Brief Communications

Group I mGluR Activation Reverses Cocaine-Induced Accumulation of Calcium-Permeable AMPA Receptors in Nucleus Accumbens Synapses via a Protein Kinase C-Dependent Mechanism

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Following prolonged withdrawal from extended access cocaine self-administration in adult rats, high conductance Ca^{2+}-permeable AMPA receptors (CP-AMPARs) accumulate in nucleus accumbens (NAc) synapses and mediate the expression of "incubated" cue-induced cocaine craving. Using patch-clamp recordings from NAc slices prepared after extended access cocaine self-administration and >45 d of withdrawal, we found that group I metabotropic glutamate receptor (mGluR) stimulation using 3,5-dihydroxyphenylglycine (DHPG; 50 μM) rapidly eliminates the postsynaptic CP-AMPAR contribution to NAc synaptic transmission. This is accompanied by facilitation of Ca^{2+}-impermeable AMPAR (CI-AMPAR)-mediated transmission, suggesting that DHPG may promote an exchange between CP-AMPARs and CI-AMPARs. In saline controls, DHPG also reduced excitatory transmission but this occurred through a CB1 receptor-dependent presynaptic mechanism rather than an effect on postsynaptic AMPARs. Blockade of CB1 receptors had no significant effect on the alterations in AMPAR transmission produced by DHPG in the cocaine group. Interestingly, the effect of DHPG in the cocaine group was mediated by mGluR1 whereas its effect in the saline group was mediated by mGluR5. These results indicate that regulation of synaptic transmission in the NAc is profoundly altered after extended access cocaine self-administration and prolonged withdrawal. Furthermore, they suggest that activation of mGluR1 may represent a potential strategy for reducing cue-induced cocaine craving in abstinent cocaine addicts.

Introduction

Cues previously associated with cocaine availability are powerful triggers for relapse in humans (O'Brien et al., 1992) and for drug seeking in cocaine-experienced rats (Shaham et al., 2003). Cocaine seeking in several rat models of addiction has been found to require AMPA receptor (AMPAR) transmission in the nucleus accumbens (NAc) (Kalivas and Volkow, 2005; Wolf and Ferrario, 2010), which is not surprising given the central role of the NAc in motivated behaviors (Groenewegen et al., 1999; Kelley, 2004) and the fact that AMPARs are the major source of excitatory drive to NAc medium spiny neurons (MSNs) (Pennartz et al., 1990; Hu and White, 1996).

Ca^{2+}-permeable AMPARs (CP-AMPARs), which lack the GluA2 subunit and have higher conductance than GluA2-containing Ca^{2+}-impermeable AMPARs (CI-AMPARs), are increasingly recognized for their important role in many types of synaptic plasticity (Cull-Candy et al., 2006; Isaac et al., 2007; Liu and Zukin, 2007). Whereas CI-AMPARs predominate in the NAc of drug-naive adult rats (Boudreau et al., 2007; Conrad et al., 2008; Reimers et al., 2011), CP-AMPARs accumulate in the NAc after prolonged withdrawal from extended access cocaine self-administration (Conrad et al., 2008; McCutcheon et al., 2011). During the withdrawal period from extended access cocaine self-administration, cue-induced cocaine craving progressively intensifies ("incubates") (Lu et al., 2004). We showed that CP-AMPARs mediate the expression of "incubated" cue-induced cocaine craving on withdrawal day 45 (Conrad et al., 2008).

Given that CP-AMPARs exhibit higher conductance than CI-AMPARs (Cull-Candy et al., 2006), reducing CP-AMPAR function should decrease NAc responsiveness to excitatory inputs and thus reduce craving. Unfortunately, currently available CP-AMPAR blockers are toxins. Thus, there is a need to identify other mechanisms that can be targeted to reduce the heightened excitatory transmission mediated by CP-AMPARs. In the present study, we used

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M.E.W., K.Y.T., and M.M. have no biomedical financial interests but have a patent on *A Possible Therapy For Cue-Induced Cocaine Craving Leading to Relapse in Abstinent Cocaine Abusers Based on Blockade of GluR2-lacking AMPA Receptors in the Nucleus Accumbens.* The other authors report no biomedical financial interests or potential conflicts of interest.

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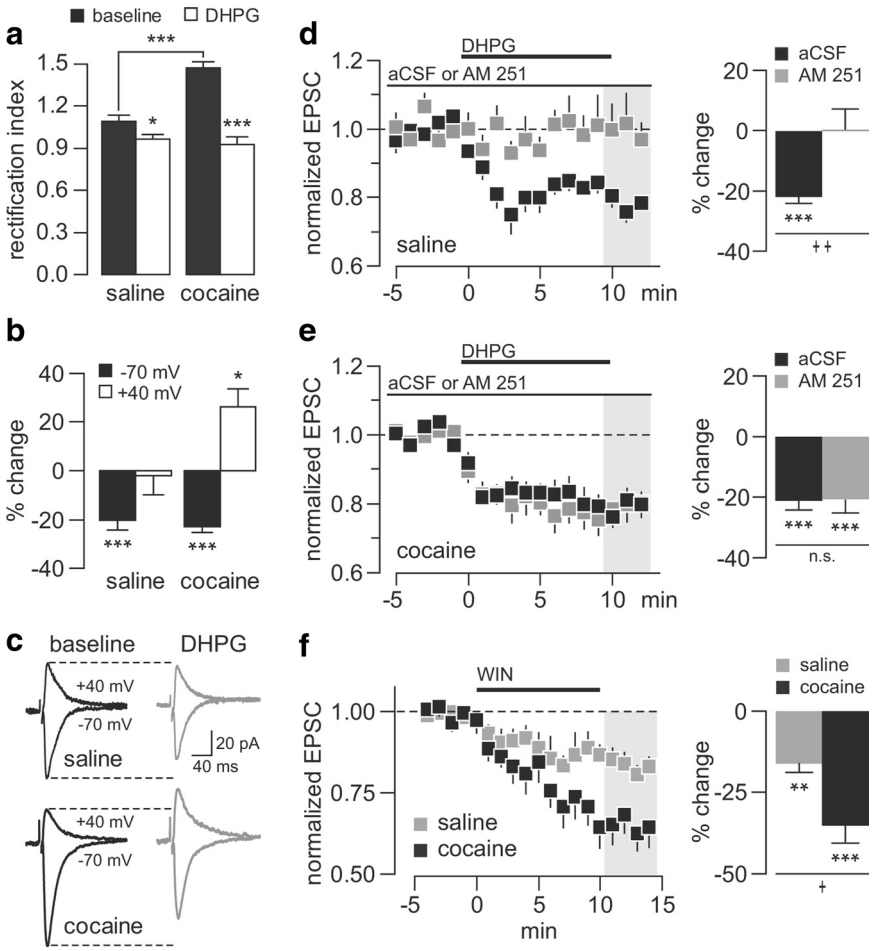

Figure 1. ***a***, RI from NAc MSNs recorded after >45 d of withdrawal from extended access self-administration of saline (controls) or cocaine (incubated rats). RI was determined before and after DHPG (50 μM, 10 min; $n = 10$ cells/7 rats per group). ***b***, Opposite effects of DHPG on $EPSC_{-70\ mV}$ and $EPSC_{+40\ mV}$. ***c***, Traces illustrating the effects of DHPG. ***d***, ***e***, AM-251 blocked DHPG-induced synaptic attenuation at −70 mV in saline controls (***d***, $n = 6$ cells/4 rats) but not in incubated rats (***e***, $n = 6$ cells/4 rats). ***f***, Time course of $EPSC_{-70\ mV}$ amplitude in MSNs recorded from control rats and incubated rats before and after bath application of the CB1R agonist WIN-55,212-2 (WIN; 2 μM, $n = 6$ cells/3 rats per group). *$p < 0.05$, **,++$p < 0.005$, ***$p < 0.0005$ vs baseline or as indicated.

electrophysiological and pharmacological approaches to (1) determine whether activation of group I metabotropic glutamate receptors (mGluR) reduces CP-AMPAR-mediated synaptic transmission in the NAc of "incubated rats" and (2) identify the mechanisms underlying this modulation.

Materials and Methods

All experimental procedures were approved by the Rosalind Franklin University of Medicine and Science Institutional Animal Care and Use Committee.

Cocaine self-administration. Adult male Sprague Dawley rats (250–275 g on arrival; Harlan) were acclimated to the animal facility for at least 1 week before use. They were housed singly and maintained on a 12 h light/dark cycle. All procedures were identical to those in our previous reports (Conrad et al., 2008; McCutcheon et al., 2011). Briefly, rats self-administered cocaine 6 h/d for 10 d in operant chambers (Med Associates). Nose-poking in the active hole delivered an infusion of saline or cocaine (0.5 mg/kg in a 100 μl/kg volume over 3 s), paired with a 30 s light cue inside the nose-poke hole. Nose-poking in the inactive hole had no consequences. After the last training session, rats were returned to their home cages for at least 45 d before electrophysiological recordings were performed.

Electrophysiology. Rats were anesthetized with chloral hydrate (400–600 mg/kg, i.p.), brains were rapidly removed and coronal slices (300 μm) were cut using a vibrating blade microtome (VT1200S; Leica) in ice-cold sucrose-based cutting solution containing the following (in mM): 200 sucrose, 20 glucose, 25 $NaHCO_3$, 2.5 KCl, 1 $CaCl_2$, 2.5 $MgCl_2$, 1 NaH_2PO_4, 10 ascorbic acid. All solutions were constantly oxygenated with 95% O_2-5% CO_2. Slices were held in an incubation chamber containing warm (32–34°C) aCSF containing the following (in mM): 120 NaCl, 20 glucose, 25 $NaHCO_3$, 2.5 KCl, 0.5 $CaCl_2$, 4 $MgCl_2$, 1 NaH_2PO_4, 1 ascorbic acid, 0.05 (2*R*)-amino-5-phosphonopentanoate (APV). For recordings, $CaCl_2$ was increased to 2.5 mM, $MgCl_2$ was reduced to 1 mM and 0.1 mM picrotoxin was added. All recordings were conducted at least 1 h after slicing and the recording chamber was constantly perfused with warm (32−34°C) aCSF. Patch electrodes (6–9 MΩ) were obtained from 1.5 mm borosilicate glass capillaries (World Precision Instruments) with a horizontal puller (P-97, Sutter Instruments) and filled with a cesium-based solution containing 0.1% Neurobiotin (Vector Laboratories) and (in mM): 140 CsCl, 10 HEPES, 2 $MgCl_2$, 5 NaATP, 0.6 NaGTP, 2 QX-314, 0.1 spermine.

NAc medium spiny neurons in the core subregion were identified under visual guidance using infrared (IR)-differential interference contrast video microscopy with a 40× water-immersion objective (Olympus BX51-WI). The image was detected with an IR-sensitive CCD camera and displayed on a monitor. Whole-cell patch-clamp recordings were performed with a computer-controlled amplifier Axopatch 200B and MultiClamp 700B, digitized with Digidata 1322A and 1440, and acquired with Axoscope 10.1 and pClamp 9.2 (Molecular Devices) at a sampling rate of 10 kHz. The liquid junction potential was not corrected and electrode potentials were adjusted to zero before obtaining the whole-cell configuration.

Electrically evoked EPSCs were elicited by local stimulation (0.05–0.15 mA square pulses of 0.3 ms duration delivered every 10–20 s) using a bipolar electrode placed ~300 μm from recording site. The intensity of stimulation was chosen from the minimum amount of current required to elicit a synaptic response with <15% variability in amplitude during the first 10 min of recording. Only neurons that continued to exhibit this synaptic response reliability during the subsequent 15 min of baseline recording were included in the analysis. EPSCs were gathered at −70 mV, +40 mV and at the reversal potential (E_{rev}). The rectification index (RI) for each cell was calculated using the following formula adapted from Kamboj et al. (1995): $RI = [EPSC_{-70\ mV}/(-70 - E_{rev})]/[EPSC_{+40\ mV}/(+40 - E_{rev})]$.

Control and drug-containing aCSF were continuously oxygenated throughout the experiments. All drugs and reagents were purchased from Sigma-Aldrich with four exceptions. The cannabinoid receptor type 1 (CB1R) agonist WIN-55,212-2 mesylate and the CB1R antagonist AM-251 (*N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide) were purchased from Tocris Bioscience. The PKA inhibitor $PKI_{[5-24]}$ peptide and the PKC inhibitor $PKI_{[19-31]}$ peptide were purchased from Calbiochem.

Histology. After completion of the recording session, the slices were fixed with 10% formalin overnight at 4°C and stored in 0.1 M phosphate buffer until staining. After a series of rinses in 0.1 M PBS, slices were incubated in 3% bovine serum albumin and 2% Triton X-100 in PBS for 1 h followed by overnight in Vectastain Elite ABC reagent (Vector Lab-

oratories) at 4°C. Following another series of rinses, slices were reacted with 3,3′-diaminobenzidine and urea-hydrogen peroxide (Sigma FAST DAB set). Slices were then rinsed, mounted on gelatin-coated slides, air-dried for 20 min, cleared in xylene, coverslipped in glycerol, and examined on a microscope.

Statistical analysis. Data are expressed as mean ± SEM. Drug effects were compared using Student's *t* test or repeated-measures ANOVA, and the differences between experimental conditions were considered statistically significant when $p < 0.05$. If data were not normally distributed or had unequal variances, Kruskal–Wallis ANOVA by ranks was used for multiple comparisons involving interrelated proportions. Normality and homogeneity of variances were estimated with the Kolmogorov–Smirnov and Levene's tests, respectively.

Results

Whole-cell patch-clamp recordings of NAc MSNs in the core subregion were conducted in brain slices from adult rats after extended access cocaine or saline self-administration (6 h/d for 10 d), as in our prior studies (Conrad et al., 2008; McCutcheon et al., 2011). All recordings were conducted in slices obtained >45 d after the last self-administration session. At these withdrawal times, rats that self-administered cocaine express significant incubation of cue-induced cocaine craving (Lu et al., 2004; Conrad et al., 2008) and will be referred to hereafter as "incubated rats." The presence of CP-AMPARs was evaluated from the rectification index (RI: ratio of evoked EPSCs recorded at −70 mV and +40 mV; see details in Materials and Methods). In the presence of NMDAR and $GABA_AR$ antagonists, both CP- and CI-AMPARs contribute to EPSCs recorded at the −70 mV holding potential ($EPSC_{-70\,mV}$), whereas only CI-AMPARs are responsible for EPSCs recorded at the +40 mV holding potential ($EPSC_{+40\,mV}$) due to voltage-dependent block of CP-AMPARs by intracellular polyamines (Kamboj et al., 1995; Cull-Candy et al., 2006). Thus, an increase in RI indicates a higher synaptic content of CP-AMPARs.

Consistent with our previous studies (Conrad et al., 2008; McCutcheon et al., 2011), AMPAR RI was significantly higher in incubated rats than in saline controls (Fig. 1*a*). Such an increased AMPAR RI was observed in all MSNs recorded from incubated rats, as we have found previously, suggesting that the accumulation of CP-AMPARs occurs globally, rather than in subpopulations of NAc MSNs. Bath application of the group I mGluR agonist 3,5-dihydroxyphenylglycine (DHPG) (50 μM, 10 min) normalized the abnormally high RI observed in incubated rats (Fig. 1*a*). This was associated with two concurrent events: $EPSC_{+40\,mV}$ facilitation and $EPSC_{-70\,mV}$ attenuation (Fig. 1*b*,*c*). In saline controls, DHPG did not alter $EPSC_{+40\,mV}$ but it did attenuate $EPSC_{-70\,mV}$ (Fig. 1*b*); the latter effect was associated with a facilitation of the paired-pulse ratio (PPR: $EPSC_2/EPSC_1$) from 0.85 ± 0.06 to 1.03 ± 0.08 in all cells tested (+20.15%; $p < 0.005$, paired *t* test; $n = 7$). Bath application of the CB1R antagonist AM-251 completely prevented this inhibition (2 μM; Fig. 1*d*), suggesting that the effect of DHPG in saline controls resembles the well studied striatal mGluR long-term depression that requires postsynaptic endocannabinoid release, presynaptic CB1R activation and reduction of glutamate release (Lovinger, 2008). In contrast, DHPG attenuation of $EPSC_{-70\,mV}$ in MSNs from incubated rats was not associated with a change in the PPR (baseline: 0.86 ± 0.07; DHPG: 0.87 ± 0.08) and was not affected by AM-251 (Fig. 1*e*). However, presynaptic CB1R signaling was intact in incubated rats as revealed by the marked attenuation of $EPSC_{-70\,mV}$ amplitude following bath application of the CB1R agonist WIN-55,212-2 (WIN; 2 μM; Fig. 1*f*). In fact, the magnitude of synaptic inhibition elicited by WIN in incubated rats was significantly larger than that observed in saline controls. Together, these results indicate a different mechanism for DHPG-dependent synaptic depression in incubated rats, an effect likely associated with a disruption of the normal mGluR-endocannabinoid interaction observed in saline controls.

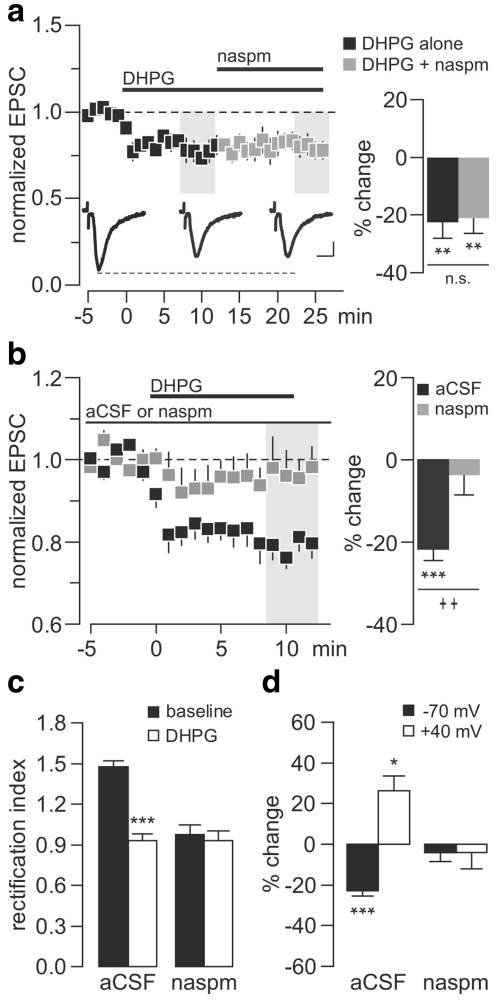

Figure 2. ***a***, In the presence of DHPG, naspm (100 μM; $n = 7$ cells/4 rats) failed to further reduce $EPSC_{-70\,mV}$ amplitude in NAc MSNs recorded from incubated rats. Inset, Traces illustrating these effects (calibration: 40 pA, 10 ms). ***b***, In the presence of naspm, bath application of DHPG ($n = 6$ cells/3 rats) also failed to reduce $EPSC_{-70\,mV}$. ***c***, Similarly, naspm prevented further reduction of RI by DHPG. ***d***, Further analyses indicated that the concurrent effects of DHPG-induced $EPSC_{-70\,mV}$ inhibition and $EPSC_{+40\,mV}$ facilitation were blocked by naspm. $^*p < 0.05$, $^{**,++}p < 0.005$, $^{***}p < 0.0005$ vs baseline or as indicated.

We hypothesized that DHPG-induced synaptic depression in incubated rats involves elimination of CP-AMPAR-mediated transmission, either through removal of CP-AMPARs from NAc synapses or attenuation of their function through other means. We tested this using the CP-AMPAR blocker 1-naphthylacetylspermine (naspm; 100 μM). When applied alone, naspm decreased $EPSC_{-70\,mV}$ by 29.8 ± 3.1% ($p < 0.005$ vs baseline, $n = 5$), which is consistent with our previous study (Conrad et al., 2008). However, once $EPSC_{-70\,mV}$ was reduced by DHPG, subsequent application of naspm had no further effect (Fig. 2*a*). Similarly, when naspm was present before DHPG application, DHPG was unable to produce further $EPSC_{-70\,mV}$ depression (Fig. 2*b*) or further reduce the RI (Fig. 2*c*). Additional analysis demonstrated that naspm also prevented the ability of DHPG to increase $EPSC_{+40\,mV}$

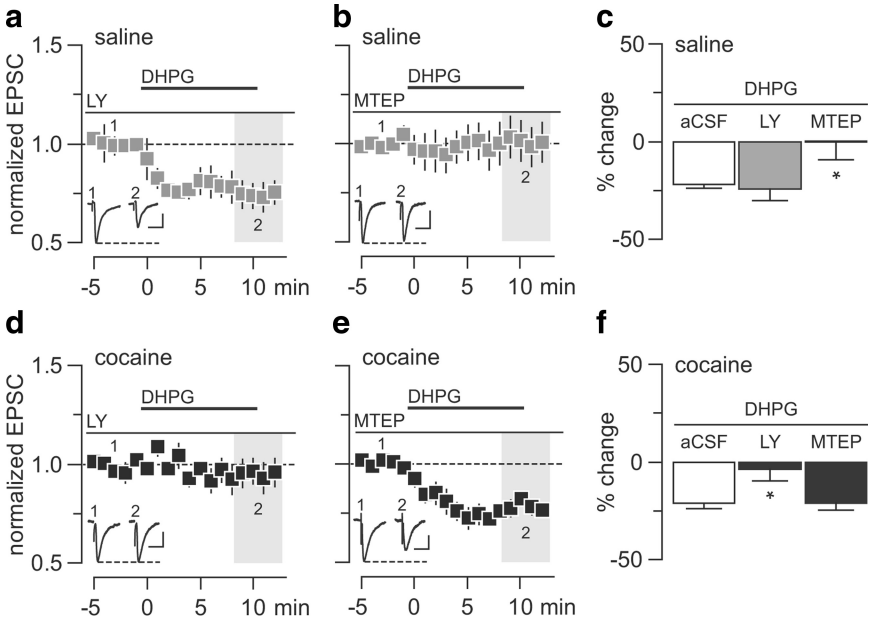

Figure 3. ***a–c***, DHPG-induced attenuation of $EPSC_{-70\ mV}$ in NAc MSNs from saline controls was unaffected by the mGluR1 antagonist LY367385 (50 μM, $n = 7$ cells/3 rats), but completely blocked by the mGluR5 antagonist MTEP (25 μM, $n = 6$ cells/3 rats). ***d–f***, In contrast, bath application of LY367385 (50 μM, $n = 5$ cells/3 rats) was sufficient to prevent the effect of DHPG on MSNs $EPSC_{-70\ mV}$ recorded from incubated rats. No apparent changes on DHPG-induced synaptic attenuation were observed in the presence of MTEP (25–50 μM, $n = 6$ cells/4 rats). $^*p < 0.05$ aCSF vs LY (***c***) or MTEP (***f***). Insets, Example traces of EPSCs recorded before (1) and after (2) bath application of DHPG illustrating the effects shown in ***a***, ***b***, ***d***, and ***e*** (calibration: 50 pA, 30 ms).

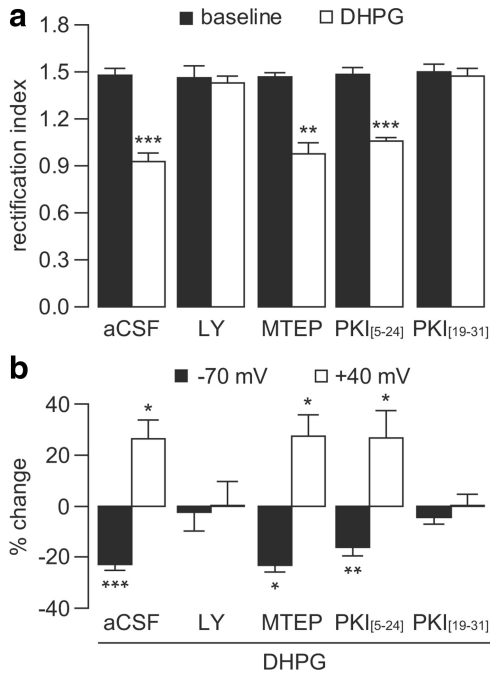

Figure 4. ***a***, DHPG-induced normalization of RI in NAc MSNs from incubated rats was blocked by the mGluR1 antagonist LY367385 (LY; 50 μM, $n = 5$ cells/3 rats) or when patch electrodes contained the PKC inhibitor $PKI_{[19-31]}$ (10 μM, $n = 8$ cells/4 rats). The mGluR5 antagonist MTEP (25–50 μM, $n = 6$ cells/4 rats) and the PKA inhibitor $PKI_{[5-24]}$ (20 μM, $n = 7$ cells/4 rats) failed to block the effect of DHPG on RI. ***b***, The mGluR1 antagonist LY367385 as well as the PKC inhibitor blocked the opposite effects of DHPG on $EPSC_{-70\ mV}$ vs $EPSC_{+40\ mV}$. $^*p < 0.05$, $^{**}p < 0.005$, $^{***}p < 0.0005$ vs baseline.

(Fig. 2*d*). Together, these results indicate that mGluR-induced attenuation of $EPSC_{-70\ mV}$ in incubated rats is expressed postsynaptically via elimination of CP-AMPAR-mediated transmission, and that CP-AMPAR activation at NAc synapses is required for mGluR-dependent potentiation of $EPSC_{+40\ mV}$, which is mediated by CI-AMPARs.

We next investigated the relative contribution of the two group I mGluR subtypes, mGluR1 and mGluR5, in mediating the differential mechanisms by which DHPG attenuates $EPSC_{-70\ mV}$ in MSNs from saline controls versus cocaine-exposed rats. We found that bath application of the mGluR5 antagonist 3-((2-methyl-4-thiazolyl) ethynyl)pyridine (MTEP; 25 μM), not the mGluR1 antagonist LY367385 (50 μM), blocked the effect of DHPG in saline controls (Fig. 3*a–c*). In contrast, DHPG attenuation of $EPSC_{-70\ mV}$ in MSNs from incubated rats was blocked by LY367385, not MTEP (Fig. 3*e–g*). Additional analysis demonstrated that LY367385 (not MTEP) also prevented the ability of DHPG to normalize the RI (Fig. 4*a*) and to increase $EPSC_{+40\ mV}$ (Fig. 4*b*) in MSN from cocaine-exposed rats. Together, these pharmacological results indicate a shift from mGluR5- to mGluR1-dependent regulation of glutamatergic synaptic transmission in the NAc of incubated rats.

We next examined the postsynaptic signaling mechanism that mediates the effects of DHPG. We found that the DHPG-induced normalization of RI in MSNs from incubated rats was blocked when the protein kinase C inhibitor (PKC) $PKI_{[19-31]}$ peptide (10 μM) was included in the recording electrode whereas intracellular administration of the protein kinase A inhibitor $PKI_{[5-24]}$ (20 μM) had no effect (Fig. 4*a*). These results are consistent with the canonical role for postsynaptic Ca^{2+}/PKC-dependent mechanisms in group I mGluR signaling (Kano et al., 2008). Importantly, both of the concurrent events (i.e., $EPSC_{-70\ mV}$ attenuation and $EPSC_{+40\ mV}$ facilitation) associated with the RI-normalizing effect of DHPG in the incubated rats were blocked by postsynaptic inhibition of PKC (Fig. 4*b*). This finding, along with the ability of naspm to block $EPSC_{+40\ mV}$ facilitation by DHPG (Fig. 2*c*), indicates a mechanistic link between DHPG-induced inhibition of CP-AMPAR function and facilitation of CI-AMPAR transmission.

Discussion

Following prolonged withdrawal from extended access cocaine self-administration, high conductance CP-AMPARs accumulate in the NAc of adult rats (Conrad et al., 2008; McCutcheon et al., 2011) and mice (Mameli et al., 2009). Our present study indicates that activation of mGluR1, a group I mGluR, is sufficient to reverse cocaine-induced accumulation of CP-AMPARs in NAc synapses. Specifically, we found that bath application of the group I mGluR agonist DHPG rapidly eliminates the CP-AMPAR component of excitatory transmission in the NAc of incubated rats, an effect that is accompanied by facilitation of CI-AMPAR-mediated excitatory transmission. Both effects are dependent on mGluR1 and postsynaptic PKC activation. In saline controls, however, DHPG does not appear to change postsynaptic AMPAR function but instead attenuates NAc glutamatergic transmission through a pathway requiring mGluR5 activation and a CB1R-dependent presynaptic mechanism. As discussed in more

detail below, these results indicate that, following prolonged withdrawal from extended access cocaine self-administration, a different form of mGluR-dependent synaptic regulation emerges in the NAc that could be exploited to reduce cocaine craving.

Given that synaptically driven Ca^{2+} influx through CP-AMPARs is known to control the targeting of CI-AMPARs (Liu and Cull-Candy, 2000), we interpret DHPG's effects in incubated rats to reflect CP-AMPAR removal ($EPSC_{-70\ mV}$ depression) accompanied by CI-AMPAR insertion ($EPSC_{+40\ mV}$ facilitation). A similar form of synaptic depression at excitatory synapses, involving a switch in AMPAR subunit composition, has been described in dopamine neurons (Bellone and Lüscher, 2005, 2006; Mameli et al., 2007) and cerebellar stellate cells (Kelly et al., 2009) from juvenile rodents. However, our results cannot rule out the possibility that $EPSC_{+40\ mV}$ facilitation is due to a modification of existing CI-AMPARs that enhances their function. While the $EPSC_{-70\ mV}$ depression can also be explained in various ways (CP-AMPAR internalization, CP-AMPAR lateral diffusion out of the synapse, or modification of CP-AMPAR properties), the first possibility is strongly supported by our prior work showing that DHPG triggers the rapid internalization of GluA1-containing AMPARs in cultured NAc neurons (Mangiavacchi and Wolf, 2004).

In the NAc of drug-naive rats, it is well established that activation of mGluR5 leads to a presynaptic CB1R-dependent attenuation of excitatory synaptic transmission (Robbe et al., 2002). Our results in saline control rats, showing that either the mGluR5 antagonist MTEP or the CB1R antagonist AM-251 block the DHPG-induced depression of excitatory transmission, are consistent with these findings. A different picture emerges in incubated rats. Here, the DHPG-induced synaptic depression is no longer affected by either mGluR5 or CB1R blockade; instead, it is mediated by mGluR1 and a postsynaptic PKC-dependent mechanism. Interestingly, the finding that DHPG inhibits synaptic transmission in incubated rats through a CB1R-independent mechanism does not reflect an impairment of CB1R signaling. On the contrary, the magnitude of synaptic depression induced by the CB1R agonist WIN is significantly more pronounced in the NAc of cocaine-exposed rats than that observed from saline controls. Together, these results suggest that, in incubated rats, mGluR5 no longer couples effectively to the formation and/or release of endocannabinoids. We speculate that the resulting decrease in local endocannabinoid tone leads to supersensitivity of presynaptic CB1R signaling, providing an explanation for the stronger effect of the CB1R agonist WIN in incubated rats. Future studies are needed to determine how the mGluR5-dependent/endocannabinoid-mediated regulation of synaptic transmission in the NAc is compromised after prolonged withdrawal from extended access cocaine self-administration. Based on our results and previous findings (Fourgeaud et al., 2004; Orio et al., 2009), it appears that the nature of cocaine exposure as well as the withdrawal period determine the effect of cocaine on CB1R-mediated transmission in the NAc, as is the case for cocaine-induced alterations in AMPAR transmission (Wolf, 2010).

A large body of work has supported an anti-craving effect of systemic and intra-NAc blockade of group I mGluRs (Olive, 2009), but none of these studies have tested cocaine seeking in animals that have experienced both extended access cocaine self-administration and a prolonged period of withdrawal. Our results indicate that the opposite strategy—stimulating group I mGluRs—may become useful once CP-AMPARs enter NAc synapses. It is not surprising that different mGluR-based pharmacological strategies may be required to reduce drug seeking depending on the mode of cocaine exposure and the duration of withdrawal, as both variables have the potential to influence the effect of cocaine on mGluR signaling (Ben-Shahar et al., 2009; Hao et al., 2010) as well as other aspects of excitatory transmission in the NAc (Mu et al., 2010; McCutcheon et al., 2011). While most prior studies on group I mGluR modulation of cocaine action have focused on mGluR5, the present results indicate that mGluR1 mediates the effect of DHPG on CP-AMPARs in the NAc of incubated rats. Similarly, mGluR1 is responsible for group I mGluR-induced removal of CP-AMPARs from synapses in other brain regions (Bellone and Lüscher, 2005, 2006; Mameli et al., 2007).

In conclusion, the present results suggest that mGluR1 agonists could potentially exert anti-craving effects during cocaine withdrawal by acting directly in the NAc to decrease CP-AMPAR function, possibly by removing CP-AMPARs from synapses. Furthermore, given that mGluR1 is a negative regulator of CP-AMPARs in NAc synapses, it is interesting to speculate that mGluR1 tone in the NAc decreases during withdrawal and that contributes to CP-AMPAR accumulation. Along the same lines, mGluR1 activation in the VTA during early withdrawal from cocaine exposure apparently opposes the cocaine-induced accumulation of CP-AMPARs in the NAc (Mameli et al., 2009). Together, these findings put forward a novel perspective on the use of mGluR1-based drugs to treat cocaine addiction.

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