incubation of cocaine craving, which is inhibited by SYN119 (PAM of mGluR1) and potentiated by A-841720 (NAM of mGluR1). These results suggest that mGluR1s facilitate reinstatement but inhibit incubation. This unexpected discrepancy might be explained by procedural differences: reinstatement studies typically use limited daily drug access, while incubation studies typically use extended daily drug access. Another potential reason is that the mechanisms of reinstatement after extinction are partially different from those that control relapse to drug-seeking after abstinence (62, 63).

mGluR5

In 2001, Chiamulera et al. (64) reported lower cocaine self-administration in mGluR5 knockout mice and in wild-type mice injected with the prototypical NAM of mGluR5, MPEP (65). Since that publication, many studies have shown that MPEP and the similar compound MTEP (66) decrease drug self-administration and reinstatement/relapse across drug classes (29, 39, 40). We will not discuss these studies here due to space limitations and because MPEP and MTEP have significant off-target effects, undergo rapid metabolism, and are not considered candidates for human use (67, 68). Below we discuss results from studies using newer NAMs and PAMs of mGluR5.

Self-administration

There is evidence that NAMs of mGluR5 decrease cocaine self-administration. Amato et al. (69) showed that the selective mGluR5 NAM VU0463841, decreased cocaine self-administration in rats under an FR10 schedule, in the absence of effects on locomotion or CPP. The absence of an effect on CPP helps rule out the possibility that VU0463841 was reducing cocaine self-administration by potentiating its rewarding effects (70). The locomotor findings are more tentative, because unconditioned locomotion in a novel environment is a poor test for ruling out motor-disrupting drugs effects on learned operant response in a familiar environment. For example, high doses of psychostimulants that increase locomotor activity typically disrupt high-rate operant responding for food (71).

Keck et al. (72) showed that another selective NAM of mGluR5, MFZ 10-7 (73), decreased cocaine self-administration in rats under an FR1 schedule. MFZ 10-7 had no effect on locomotion, but decreased sucrose self-administration. Using similar procedures, Keck et al. (67) also assessed the effect of fenobam-sulfate (McN-3377) (74), which had originally been

developed as a nonbenzodiazepine anxiolytic by McNeil Laboratories and was subsequently discovered to be a selective NAM of mGluR5 (75). The effect of fenobam were like those of MFZ 10-7: decreased cocaine and sucrose self-administration without no change in locomotion.

Martinez et al. (76) assessed the effect of the PAM of mGluR5, CDPPB (77) and further assessed the older NAM MPEP. The dependent measure was estradiol-induced increases in cocaine self-administration in ovariectomized female rats. MPEP prevented the estradiol-induced increases, but CDPPB did not mimic them. One interpretation is that in concert with other receptors and signaling mechanisms, mGluR5 plays a modulatory role in estradiol's effect on cocaine self-administration. Another interpretation is that mGluR5 does not play a role and that MPEP's effect is due to actions on other targets, such as NMDAR (78), mGluR4 (79), or norepinephrine transporter (80).

Reinstatement

PAM of mGluR5—There is evidence that PAMs of mGluR5 decrease reinstatement of alcohol or cocaine-seeking. Gass et al. (81) reported that repeated CDPPB injections during operant extinction training (in the absence of the discrete alcohol-associated cue) decrease both resistance to extinction and subsequent cue-induced reinstatement of alcohol-seeking. Perry et al. (82) reported that acute CDPPB treatment a day before reinstatement testing in which rats were exposed non-contingently to cocaine-associated discrete cues after operant extinction in the absence of these cues, decreases subsequent cue-induced reinstatement of cocaine-seeking.

In contrast, Kufahl et al. (83) reported that chronic CDPPB treatment during extinction training after limited (2-h/d) or extended (6-h/d) access methamphetamine self-administration has no effect on cue-induced reinstatement of methamphetamine-seeking. Similarly, Widholm et al. (84) reported that chronic treatment with CDPPB during extinction training in a different non-drug context has no effect on context-induced reinstatement of methamphetamine-seeking.

One study assessed the effect of perirhinal cortex injections of the PAM of mGluR5, DPFE (85), using both the standard cue-induced reinstatement of methamphetamine-seeking procedure and a novel cue-induced relapse test in which rats can lever-press for both the methamphetamine-conditioned cue and a novel cue (86). The authors reported that perirhinal cortex DPFE injections have no effect on cue-induced reinstatement in the standard procedure (87) but decrease this reinstatement when rats were also given an opportunity to lever-press for a novel cue during the reinstatement test. The reasons for the different effects of perirhinal cortex injections of DPFE in the two procedures are unknown.

NAM of mGluR5—Acute injections of fenobam or MFZ 10-7 (73), each a NAM of mGluR5, have been shown to decrease cue- and drug-priming-induced reinstatement of cocaine-seeking in rats (67, 72). Additionally, Watterson et al. (88) reported that fenobam decreases cue- and drug-priming-induced reinstatement of methamphetamine-seeking (as well as cue-induced reinstatement of food-seeking).

Summary

The results from studies on the acute inhibitory effects of newer NAMs of mGluR5 on cocaine self-administration and reinstatement of cocaine-seeking confirm results from previous studies using the classical compounds, MPEP and MTEP (23, 40, 89). Additionally, like the classical compounds (90) the newer compounds decrease sucrose self-administration, suggesting a general role of mGluR5-mediated glutamate transmission in reward-seeking.

The results from recent studies on the inhibitory effect of repeated exposure to PAMs of mGluR5 during extinction training on subsequent cue-induced reinstatement of alcohol and cocaine-seeking supports the notion that activation of mGluR5 promotes extinction learning, which in turn leads to decreased subsequent reinstatement. These findings have implications to cue exposure therapies in the clinic that we will discuss in the next section. Finally, a major conclusion from the studies reviewed is that the inhibitory effect of activation of mGluR5s by PAMs during extinction training on reinstatement of drug-seeking does not appear to generalize to methamphetamine. This is an unexpected finding but dissociations in mechanisms of cocaine versus methamphetamine-seeking have been previously reported for both reinstatement after extinction (91) and incubation of drug craving (92, 93).

Group II metabotropic glutamate receptors

Group II mGluRs include mGluR2 and mGluR3 (Fig. 1). Group II mGluRs are coupled predominantly to $G\alpha_{i/o}$ (94) and are widely distributed throughout the brain (95, 96). mGluR2s are expressed primarily on presynaptic glutamate neurons and their activation leads to decreased evoked glutamate release (94, 97, 98). mGluR3s are expressed primarily on postsynaptic neurons and glia and their physiological function is unknown (94, 95).

The prototypical Group II mGluRs agonist LY379268 (99) decreases reinstatement of drug-seeking induced by exposure to discrete, discriminative, or contextual cues previously associated with self-administration of alcohol (100), heroin (101, 102), cocaine (55, 103), or methamphetamine (104) (for review see ref. (28)). LY379268 also decreases cue-induced and cocaine- or nicotine-priming-induced reinstatement in monkeys (105, 106), self-administration of nicotine or methamphetamine in rats (107, 108), and incubation of cocaine craving in rats (109). Below we discuss results from studies on the effects of recently developed mGluR2 PAMs.

Self-administration

There is evidence that PAMs of mGluR2 decrease drug self-administration. Jin et al. (110) showed that the selective mGluR2 PAM BINA (111), decreases cocaine self-administration in rats under both limited- and extended-access training conditions, with no effect on food self-administration. Dhanya et al. (112) developed a selective PAM called compound 14 and showed that it decreases cocaine self-administration in rats under an FR1 schedule; the decrease was selective to cocaine at lower doses of compound 14 and generalized modestly to food self-administration at the highest dose. Sidique et al. (113) developed a selective PAM called compound 2 and showed that it decreases nicotine self-administration in rats

under an FR5 schedule. Dhanya et al. (114) developed a PAM with action at both mGluR2 and mGluR3, compound 74, and showed that it produced only a modest decrease in cocaine self-administration in rats under an FR1 schedule; this was at the highest dose of compound 74 tested, which also decreased food self-administration.

Another selective PAM of mGluR2, AZD8529 (115), has been shown in three studies to decrease nicotine or alcohol self-administration. Justinova et al. (116) reported that AZD8529 decreases nicotine self-administration at doses that have no effect on food self-administration in squirrel monkeys. Similarly, Li et al. (117) reported that acute injections of AZD8529 or its derivative compound AZD8418, decreases nicotine but not food self-administration in rats. In the same study, chronic administration of AZD8529 decreased nicotine self-administration throughout the 14 treatment days, confirming the results of Justinova et al. (116) in monkeys. However, unlike the monkey study, Li et al. (117) reported that chronic treatment with either PAMs decreases food self-administration. The reasons for this dissociation are unknown but may be due to species differences or the route of AZD8529 administration. In a third study, Augier et al. (118) reported that in rats AZD8529 decreases alcohol self-administration at doses that have no effect on saccharin self-administration or locomotion.

Reinstatement

There is evidence that PAMs of mGluR2 decrease reinstatement of drug-seeking after extinction. Jin et al. (110) reported that BINA injections decrease cue-induced reinstatement of cocaine-seeking after limited- or extended-access cocaine self-administration training without affecting reinstatement of food-seeking. Justinova et al. (116) reported that subchronic treatment with AZD8529 decreases drug-priming- and cue-induced reinstatement of nicotine-seeking after extinction in monkeys. Similarly, Li et al. (117) reported that acute or subchronic treatment with AZD8529 or acute treatment with its derivative compound AZD8418 decreases cue-induced reinstatement of nicotine-seeking in rats.

Augier et al. (118) reported that AZD8529 decreases cue-induced but not stress-induced reinstatement of alcohol-seeking in rats. In this study, capitalizing on the fact that P-rats do not express functional mGluR2s (119) due to a mutation that disrupts the gene encoding *mGluR2*, the authors established a mechanism for the effect of AZD8529: without functional mGluR2s, P-rats showed no diminution of cue-induced reinstatement of alcohol-seeking when given AZD8529, indicating that AZD8529's effect on reinstatement in rodents and monkeys is mediated by activation of mGluR2s.

Incubation of craving

There is evidence that PAMs of mGluR2 decrease incubation of drug craving in rats. Caprioli et al. (120) showed that AZD8529 injections just prior to the late (day 21) but not early (day 1) forced-abstinence relapse tests decreases methamphetamine-seeking, suggesting a selective effect of AZD8529 on 'incubated' drug-seeking. The authors also developed a rat model of incubation of methamphetamine craving after prolonged voluntary abstinence induced by availability of an alternative reward. In this model, rats given a choice

between palatable food versus methamphetamine or heroin show strong preference for the food and voluntarily abstain from drug self-administration (120–123). This procedure resulted in incubation of methamphetamine craving, and like in the more traditional incubation of craving after forced abstinence, AZD8529 selectively decreased drug-seeking after 21 days of voluntary abstinence but had no effect on non-incubated drug-seeking on day 1 (120).

Summary

AZD8529 and other PAMs of mGluR2 decrease both reinforced drug self-administration and non-reinforced drug-seeking during abstinence (relapse) across drug classes. These results agree with results from studies using the orthosteric mGluR2 agonist LY379268 and related compounds (23, 28, 106, 107). Neither monkeys nor rats appear to develop tolerance to the effect of AZD8529 on nicotine self-administration or reinstatement (116, 117); this is important from a medication-development perspective, because LY379268 (in addition to being nonspecific, as it activates mGluR3s) does produce tolerance (107).

Group III metabotropic glutamate receptors

Group III mGluRs includes mGluR4, mGluR6, mGluR7, and mGluR8 (Fig. 1). They are coupled predominantly to $G_{i/o}$, are typically located presynaptically (94), and are distributed heterogeneously in the brain (124–126), except mGluR6, which is selectively expressed in the retina (127). Studies using the broad-spectrum Group III mGluRs agonist L-AP4 (128) showed that activation of these presynaptic mGluRs inhibits evoked glutamate release (129). Glutamate's affinity to mGluR7 is lower than its affinity to mGluR4 and mGluR8; thus, presynaptic mGluR7s are activated only when glutamate concentrations are high (129). The investigation of group III mGluRs is very limited compared with mGluR groups I and II (130). Below, we discuss results from studies using recently synthesized PAM of mGluR7, AMN082 (131).

Self-administration

Two studies showed that AMN082 decreases drug self-administration. Salling et al. (132) reported that AMN082 injections in mice decrease alcohol self-administration under an FR4 schedule. However, AMN082 also decreased sucrose self-administration and locomotion, suggesting nonspecific motor disruption. Li et al. (133) found that AMN082 injections in rats decrease cocaine-induced enhancement of brain-stimulation reward (BSR) and cocaine self-administration under both fixed-ratio (FR2) and PR reinforcement schedules. These effects seemed selective; there were no accompanying decreases in basal or cocaine-enhanced locomotion or sucrose self-administration. Additionally, cocaine self-administration was decreased by AMN082 injections into NAc or ventral pallidum (VP), but not dorsal striatum (DS). Additionally, AMN082's actions were blocked by NAc or VP co-administration of MMPiP (134), a selective NAM of mGluR7, indicating an important role of local mGluR7 in cocaine self-administration.

Reinstatement

One study showed that AMN082 decreases reinstatement of cocaine-seeking in rats. Li et al. (135) reported that systemic AMN082 injections decrease cocaine priming-induced reinstatement. The decrease could also be elicited by AMN082 injections into NAc or VP, but not DS, and was blocked by local co-administration of MMPIP.

Summary

The limited data from studies using AMN082 indicate a potential role of mGluR7s in cocaine self-administration and reinstatement of cocaine-seeking. In contrast, it has not been established that mGluR7s play a role in alcohol self-administration.

Conclusions and clinical implications

Despite decades of basic and clinical research, FDA-approved medications for psychostimulant addiction do not exist, and there is an unmet need for novel pharmacotherapies to treat nicotine, alcohol, and opioid addiction (136). Glutamatergic medications have been suggested because, in animal models, glutamatergic transmission plays a role in self-administration of several drug classes (23, 29, 137) and plays a particularly important role in reinstatement of drug-seeking and incubation of drug craving (25, 26, 138). Here, we reviewed results from studies on the effect of allosteric modulators of mGluRs on drug self-administration and relapse, as assessed in rodent and non-human primate models. PAMs and NAMs of mGluRs were developed because orthosteric ligands that showed promise in preclinical studies were plagued by lack of selectivity, pharmacokinetic disadvantages, and side-effects that precluded clinical use (28, 68, 139). Allosteric modulation can be more selective because its effects can be limited to receptors occupied by an orthosteric (typically endogenous) ligand; the affinity and/or efficacy of the orthosteric ligand is modified by the binding of an allosteric ligand (139).

The results reviewed indicate a straightforward and consistent effect of PAMs of presynaptic mGluR2 and possibly mGluR7, whose activation leads to inhibition of stimulus-induced evoked synaptic glutamate transmission (94, 129), on drug self-administration, reinstatement, and incubation of drug craving across drug classes (Table 1). These results support the idea that these compounds should be tested as potential medications for addiction treatment (112). Indeed, based on the results of preclinical studies reviewed here, AZD8529 is currently undergoing a clinical trial in smokers (NCT02401022).

In contrast, studies using PAMs and NAMs of post-synaptic mGluR1 and mGluR5 show complicated, time-dependent patterns of effects, often varying across animal models. For example, NAMs of mGluR1 decrease context-, cue- and drug priming-induced reinstatement after extinction (49–51, 53, 55). In contrast, NAM of mGluR1 potentiates incubation of cocaine craving (59), while PAM of mGluR1 decreases incubation of cocaine and methamphetamine craving (57, 58). Additionally, acute pretreatment with NAMs of mGluR5 decreases drug self-administration and reinstatement of drug-seeking (67, 69, 72, 88). In contrast, PAMs of mGluR5, injected during extinction training, decrease resistance to extinction, a putative measure of persistent drug-seeking (27), and also decrease subsequent

cue-induced reinstatement of cocaine- and alcohol-seeking (81, 82). These effects appear to vary across drug of abuse, as well; they were not observed in rats trained to self-administer methamphetamine (83, 84).

These diverse and potentially discrepant effects of allosteric modulators of mGluR1 and mGluR5 make it difficult to predict whether these compounds will increase or decrease human drug use and relapse. One potentially ‘safer’ approach would be to use PAM of mGluR5 as an adjunct to cue-exposure therapy, which decreases drug addicts’ responses to drug-associated cues in the clinic (140). Cue-exposure therapy has the disadvantage of being context-specific (141); most addicts relapse after ‘successful’ cue-exposure therapy in the clinic (142). A question for future research is whether promoting extinction of drug-related cues with PAMs of mGluR5 will overcome this limitation.

Finally, a word of caution: addiction is a complex human condition that is strongly influenced by human-specific cognitive and social factors, many of which cannot be readily modeled in laboratory animals. Thus, converging results across drug classes from a given animal model or even multiple animal models may or may not reliably predict treatment efficacy in humans (143–150). We hope that the preclinical data reviewed here will be useful in guiding choices about allosteric modulators of mGluRs to be tested in clinical trials for addiction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Schematic representation of ionotropic and metabotropic glutamate receptors in neurons and glia

(A) A glutamatergic synapse showing presynaptic and postsynaptic localization of ionotropic and metabotropic glutamatergic receptors (mGluRs). (B) Schematic of a single metabotropic glutamatergic receptor containing seven transmembrane domains, a glutamate binding (orthosteric) site, and an allosteric binding site (one example of a possible location). Intracellularly located G-protein effectors are also shown. (C) The panels show examples of the effects of NAMs and PAMs binding to an allosteric binding site. NAMs (top panel)

inhibit and PAMs (bottom panel) enhance the binding affinity and/or functional efficacy of the orthosteric ligands. The figure was produced, in part, by using Servier Medical Art.

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Brain drawing summarizes the data from intracranial injection studies

Figure 2. Effects of intracranial injections of mGluR allosteric modulators on drug self-administration and relapse

The figure summarizes results from studies on the effects of PAMs and NAMs of mGluRs on drug self-administration, reinstatement of drug-seeking, and incubation of drug craving. Cocaine studies are shown in red and methamphetamine in purple. $\downarrow$ indicates decreased drug taking (self-administration) or drug-seeking (reinstatement or incubation); $\leftrightarrow$ indicates no change. Abbreviations: DS, dorsal striatum; VP, ventral pallidum; NAc, nucleus accumbens; PRh, perirhinal cortex; dHipp, dorsal hippocampus; SSt, somatosensory cortex trunk region; mPFC, medial prefrontal cortex.

Table 1

Effect of systemic administration of allosteric modulators of mGluRs on drug self-administration, reinstatement and incubation of craving procedures.

Group	Receptor	mGluR modulators and dose	Species/sex	Training drug	Self-administration	Reinstatement	Incubation of craving	Reference
Group I	mGluR1	PAM: SYN119 10 mg/kg i.p. (acute/chronic)	Rat (M)	Cocaine	Not tested	Not tested	↓	(57)
		PAM: SYN119 10 mg/kg, i.p. (acute)	Rat (M)	Meth	Not tested	Not tested	↓	(58)
		NAM: CPCCOEt 1–10 mg/kg i.p. (acute)	Rat (M)	Alcohol	↔	Not tested	Not tested	(45)
		NAM: CPCCOEt 1–10 mg/kg i.p. (acute)	Mouse (M)	Alcohol	↔	Not tested	Not tested	(46)
		NAM: CPCCOEt 1–10 mg/kg i.p. (acute)	Mouse (M)	Alcohol	↓	Not tested	Not tested	(48)
		NAM: A-841720 10 mg/kg i.p. (chronic)	Mouse (M)	Cocaine	Not tested	Not tested	↑	(59)
		NAM: EMQMC 2.5–10 mg/kg i.p. (acute)	Rat (M)	Nicotine	Not tested	Priming↓ Cue ↓	Not tested	(55)
		NAM: JNJ-16259685 0.1–0.56 mg/kg i.m. (acute)	Squirrel Monkey (M)	Cocaine Meth	↓	Cocaine Priming↓ Meth (Not tested)	Not tested	(49)
		NAM: JNJ-16259685 0.1–1.0 mg/kg i.p. (acute)	Rat (M)	Alcohol	↓	Not tested	Not tested	(44)
		NAM: JNJ-16259685 0.1–1.0 mg/kg i.p. (acute)	Rat (M)	Alcohol	↓ (break-point)	Not tested	Not tested	(43)
	mGluR5	PAM: CDPBP 10–25 mg/kg, i.p. (chronic)	Rat (F) ovariectomized	Cocaine	↔	Not tested	Not tested	(76)
		PAM: CDPBP 60 mg/kg, i.p. (acute)	Rat (M)	Cocaine	Not tested	Cue ↓	Not tested	(82)
		PAM: CDPBP 30 mg/kg, s.c. (chronic)	Rat (M)	Alcohol	Not tested	Cue ↓	Not tested	(81)
		PAM: CDPBP 30–60 mg/kg, s.c. (chronic)	Rat (M)	Meth	Not tested	Context ↔	Not tested	(84)
		PAM: CDPBP 30 mg/kg, s.c. (chronic)	Rat (M)	Meth	Not tested	Cue ↓ (modest)	Not tested	(83)
Group II	mGluR2	NAM: MFZ 10–7 3–10 mg/kg, i.p. (acute)	Rat (M)	Cocaine	↓	Priming↓ Cue ↓	Not tested	(72)
		NAM: fenobam sulfate 30–60 mg/kg p.o. (acute)	Rat (M)	Cocaine	↓	Priming↓ Cue ↓	Not tested	(67)
		NAM: fenobam 5–15 mg/kg i.p. (acute)	Rat (M)	Meth	Not tested	Priming↓ Cue ↓	Not tested	(88)
Group II	mGluR2	NAM: VU0463841 3.2–32 mg/kg i.p. (acute)	Rat (M)	Cocaine	↓	Not tested	Not tested	(69)
		PAM: BINA 10–40 mg/kg, i.p. (acute)	Rat (M)	Cocaine	↓	Cue ↓	Not tested	(110)

Group	Receptor	mGluR modulators and dose	Species/sex	Training drug	Self-administration	Reinstatement	Incubation of craving	Reference
		PAM: compound 2 10–20 mg/kg, p.o. (acute)	Rat (M)	Nicotine	↓	Not tested	Not tested	(113)
		PAM: compound 14 5–40 mg/kg p.o. (acute)	Rat (M)	Cocaine	↓	Not tested	Not tested	(112)
		PAM: AZD8529 20–40 mg/kg, s.c. (acute)	Rat (M)	Alcohol	↓	Cue ↓ Yohimbine ↓	Not tested	(118)
		PAM: AZD8529 0.3–30 mg/kg, i.m. (acute/chronic)	Squirrel Monkey (M)	Nicotine	↓	Priming ↓ Cue ↓	Not tested	(116)
		PAM: AZD8529 1.75–58 mg/kg, p.o. AZD8418 0.4–14.9 mg/kg, p.o. (acute/chronic)	Rat (M)	Nicotine	↓	Cue ↓	Not tested	(117)
		PAM: AZD8529 20–40 mg/kg, s.c. (acute)	Rat (M)	Meth	Not tested	Not tested	↓	(120)
Group III	mGluR7	PAM: compound 74 10–40 mg/kg, i.p. (acute)	Rat (M)	Cocaine	↓ (modest)	Not tested	Not tested	(114)
		Allosteric agonist: AMN082 1–17 mg/kg, i.p. (acute)	Mice (M)	Alcohol	↓	Not tested	Not tested	(132)
		Allosteric agonist: AMN082 1–20 mg/kg, i.p. (acute)	Rat (M)	Cocaine	↓	Not tested	Not tested	(133)
		Allosteric agonist: AMN082 1–20 mg/kg, i.p. (acute)	Rat (M)	Cocaine	Not tested	Priming ↓	Not tested	(135)

Abbreviations/symbols: ↔, no effect; ↓, decrease; ↑, increase; ↓↑, inconsistent results.

Table 2

Effect of intracranial injections of allosteric modulators of mGluRs on drug self-administration, reinstatement, and incubation of craving procedures.

Group	Receptor/brain area	mGluRs modulators and dose	Species/sex	Training drug	Self-administration	Reinstatement	Incubation of craving	Reference
Group I	mGluR1/ NAc core	PAMs: SYN119 and Ro67-7476 0.005 nmol/side (acute)	Rat (M)	Cocaine	Not tested	Not tested	↓	(57)
	NAc core and shell	NAM: YM298198 5–50 μM (acute)	Rat (M)	Cocaine	Not tested	Priming↓ (NAc core selective)	Not tested	(53)
	mPFC	NAM: JNJ-16259685 30 ng/side (acute)	Rat (M)	Cocaine	Not tested	Cue ↔ (abstinence day3)	Not tested	(61)
	NAc core and shell, dorsal striatum	NAM: JNJ-16259685 0.6–30 pg/side (acute)	Rat (M)	Cocaine	Not tested	Context ↓ (NAc core selective)	Not tested	(50)
	dHipp, Somatosensory cortex	NAM: JNJ-16259685 0.6–120 pg/side (acute)	Rat (M)	Cocaine	Not tested	Context ↓ (dHipp selective)	Not tested	(51)
	mGluR5/ Perirhinal cortex	PAM: DPPE/0.5 μg/side (acute)	Rat (M)	Meth	Not tested	Cue ↔ [§] Novel cue ↓	Not tested	(86)
Group III	mGluR7 NAc shell, VP and dorsal striatum	Allosteric agonist: AMN082 1–5 μg/side (acute)	Rat (M)	Cocaine	↓ (NAc shell and VP selective)	Not tested	Not tested	(133)
	NAc shell, VP and dorsal striatum	Allosteric agonist: AMN082 3–5 μg/side (acute)	Rat (M)	Cocaine	Not tested	Priming↓ (NAc shell and VP selective)	Not tested	(135)

* The cue-relapse index reflects the within-subject choice between meth-cue vs novel-cue

Abbreviations/symbols: ↔, no effect; ↓, decrease; ↑, increase; ↓, increase; ↑, inconsistent results.