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Using metabotropic glutamate receptors to modulate cocaine's synaptic and behavioral effects: mGluR1 finds a niche

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Abstract

Group I metabotropic glutamate receptors (mGluR) are important modulators of excitatory synaptic transmission and therefore potential targets for drug development. In several brain regions (ventral tegmental area, cerebellum, and amygdala), stimulation of mGluR1 selectively inhibits synaptic transmission mediated by calcium-permeable AMPA receptors (CP-AMPA) and thus produces synaptic depression. The same relationship has now been demonstrated in the nucleus accumbens (NAc), a region that is critical for cocaine craving. CP-AMPA levels in NAc synapses are normally low, but they increase after prolonged withdrawal from extended-access cocaine self-administration. These CP-AMPA mediate the intensified (“incubated”) cue-induced cocaine craving observed under these conditions. Therefore, activation of mGluR1 with positive allosteric modulators may reduce cue-induced relapse in abstinent cocaine addicts.

Introduction

The group I metabotropic glutamate receptors (mGluR1 and mGluR5) are predominantly postsynaptic receptors that couple to the G_q-like class of G-proteins and are important in modulating neurotransmission and plasticity through their linkages with multiple signaling pathways as well as NMDA receptors [1]. Compounds that negatively or positively modulate group I mGluRs have been the focus of intense interest due to their potential to tune glutamate transmission up or down in disease states. Drug addiction has been recognized for many years as a disorder involving glutamate transmission and maladaptive plasticity [2,3], so it is not surprising that considerable effort has been directed at evaluating group I mGluR modulators in animal models of addiction [4,5].

This review will focus on group I mGluRs in the nucleus accumbens (NAc) and cocaine addiction. The NAc is a critical brain region for cocaine craving that expresses significant levels of both mGluR1 and mGluR5, mainly in extrasynaptic and perisynaptic regions [6,7,8,9]. While most studies on the role of group I mGluRs in addiction have focused on negative allosteric modulators (NAM) of mGluR5, we will argue that the optimal group I mGluR-based strategy for treating cocaine addiction depends on the nature of cocaine

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exposure which in turn defines the nature of adaptations in the NAc. In particular, emerging evidence reviewed herein suggests that positive allosteric modulators (PAM) of mGluR1 may prevent cue-induced relapse in abstinent cocaine addicts by removing Ca^{2+} -permeable AMPA receptors (CP-AMPA) from NAc synapses.

Negative allosteric modulators of group I mGluRs in animal models of cocaine addiction

The focus on negative modulation of mGluR5 dates from a report in 2001 that mGluR5 knockout mice do not exhibit increased locomotor activity after cocaine injection nor learn to self-administer cocaine [•10]. Subsequent studies extended these findings by showing that mGluR5 NAMs such as MPEP or MTEP prevented the development of cocaine conditioned place preference, reduced motivation to self-administer cocaine in progressive ratio experiments, and reduced reinstatement of cocaine seeking in models of relapse [4,5]. Much less attention has been paid to mGluR1, although a few studies have found that its negative modulation also opposes effects of cocaine exposure. Thus, mGluR1 NAMs reduced context-induced reinstatement of cocaine seeking when infused into the NAc core [11] or dorsal hippocampus [12], while systemic administration of an mGluR1 antagonist blocked the expression of locomotor sensitization to cocaine [13].

CP-AMPA and mGluR1: A unique relationship

AMPA receptors are tetramers comprised of GluA1–4 subunits. In most brain regions of the adult drug-naïve rat, including the NAc [14,15,••16,17], the majority of AMPARs on principal neurons contain the GluA2 subunit. However, there is a minority population that lacks GluA2. Compared to GluA2-containing receptors, this population exhibits Ca^{2+} -permeability, larger single channel conductance and faster kinetics, and voltage-dependent block by intracellular polyamines resulting in inward rectification. These CP-AMPA receptors have emerged as a highly regulated AMPAR subtype that mediates diverse types of neuronal plasticity [18,19,20,21].

There are many forms of group I mGluR-dependent long-term depression (mGluR-LTD), some of which are implicated in disease states [1,22,23]. As described below, when CP-AMPA receptors are present in synapses, stimulation of mGluR1 produces a form of mGluR-LTD that is mediated by CP-AMPA receptor removal. We will review evidence for this form of mGluR1-LTD in the ventral tegmental area (VTA), cerebellum and amygdala before considering mGluR1's role in the NAc.

VTA dopamine neurons

Over 10 years ago it was shown that exposure to cocaine (even a single injection) rapidly increases the AMPA/NMDA ratio at excitatory synapses onto VTA dopamine neurons [24,25]. This occurs because high conductance CP-AMPA receptors are inserted into synapses and lower conductance GluA2-containing Ca^{2+} -impermeable AMPARs (CI-AMPA receptors) are removed [26,••27,28,29]. The insertion of CP-AMPA receptors is accompanied by decreased NMDAR transmission, further contributing to elevation of the AMPA/NMDA ratio [30]. The functional significance of the increased AMPA/NMDA ratio may be related to the fact that CP-AMPA receptor incorporation alters the rules for subsequent induction of LTP [30], although the behavioral correlates of this alteration remain to be worked out [31]. Stimulation of mGluR1 leading to mGluR-LTD reverses this process --- CP-AMPA receptors are removed from synapses and replaced with CI-AMPA receptors through a mechanism that requires locally translated GluA2 [26,••27,28]. Thus, acute mGluR1 stimulation rapidly removes CP-AMPA receptors from VTA synapses. Subsequent *in vivo* studies showed that tonic mGluR1 activation in the VTA limits the duration of cocaine-induced CP-AMPA receptor synaptic

incorporation, helping to restore these synapses to the precocaine state [•32]. A similar mechanism controls the maturation of VTA synapses during development [33].

Cerebellar stellate cells

CP-AMPA receptors are normally present in synapses on cerebellar stellate cells [34,35,••36]. A recent study showed that acute mGluR1 stimulation removes these CP-AMPA receptors and replaces them with GluA2-containing, CI-AMPA receptors. In addition, experiments with mGluR1 antagonists revealed that ongoing mGluR1 tone exerts a suppressive effect on CP-AMPA receptor levels in these synapses [••36]. While this is reminiscent of the VTA, there may be mechanistic differences. Thus, while protein synthesis is required to produce this form of mGluR1-LTD in both brain regions, it is not necessarily due to de novo GluA2 protein synthesis in stellate cells as it is in the VTA [28].

Instead, the increase in CI-AMPA receptors in stellate cells following mGluR1 stimulation may be attributable in part to their lateral movement from extrasynaptic sites [37]. Furthermore, CP-AMPA receptors may be mainly GluA3 homomers in stellate cells [35,38] but GluA1A3 receptors or GluA1 homomers in the VTA [29,39], which could alter the influence of some mechanisms that regulate AMPAR trafficking. Despite these differences, in both cell types mGluR1 activation produces a form of postsynaptically expressed LTD in which high conductance CP-AMPA receptors are removed and replaced by lower conductance CI-AMPA receptors.

Lateral amygdala

A related form of mGluR1-LTD has been implicated in extinction of fear memories [••40]. This study utilized a rodent model in which fear conditioning is produced by pairing an auditory tone (conditioned stimulus) with a footshock. Re-exposure to the conditioned stimulus (i.e., memory retrieval) during a critical interval after conditioning renders the memory labile and therefore vulnerable to erasure via extinction training. This process of memory erasure is termed reconsolidation update. The authors showed that fear conditioning leads to an increase in synaptic CP-AMPA receptor levels in the lateral amygdala that is detectable within hours of conditioning, peaks after 1 day and disappears by 7 days. They hypothesized that the presence of CP-AMPA receptors, by increasing the capacity for synaptic weakening, enables reconsolidation update. Confirming this, memory erasure via reconsolidation update could be elicited when CP-AMPA receptors were present, but not after they had dissipated. Furthermore, it depended on a form of mGluR1-LTD mediated by CP-AMPA receptor removal.

CP-AMPA receptors and mGluR1 in the NAc: regulators of cocaine craving

Our interest in the aforementioned effects of mGluR1 on CP-AMPA receptor transmission arose from our studies in a particular animal model of cocaine addiction called the incubation model. Incubation refers to the progressive intensification of cue-induced cocaine craving that occurs over the first two months of withdrawal from extended-access cocaine self-administration (SA); this reflects very persistent neuroadaptations, because craving remains elevated even 6 months after the last drug exposure [41,42].

In attempting to understand the mechanism of incubation, we evaluated AMPAR transmission in the NAc based on its demonstrated importance for cocaine seeking in other animal models [43,44]. Through a combination of biochemical and electrophysiological studies, we found that CP-AMPA receptor transmission onto NAc medium spiny neurons increases after ~4 weeks of withdrawal from a regimen leading to incubation (6 h/day of cocaine SA for 10 days) [••16,31]. Most importantly, intra-NAc administration of the selective CP-AMPA receptor antagonist naspam blocked the expression of incubated cue-induced cocaine craving on withdrawal day 45, indicating that expression of incubation after prolonged withdrawal is mediated by these CP-AMPA receptors [••16]. We interpret these results to indicate that the

synaptic incorporation of high conductance CP-AMPA receptors increases the ability of medium spiny neurons to respond and engage the motor circuitry when presentation of a cocaine-related cue leads to glutamate release in the NAc. At early withdrawal times prior to CP-AMPA accumulation, adaptations in other brain regions may account for expression of incubation (see 42). Although CP-AMPA receptors accumulate in both core and shell subregions of the NAc during incubation [•16,•32,•45], the core appears critical given that intra-core injection of naspm is sufficient to block incubated cocaine craving [•16].

Our results with naspm suggest that blocking CP-AMPA transmission in the NAc has therapeutic potential in addiction. However, naspm and other CP-AMPA antagonists are not candidates for drug development, necessitating the identification of alternate strategies for reducing CP-AMPA transmission and thereby reducing cocaine craving. Since mGluR1 negatively regulates CP-AMPA receptors in other brain regions (see above), might the same relationship exist in the NAc? As described below, our recent findings indicate that this is indeed the case and identify mGluR1 as a potential therapeutic target for reducing cue-induced relapse in abstinent addicts.

mGluR1 negatively regulates CP-AMPA function in the NAc

In medium spiny neurons of dorsal striatum and NAc, there is a well-studied form of mGluR-LTD that involves mGluR5, postsynaptic endocannabinoid release, and presynaptic attenuation of glutamatergic transmission via CB1R activation [46,47]. To determine if this would change after incubation of cocaine craving and CP-AMPA accumulation, we performed patch-clamp recordings in NAc brain slices from saline SA controls and “incubated rats”. We will use the term “incubated rats” to denote rats that underwent extended-access cocaine SA (6 h/day for 10 days) and >30 days of withdrawal, a period sufficient for CP-AMPA accumulation and robust incubation of cocaine craving [•16,31,48]. As expected from results in drug-naïve animals (above), bath application of the nonselective group I mGluR agonist DHPG in slices from saline SA controls elicited synaptic depression in NAc medium spiny neurons that depended on mGluR5 stimulation and presynaptic CB1Rs. However, in NAc synapses from “incubated rats”, this form of synaptic depression was no longer detected. Instead DHPG-induced synaptic depression was mediated through an mGluR1- and PKC-dependent mechanism that reduces CP-AMPA transmission and simultaneously enhances CI-AMPA transmission, producing a net effect of decreased AMPA transmission at negative potentials [•49]. Although the exact mechanism remains to be identified, we speculate that CP-AMPA receptors are removed from synapses and replaced by CI-AMPA receptors, similar to the “swap” observed in VTA and cerebellum (see above). Regarding the loss of mGluR5-mediated synaptic depression, it should be noted that there are other reports of decreased mGluR5-LTD in the NAc after cocaine exposure [51,52,53,54], but these studies used different cocaine regimens and withdrawal times, so underlying mechanisms may differ.

Overall, these results indicate a dramatic shift in the mechanism of group I mGluR-LTD in the NAc after incubation. In saline-exposed rats, group I mGluR-mediated synaptic depression depends on mGluR5 and is expressed presynaptically. After extended-access cocaine SA and prolonged withdrawal, a postsynaptically-expressed form of synaptic depression emerges that relies on mGluR1 and decreased CP-AMPA transmission (Figure 1). One factor enabling negative modulation of CP-AMPA receptors by mGluR1 may be physical proximity of the two receptors. Biochemical results indicate that CP-AMPA receptors in the NAc are loosely associated with the PSD [48], reminiscent of results in hippocampus and cortex [55], and thus may be perisynaptic. This may place them in close proximity to a perisynaptic subpopulation of mGluR1 that has been detected by electron microscopy in the NAc of drug-naïve rats [•7,•8,9], although mGluR5 also exhibits perisynaptic expression yet does not modulate CP-AMPA receptors.

mGluR1 negatively regulates cocaine craving

Given that CP-AMPA receptors in the NAc mediate the expression of incubated cue-induced cocaine craving [••16], we recently tested the hypothesis that mGluR1 activation, leading to CP-AMPA receptor removal, would reduce cocaine craving in "incubated rats" [JA Loweth et al., abstract in Soc Neurosci Abstr 2012, 669.14]. Indeed, we found that either intra-NAc or systemic delivery of an mGluR1 positive allosteric modulator (PAM) attenuated incubated cocaine craving - in the case of systemic delivery, we further showed that this was associated with decreased CP-AMPA receptor function (Figure 1C). This protective effect endures for ~24 hours after a single systemic PAM injection and for several days after repeated PAM injections. Together, these findings identify mGluR1 as a negative regulator of CP-AMPA receptors in the NAc and point to the potential utility of systemically active mGluR1 PAMs in the treatment of cue-induced cocaine craving and relapse.

Despite the robust effect of mGluR1 activation in NAc medium spiny neurons from "incubated rats", mGluR1 blockade does not affect DHPG-induced synaptic depression in drug-naïve animals [••49]. The simplest explanation is that no mGluR1 effect is detected because these animals express low synaptic levels of CP-AMPA receptors (i.e., a "floor effect"). Nevertheless, mGluR1-mediated regulation of CP-AMPA receptor levels may be "running in the background". In other words, CP-AMPA receptor levels in the NAc of drug-naïve animals may be low because endogenous glutamate, acting on mGluR1 receptors in the NAc, is exerting a tonic braking effect on CP-AMPA receptor synaptic accumulation. Our recent studies suggest that loss of this brake, due to a decrease in mGluR1 surface expression in the NAc during cocaine withdrawal, helps enable CP-AMPA receptor accumulation in "incubated rats" [JA Loweth et al., abstract in Soc Neurosci Abstr 2012, 669.14].

Concluding remarks

As noted in the Introduction, many studies have found that group I mGluRs contribute to behavioral responses to cocaine and that negative modulation of group I mGluRs may therefore be useful in treating addiction [4,5]. Contrary to this literature, our preliminary studies show that mGluR1 *activation* is sufficient to block the NAc CP-AMPA receptor transmission that mediates incubated cue-induced cocaine craving. Thus, after extended-access cocaine SA and prolonged withdrawal (the conditions that lead to incubation and CP-AMPA receptor accumulation [••16,31]), craving may be more effectively reduced by activating mGluR1 than by blocking group I mGluRs. Indeed, none of the animal studies supporting the "blocking" strategy have tested cocaine seeking after extended-access cocaine SA combined with prolonged withdrawal. Instead, animals were studied after non-contingent cocaine injections, limited-access cocaine self-administration, or extended-access cocaine self-administration followed by a brief withdrawal. None of these three conditions are sufficient to increase CP-AMPA receptor levels in the NAc of adult rats [•45, A Purgianto et al., abstract in Soc Neurosci Abstr 2012, 669.12].

Therefore, mGluR1 stimulation would not be predicted to reduce cocaine craving under these conditions. On the other hand, mGluR5 function in the NAc is dramatically altered after extended-access cocaine self-administration [••49,56] but also by other types of cocaine regimens [51,52,53,54]. These results indicate that the particular pattern of cocaine exposure will be an important determinant of the outcome of group I mGluR-based therapeutic strategies.

The above discussion presents a specific example of a more general principle – animal models of cocaine addiction differ widely and are therefore associated with different types of plasticity in the reward circuitry. Each model provides insight into different aspects of addiction and is therefore predictive of therapeutic approaches tailored to those aspects. For

example, the drug N-acetylcysteine normalizes NAc glutamate transmission and behavioral changes observed during the first few weeks of withdrawal from non-contingent or limited-access cocaine self-administration [57], and has shown promise in reducing drug-taking in users who have yet to achieve prolonged abstinence [58,59,60]. In contrast, the incubation model is relevant to heavy cocaine users who undergo a period of forced abstinence, e.g., due to incarceration or hospitalization [61]. Importantly, the cocaine experience required for CP-AMPA accumulation in rat NAc synapses is not extreme (6 h/day×10 days and ~30 days of withdrawal). Thus, if this adaptation occurs in humans, it may be relatively common in users who undergo forced abstinence as described above. When they return to a world full of drug-related cues, accumulated CP-AMPA would mediate enhanced cue-induced craving. Our results suggest that mGluR1 PAMs may help maintain abstinence under these conditions. Furthermore, as discussed in detail elsewhere, PAMs of group I mGluRs may ameliorate cognitive deficits associated with cocaine use [5].

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Highlights

- The review focuses on group I mGluR-based strategies for reducing cocaine craving
- Across brain regions, mGluR1 inhibits Ca^{2+} -permeable AMPAR (CP-AMPA) function
- CP-AMPA receptors accumulate in nucleus accumbens after specific types of cocaine exposure
- Positive allosteric modulators of mGluR1 may reduce craving after such exposure
- Cocaine history and resulting adaptations determine optimal therapeutic strategy

Figure 1. CP-AMPA plasticity in the NAc and its reversal by mGluR1 stimulation

A. In the NAc of drug-naïve animals, group I mGluR activation leads to an mGluR5-dependent, presynaptically-expressed form of synaptic depression mediated by CB1Rs [46,47,49]. **B.** After extended-access cocaine self-administration, cue-induced cocaine craving progressively intensifies (“incubates”) over the first two months of withdrawal, remaining higher than “withdrawal day 1” levels for at least 6 months. Mechanisms underlying the expression of incubated craving during the first several weeks of withdrawal may involve brain regions other than the NAc [41,42]. However, after ~4 weeks of withdrawal, CP-AMPA receptors accumulate in NAc synapses and blocking these receptors in the

NAc core prevents the expression of incubated cocaine craving on withdrawal day 45 [••16]. We speculate that the presence of high conductance CP-AMPA receptors enhances the ability of NAc medium spiny neurons to respond to the glutamate released from cortical and limbic afferents by cocaine-related cues, and thereby enhances cue-induced seeking. Another adaptation observed in the NAc of “incubated rats” is that mGluR5-mediated synaptic depression is disabled (black “X”) [••49]. It should be noted that the situation depicted in this panel is specific to the NAc of rats exposed to extended-access cocaine self-administration and prolonged withdrawal, as adult rats do not exhibit elevated CP-AMPA receptors after non-contingent cocaine [•45] or limited-access cocaine (A Purgianto et al., abstract in Soc Neurosci Abstr 2012, 669.12), even after prolonged withdrawal. **C.** Once CP-AMPA receptors have accumulated in the NAc, group I mGluR activation leads to a postsynaptically-expressed, mGluR1-dependent form of synaptic depression in which CP-AMPA transmission is eliminated (orange “X”) and CI-AMPA transmission is enhanced [••49]. We speculate that this occurs as a result of CP-AMPA receptor removal and CI-AMPA receptor insertion, as demonstrated in the VTA [28]. The removal of high conductance CP-AMPA receptors from NAc synapses is expected to decrease the responsiveness of NAc medium spiny neurons to glutamatergic inputs that are activated by cocaine-associated cues. This in turn should reduce NAc output to motor areas and thereby decrease cocaine seeking. eCB, endocannabinoid.