Psychostimulant-Induced Neuroadaptations in Nucleus Accumbens AMPA Receptor Transmission

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Medium spiny neurons of the nucleus accumbens serve as the interface between cortico-limbic regions that elicit and modulate motivated behaviors, including those related to drugs of abuse, and motor regions responsible for their execution. Medium spiny neurons are excited primarily by AMPA-type glutamate receptors, making AMPA receptor transmission in the accumbens a key regulatory point for addictive behaviors. In animal models of cocaine addiction, changes in the strength of AMPA receptor transmission onto accumbens medium spiny neurons have been shown to underlie cocaine-induced behavioral adaptations related to cocaine seeking. Here we review changes in AMPA receptor levels and subunit composition that occur after discontinuing different types of cocaine exposure, as well as changes elicited by cocaine reexposure following abstinence or extinction. Signaling pathways that regulate these cocaine-induced adaptations will also be considered, as they represent potential targets for addiction pharmacotherapies.

Functionally relevant changes in nucleus accumbens glutamatergic transmission induced by psychostimulants (i.e., amphetamine or cocaine) were first identified in the 1990s following two scientific advances: (1) the development of relatively selective AMPA/kainate and NMDA receptor antagonists (Wong et al. 1986; Honore et al. 1988), and (2) a greater appreciation of the influence of glutamatergic afferents to the nucleus accumbens (Albin et al. 1989; Alexander et al. 1990). Studies on the effects of psychostimulants on glutamate transmission were also driven by the realization that the regulated trafficking of glutamate receptors in and out of synapses is a major contributor to changes in synaptic strength during hippocampal synaptic plasticity (Malinow and Malenka 2002).

Early studies of glutamate's role in psychostimulant addiction focused primarily on a form of psychostimulant-induced neuronal and behavioral plasticity known as behavioral sensitization wherein repeated exposure to psychostimulants (usually in the form of experimenter-delivered injections) results in a progressive and enduring enhancement of psychostimulant-induced behavioral responses. By the early 1990s,
strong evidence had accumulated to support a requirement for glutamate transmission in the development of behavioral sensitization (Wolf 1998). Shortly thereafter, it was found that administration of AMPA/kainate receptor antagonists into the core subregion of the nucleus accumbens attenuated the expression of psychostimulant behavioral sensitization, whereas microinjection of AMPA into the accumbens core produced greater hyperactivity in cocaine-pretreated rats (Pierce et al. 1996). Although subsequent work indicated that the role of AMPA receptor transmission in behavioral sensitization is more complex than was originally appreciated (Bachtell et al. 2008; Ferrario et al. 2010; Wolf and Ferrario 2010; Kourrich et al. 2012), these initial studies laid the groundwork for increasingly sophisticated cellular, molecular, neurochemical, and electrophysiological studies aimed at defining the role of accumbal glutamate transmission in psychostimulant addiction. This review focuses on psychostimulant-induced changes in glutamatergic transmission in the nucleus accumbens with a particular emphasis on changes in nucleus accumbens AMPA receptor number and function resulting from repeated exposure to cocaine.

**CHRONIC COCAINE, SYNAPTIC AND NONSYNAPTIC GLUTAMATE, AND AMPA RECEPTOR EXPRESSION IN THE NUCLEUS ACCUMBENS**

Microdialysis studies revealed that repeated exposure to cocaine followed by a drug-free period resulted in reduced basal extracellular glutamate levels in the nucleus accumbens core owing to decreased activity of the cystine-glutamate antiporter (Pierce et al. 1996; Baker et al. 2002; Baker et al. 2003). These changes are functionally relevant in that administration of N-acetylcysteine, a cystine prodrug that increases activity of the cystine-glutamate antiporter, prevented the reinstatement of drug seeking induced by a priming injection of cocaine (Baker et al. 2003). This line of work, which has since led to clinical trials assessing the effect of N-acetylcysteine on cocaine craving in humans (LaRowe et al. 2007; Mardikian et al. 2007), was among the first to indicate that repeated cocaine resulted in changes in accumbens glutamatergic transmission that influenced drug-seeking behavior (Kalivas et al. 2005). In addition to the microdialysis studies mentioned above, which showed changes in nonsynaptic glutamate pools, other results suggested decreased activity of glutamatergic afferents to the nucleus accumbens during cocaine withdrawal (Hammer and Cooke 1994; Goldstein and Volkow 2002; Sun and Rebec 2006; Porrino et al. 2007). In addition, electrophysiological studies showed that repeated cocaine exposure decreased the intrinsic excitability of accumbens neurons by altering voltage-gated conductances (Zhang et al. 1998, 2002; Hu et al. 2004, 2005; Dong et al. 2006; Ishikawa et al. 2009; Kourrich and Thomas 2009; Mu et al. 2010). Each of these three adaptations—decreased nonsynaptic glutamate, decreased activity of glutamatergic afferents, and decreased intrinsic excitability—has the potential to result in a compensatory increase in glutamate receptor expression in the accumbens (for a critical evaluation of the role of each adaptation see Wolf 2010a). Indeed, a growing literature indicates that repeated contingent or noncontingent exposure to cocaine followed by an abstinence period is associated with increased expression of AMPA receptor subunits in the nucleus accumbens (for a review, see Schmidt and Pierce 2010; Wolf and Ferrario 2010; Wolf and Tseng 2012). Consistent with these findings, repeated cocaine administration has been reported to augment AMPA receptor-mediated synaptic transmission in the nucleus accumbens (Kourrich et al. 2007; Conrad et al. 2008; Ortinski et al. 2012).

Multiple subtypes of AMPA receptors with distinct channel properties and pharmacological profiles are composed from different combinations of subunits termed GluA1-4, as well as auxiliary subunits (transmembrane AMPA receptor regulatory proteins, or T ARPs, and cornichon-like proteins) that modulate AMPA receptor trafficking and channel function (Straub and Tomita 2011). All AMPA receptors, regardless of subunit composition, are permeable to sodium and potassium. However, a profound difference in AMPA receptor channel properties...
results when the GluA2 subunit is absent from the tetrameric receptor. This reflects the fact that GluA2 RNA undergoes an editing process, whereby the conversion of a neutral glutamine codon (Q) to a positively charged arginine (R) renders the channel impermeable to calcium. Because most GluA2 subunits are edited in this manner, GluA2-containing AMPA receptors are primarily calcium-impermeable (Tanaka et al. 2000), and will be referred to herein as calcium-impermeable AMPA receptors (CI-AMPARs). In contrast, GuA2-lacking AMPA receptors are calcium-permeable AMPA receptors (CP-AMPARs). Relative to CI-AMPARs, CP-AMPARs have larger single channel conductance and faster kinetics, are influenced by different pharmacological agents, and display inward rectification owing to voltage-dependent block by endogenous polyamines. CP-AMPAR synaptic incorporation is highly regulated and plays an important role in increased synaptic strength associated with several forms of neuronal plasticity (Cull-Candy et al. 2006; Isaac et al. 2007; Liu and Zukin 2007; Lee 2012).

In the nucleus accumbens of drug-naïve rodents, CP-AMPARs are a minority, accounting for only 5%–10% of evoked excitatory postsynaptic current (EPSC) amplitude (Conrad et al. 2008). The predominant CI-AMPARs are comprised mainly of GluA1A2-containing receptors, although GluA2A3-containing receptors are also present (Reimers et al. 2011). However, as outlined in detail below, extended access cocaine self-administration, but apparently not other types of cocaine regimens, leads to a substantial increase in the synaptic levels of CP-AMPARs in the nucleus accumbens, such that they account for approximately 30% of evoked EPSC amplitude after a month or so of withdrawal (Conrad et al. 2008; Mameli et al. 2009; for a review, see Wolf and Tseng 2012).

**AMPA RECEPTOR TRAFFICKING AND COCAINE-INDUCED PLASTICITY**

A growing body of evidence indicates that accumbal AMPA receptors contribute significantly to the reinstatement of cocaine seeking, an animal model of relapse. Thus, administration of AMPA directly into the nucleus accumbens promotes reinstatement of cocaine seeking, whereas intra-accumbal administration of an AMPA receptor antagonist blocks reinstatement induced by a systemic priming injection of cocaine (Cornish et al. 1999; Cornish and Kalivas 2000; Suto et al. 2004; Kruzich and Xi 2006; Ping et al. 2008) or cues previously paired with cocaine (Bäckström and Hyytia 2007). Although most of these microinjection studies did not directly compare core and shell subregions of the nucleus accumbens, there is evidence that increased glutamate transmission in both the core and shell contributes to the reinstatement of cocaine seeking. Increased extracellular glutamate release in the nucleus accumbens core was observed during cocaine priming-induced reinstatement of drug seeking (McFarland et al. 2003), whereas administration of an AMPA receptor antagonist into the accumbens shell inhibited the reinstatement of cocaine seeking prompted by administration of cocaine into the medial prefrontal cortex (Park et al. 2002). Subsequent findings indicated that administration of an AMPA receptor antagonist into the accumbens core or shell attenuated the reinstatement of cocaine seeking (Famous et al. 2008). Consistent with these results, microinjection of AMPA directly into the accumbens core or shell reinstates cocaine seeking (Ping et al. 2008). Taken together, these findings clearly indicate that increased transmission through AMPA receptors in both of the major subregions of the nucleus accumbens promotes the reinstatement of cocaine seeking. In addition to results in reinstatement models, AMPA receptor transmission in the accumbens is also required for drug seeking under second-order schedules of reinforcement (Di Ciano and Everitt 2001, 2004) and for cue-induced seeking after prolonged abstinence (Conrad et al. 2008; but see also See et al. 2007).

The findings outlined above raise the possibility that cocaine exposure alters AMPA receptor levels in nucleus accumbens synapses. The first study to provide direct support for this idea revealed that the ratio of cell-surface to intracellular GluA1 and GluA2/3 (identified with an antibody that recognized both subunits) in the
accumbens was increased 3 weeks, but not 1 day, after discontinuing a sensitizing regimen of repeated intraperitoneal (i.p.) cocaine injections (Boudreau and Wolf 2005). A number of studies have confirmed this finding and investigated the underlying mechanisms of AMPA receptor redistribution, with ERK emerging as a leading candidate but other signaling pathways also implicated (Boudreau et al. 2007, 2009; Schumann and Yaka 2009; Pascoli et al. 2011; Schierberl et al. 2011). Here, we will focus on mechanisms underlying changes in AMPA receptor subunit trafficking in the nucleus accumbens after self-administered cocaine. The next two sections outline the roles of GluA1- and GluA2-containing AMPA receptors, respectively, in adaptations related to cocaine seeking during withdrawal. GluA1 and GluA2 are considered separately, even though they can obviously be colocalized in the same tetrameric receptor (i.e., the GluA1A2-containing CI-AMPARs that predominate in the nucleus accumbens of drug-naïve animals and after most types of cocaine exposure), because their carboxyl termini differ with respect to phosphorylation sites and protein–protein interaction domains that influence receptor trafficking (Derkach et al. 2007; Shepherd and Huganir 2007; Anggono and Huganir 2012).

NUCLEUS ACCUMBENS GluA1-CONTAINING AMPA RECEPTORS AND THE REINSTATEMENT OF COCAINE SEEKING

GluA1 subunits play a particularly prominent role in the reinstatement of cocaine seeking. Suppression of GluA1 transcription in either the accumbens core or shell impaired the reinstatement of drug seeking induced by a cocaine priming injection (Ping et al. 2008). In addition, viral-mediated overexpression of pore-dead GluA1 subunits in the accumbens shell attenuated cocaine reinstatement (White et al. 2012). In contrast, when pore-dead GluA1 was overexpressed in the accumbens core the reinstatement of cocaine seeking was enhanced (Bachtell et al. 2008). This latter finding, however, is difficult to reconcile with compelling evidence that AMPA receptor transmission in the nucleus accumbens core, which is mediated primarily by GluA1A2-containing receptors (Reimers et al. 2011), is required for cocaine seeking (Kalivas and Volkow 2005; Wolf and Ferrario 2010). Overall, we suggest that these studies, especially when combined with evidence for posttranslational modification of GluA1 during reinstatement (see below), suggest that increased transmission through GluA1-containing AMPA receptors in both the core and shell of the nucleus accumbens promotes the reinstatement of cocaine-seeking behavior (Anderson et al. 2008).

Reinstatement experiments typically use a short access paradigm in which rats self-administer cocaine 2 h/d for 2–3 wk, followed by extinction. Interestingly, when daily cocaine exposure is extended to 6 h and followed by a period of withdrawal (rather than extinction training), cue-induced cocaine seeking progressively intensifies (or “incubates”) over the first several months of withdrawal (Grimm et al. 2001; Pickens et al. 2011). Following 45 d of withdrawal from 10 d of extended access cocaine self-administration, Conrad et al. (2008) found an increase in cell surface GluA1, but not GluA2, in the nucleus accumbens compared to either saline controls or cocaine-exposed rats tested on withdrawal day 1. GluA3 was also increased, but this was observed in cocaine-exposed rats on both withdrawal days 1 and 45, leaving open the question of whether GluA3 contributes to withdrawal-dependent changes in synaptic transmission and craving. Parallel electrophysiological studies showed inward rectification of evoked AMPA receptor EPSCs, a hallmark of CP-AMPARs, in cocaine-exposed rats recorded on withdrawal days 42–47 (Conrad et al. 2008). These biochemical and electrophysiological results indicated an increase in CP-AMPARs (GluA1 homomers or GluA1A3 receptors) in accumbens synapses after prolonged withdrawal. Supporting the functional significance of these findings, injection of the CP-AMPAR antagonist NASPM into the accumbens core on withdrawal day 45 blocked the expression of incubated cue-induced cocaine seeking. Collectively, these findings suggest that synaptic
incorporation of CP-AMPARs translates into enhanced drug seeking, although whether this is a consequence of enhanced calcium signaling or other differences (e.g., larger single channel conductance) is unclear (Conrad et al. 2008; Wolf and Tseng 2012).

Subsequent work confirmed the presence of CP-AMPARs in the accumbens core after extended access cocaine self-administration (Ferrario et al. 2011a; McCutcheon et al. 2011a,b) and showed that CP-AMPARs also accumulate in the shell subregion (Mameli et al. 2009; McCutcheon et al. 2011b). In addition, time course studies have shown that CP-AMPARs are first detected after approximately a month of withdrawal from extended access cocaine self-administration (Wolf and Tseng 2012). Thus, other mechanisms must be responsible for the expression of incubated cocaine craving at earlier withdrawal times. The reason for the delay in CP-AMPAR accumulation is unclear, although one contributing factor may be a slowly developing withdrawal-dependent decrease in surface expression of mGluR1. Because mGluR1 normally exerts a braking influence on CP-AMPAR accumulation, loss of mGluR1 tone may help enable CP-AMPAR accumulation during withdrawal (Loweth et al. 2012). Once CP-AMPARs are present, they remain in nucleus accumbens synapses at least through withdrawal day 70, making this a very persistent form of plasticity that likely contributes to protracted risk of relapse (Wolf and Tseng 2012).

Recently, whole cell patch clamp recordings showed that CP-AMPAR accumulation in the nucleus accumbens is specifically linked to extended access cocaine self-administration, as it does not occur in rats treated with experimenter-delivered cocaine (McCutcheon et al. 2011b) or following limited access cocaine self-administration (Purgianto et al. 2012). These results do not, however, preclude the possibility of CI-AMPAR up-regulation after limited access cocaine self-administration. Indeed, a recent study found increased mEPSC amplitude and AMPA/NMDA ratios in the nucleus accumbens shell after 3–4 wk, but not 1–2 d, of abstinence from a limited access regimen (Ortinski et al. 2012). Together, these studies indicate a withdrawal-dependent increase in synaptic levels of CI-AMPARs after limited access cocaine self-administration. Consonant with these findings, long-term potentiation (LTP) but not long-term depression (LTD) is impaired in the nucleus accumbens on withdrawal day 21 after limited access cocaine self-administration (Knackstedt et al. 2010). The results of Ortinski et al. (2012) suggest that this may reflect occlusion of LTP by prior AMPA receptor up-regulation. However, as discussed elsewhere in detail (Wolf 2010a; Wolf and Ferrario 2010), the literature on induction of LTP or LTD after cocaine exposure is full of contradictions. In many cases, this may be attributed to the fact that plasticity was assessed at short withdrawal times when AMPA receptor levels were in flux. For this and many other reasons, it can be problematic to infer AMPA receptor levels from changes in the ability to elicit LTP or LTD following cocaine exposure.

The carboxy-terminal region of the GluA1 subunit contains all of the known protein phosphorylation sites, including serines phosphorylated by cyclic AMP-dependent protein kinase (PKA), protein kinase C (PKC), and/or calcium/calmodulin-dependent protein kinase II (CaMKII) (Derkach et al. 2007; Shepherd and Huganir 2007; Anggono and Huganir 2012). Stimulation of D1 dopamine receptors in the nucleus accumbens promotes cocaine reinstatement by activating Gs/adenyl cyclase/cAMP (Schmidt and Pierce 2006; Schmidt et al. 2006). D1 dopamine receptor stimulation of cAMP results in the activation of PKA, which is linked to cocaine seeking (Self et al. 1998) and, based on work in cultured accumbens neurons, increases the insertion of GluA1-containing AMPA receptors into the plasma membrane (Chao et al. 2002a,b; Mangiavacchi and Wolf 2004a). Moreover, repeated exposure to cocaine enhances enzyme activity of PKA in the nucleus accumbens of rodents (Terwilliger et al. 1991; Lu et al. 2003). No changes in total GluA1-pSer845 (PKA phosphorylation site) were observed during the reinstatement of cocaine seeking (using a short access paradigm) (Anderson et al. 2008). However, it was recently shown that
surface expression of GluA1-pSer845 was increased in the nucleus accumbens 35 days following cocaine self-administration (using a long access paradigm) (Ferrario et al. 2011a), which may prime accumbens AMPA receptors for synaptic insertion (Sun et al. 2005, 2008; Gao et al. 2006; Oh et al. 2006; Man et al. 2007; for a review, see Wolf 2010b). Direct interactions between PKA and GluA1 during cocaine self-administration and subsequent cocaine seeking clearly need to be examined in greater detail.

Another target of PKA is the L-type calcium channel, which plays a critical role in psychostimulant-induced behavioral and neuronal plasticity (Gnegy 2000; Licata and Pierce 2003; Rajadhyaksha and Kosofsky 2005). Calcium influx through L-type channels activates a family of protein kinases including CaMKII, an enzyme that plays a critical role in several forms of neuronal plasticity including changes induced by repeated cocaine exposure (Licata and Pierce 2003; Giordano et al. 2010; Loweth and Vezina 2011). Recent work specifically implicates CaMKII in nucleus accumbens AMPA receptor plasticity produced by repeated non-contingent psychostimulant exposure (Boudreau et al. 2009; Loweth et al. 2010; Schierberl et al. 2011) as well as motivation to self-administer amphetamine (Loweth et al. 2008, 2010). After cocaine self-administration, stimulating D1-like dopamine receptors in the medial nucleus accumbens shell promotes the reinstatement of cocaine seeking by serially stimulating L-type calcium channels and phosphorylation of CaMKII (Anderson et al. 2008). Furthermore, reinstatement of cocaine-seeking behavior was associated with an increase in phosphorylation of GluA1-pSer831, a site phosphorylated by CaMKII and PKC, and enhanced cell-surface expression of GluA1-containing AMPA receptors in the accumbens shell (Anderson et al. 2008). Consistent with these findings, impairing the trafficking of GluA1-containing AMPA receptors to the cell surface within the nucleus accumbens shell attenuated the ability of a priming injection of cocaine to reinstate drug-seeking behavior (Anderson et al. 2008). These results indicate that D1-like dopamine receptor stimulation-dependent activation of L-type calcium channels and CaMKII facilitates the reinstatement of cocaine seeking by promoting the synaptic incorporation of GluA1-containing AMPA receptors in the nucleus accumbens shell. Thus, CaMKII activity in the nucleus accumbens shell may be an essential link between dopamine and glutamate systems involved in the neuronal plasticity underlying cocaine craving and relapse.

Anderson et al. (2008) used a limited access cocaine self-administration regimen, which does not lead to persistent CP-AMPAR accumulation in the nucleus accumbens (see previous section). Therefore, the CaMKII-dependent increase in GluA1 surface expression may primarily reflect an increase in GluA1A2 receptors. Alternatively, it could involve insertion of homomeric GluA1 CP-AMPARs, given that CP-AMPARs are present in the nucleus accumbens of drug-naive rats, albeit at low levels, in homogenates (Reimers et al. 2011), synapses (Conrad et al. 2008), and in extrasynaptic AMPA receptor pools that supply the synapse (Ferrario et al. 2011b). A relationship between CP-AMPARs and CaMKII may also be suggested by an increased ratio of phosphorylated to total CaMKII in the accumbens on withdrawal day 45, but not withdrawal day 1, after extended access cocaine self-administration, in concert with CP-AMPAR accumulation (Ferrario et al. 2011a). However, it is not clear whether CaMKII activation helped to promote CP-AMPAR accumulation or whether CaMKII activation on withdrawal day 45 was secondary to CP-AMPAR accumulation, because CP-AMPARs would represent a new source of calcium influx into the medium spiny neuron, which could underlie persistent activation of CaMKII signaling. Increased ERK activation was also observed in conjunction with CP-AMPAR synaptic accumulation (Ferrario et al. 2011a).

Although the CaMKII signaling pathway clearly plays a role in cocaine reinstatement in the accumbens shell, the specific role of CaMKII phosphorylation in GluA1 subunit trafficking remains an area of active study. Early studies examining CaMKII involvement in AMPA receptor synaptic delivery in hippocampus
indicated that increasing CaMKII activity enhanced insertion of GluA1 subunits into synapses; however, this effect was not influenced by mutating the GluA1 Ser831 residue (Hayashi et al. 2000). This result indicated that CaMKII substrates other than GluA1 influence the trafficking of AMPA receptors. Stargazin, a member of the family of transmembrane AMPA receptor regulatory proteins (TARPs) that serve as AMPA receptor auxiliary subunits, is now considered the strongest candidate. CaMKII phosphorylation of stargazin enables it to interact with PSD95 and thus immobilize AMPA receptors at the synapse (for a review, see Lisman et al. 2012). The interactions among CaMKII, stargazin, and other potentially important CaMKII substrates (i.e., SAP97) that may influence the trafficking of GluA1 subunits during cocaine reinstatement remain to be examined in detail. However, the TARPs, as well as stargazin, have been implicated in CP-AMPAR accumulation after prolonged withdrawal from extended access cocaine self-administration (Ferrario et al. 2011b), suggesting TARPs as players in cocaine-induced neuroadaptations.

The data summarized in this section indicate that repeated cocaine exposure promotes the synaptic expression of GluA1-containing AMPARs in core and shell subregions of the nucleus accumbens. After noncontingent cocaine self-administration, GluA1A2-containing AMPA receptors, the predominant AMPA receptor type in the accumbens, are up-regulated. After extended access cocaine self-administration, levels of GluA1-containing CP-AMPARs are increased after approximately a month of withdrawal and then remain in synapses. Although limited access cocaine self-administration leads to increased synaptic levels of CI-AMPARs but not CP-AMPARs during withdrawal, a subsequent cocaine challenge injection rapidly increases the surface expression of GluA1, potentially indicating up-regulation of either CP-AMPARs or GluA1A2-containing CI-AMPARs. The next section will consider growing evidence for the specific regulation of the GluA2 subunit in the nucleus accumbens of cocaine-exposed animals.

PKC phosphorylation of GluA2 subunits at Ser880 influences the trafficking of GluA2-containing AMPA receptors (Song and Huganir 2002; Shepherd and Huganir 2007). The same region of the GluA2 carboxyl terminus is required for interactions with glutamate receptor interacting protein 1 (GRIP1) and protein interacting with C kinase 1 ( PICK1), two important proteins for AMPA receptor trafficking. Based on studies of hippocampal and cerebellar LTD, a model has been developed whereby PKC phosphorylation of GluA2 at Ser880 leads to detachment from GRIP1 and increased association with PICK1, resulting in an increased rate of internalization. However, other evidence supports alternative functions for GRIP1 and PICK1, including different interactions of PICK1 in regulating trafficking of CI-AMPARs versus CP-AMPARs (Anggono and Huganir 2012).

Although the literature is not extensive, previous studies have shown a role for PKC in psychostimulant-mediated behaviors. For example, repeated cocaine administration increases the phosphorylation of some, but not all, isoforms of PKC in the nucleus accumbens (Steketee et al. 1998; Chen et al. 2007). Behavioral experiments indicated that intra-accumbal administration of a PKC inhibitor attenuated amphetamine-mediated conditioned place preference (CPP) (Aujla and Beninger 2003) and systemic administration of a PKC inhibitor attenuated cocaine-induced CPP (Cervo et al. 1997). Similarly, administration of a PKC inhibitor directly into the accumbens blocked the expression of cocaine-induced behavioral sensitization (Pierce et al. 1998). In terms of the reinstatement of cocaine seeking, increased phosphorylation of GluA2 Ser880 (PKC site) was observed during priming-induced reinstatement, whereas administration of a peptide into the nucleus accumbens shell that inhibits GluA2-PICK1 interactions attenuated cocaine-seeking behavior (Famous et al. 2008). Based on the results summarized in the previous
paragraph, these results suggest that impairing the endocytosis of GluA2-containing AMPA receptors in the nucleus accumbens disrupts the reinstatement of drug seeking. Combined with results showing increased GluA1 surface expression 30 min after cocaine-primed reinstatement (Anderson et al. 2008; previous section), these findings suggest the possibility that a rapid exchange between a GluA1-containing population of AMPA receptors and a GluA2-containing population of AMPA receptors occurs in concert with cocaine-induced reinstatement.

Activation of a number of receptor subtypes increases the activation of PKC. For example, group I metabotropic glutamate receptors (i.e., mGluR1, mGluR5) signal through PKC (Conn 2003) and these receptors play a significant role in cocaine-induced neuroadaptations and behavioral responses (Olive 2009). Initial evidence indicating that repeated cocaine injections increased mGluR5 mRNA levels in the nucleus accumbens shell (Ghasemzadeh et al. 1999) was followed by the discovery that constitutive mGluR5 receptor knockout mice were insensitive to the locomotor stimulant properties of cocaine and would not self-administer this psychostimulant (Chiamulera et al. 2001). Consistent with these findings, subsequent work showed that administration of the mGluR5 receptor antagonists, MPEP or MTEP, decreased cocaine self-administration (Kenny et al. 2003, 2005; Lee et al. 2005; Paterson et al. 2005; Platt et al. 2008) and attenuated the ability of a priming injection of cocaine (Lee et al. 2005; Kumaresan et al. 2009) or cocaine-associated cues (Bäckström and Hyytia 2006; Kumaresan et al. 2009) to reinstate cocaine seeking. Moreover, administration of an mGluR1 antagonist into the accumbens core, but not the shell, attenuated context-dependent cocaine seeking (Xie et al. 2011) and intra-accumbens shell microinjection of MPEP attenuated cocaine-induced reinstatement of drug seeking (Kumaresan et al. 2009).

Stimulation of group I mGluRs activates phospholipase C (PLC) resulting in the generation of inositol triphosphate (IP3) and diacylglycerol (DAG), which activates PKC (Conn and Pin 1997; Kim et al. 2008). As would be predicted from the effects of group I mGluR antagonists described above, recent evidence indicates that activation of this signaling pathway contributes significantly to the reinstatement of cocaine seeking. Thus, administration of a PLC or PKC inhibitor into the accumbens core or shell dose-dependently attenuated the reinstatement of cocaine seeking (Schmidt et al. 2011; Wang et al. 2012). Moreover, intrashell microinjection of the mGluR1/5 agonist, DHPG (Schmidt et al. 2011), or the mGluR5 agonist, CHPG (Wang et al. 2012), dose-dependently promoted the reinstatement of cocaine seeking (in the absence of a cocaine challenge injection). Moreover, the DHPG effect was blocked by pre-treatment with a PKC inhibitor (Schmidt et al. 2011).

Taken together, studies with group I agonists and antagonists show that activation of mGluR1/5 receptors and the associated PLC/IP3/DAG/PKC signaling pathway in the nucleus accumbens promotes the reinstatement of cocaine seeking. The simplest interpretation of these results is that postsynaptic mGluRs contribute, along with AMPA receptors, to the activation of medium spiny neurons that is required for reinstatement. One might expect this effect to be opposed by the ability of mGluR5 stimulation to elicit presynaptically expressed LTD (through a mechanism that depends on retrograde endocannabinoid signaling leading to activation of CB1 receptors on glutamate nerve terminals) and thereby attenuate excitatory synaptic transmission onto medium spiny neurons (Robbe et al. 2002; Lovinger 2008). Perhaps the balance is tipped away from LTD because many types of cocaine exposure, even a single i.p. injection (Fourgeaud et al. 2004), blunt or even eliminate this form of mGluR5-LTD in accumbens neurons (Wolf and Tseng 2012), although it is not clear how long this blunting persists after different types of cocaine exposure.

Notably, all studies indicating stimulatory effects of group I mGluRs on reinstatement of cocaine seeking have been conducted after limited access cocaine self-administration. After extended access cocaine self-administration and prolonged withdrawal (>1 mo) leading to
incubation of cocaine craving, there appears to be a dramatic rearrangement of interactions between group I mGluRs and AMPA receptors. First, CB1R-dependent, presynaptically expressed mGluR5-LTD is eliminated (McCutcheon et al. 2011a). This is not surprising because, as noted in the previous paragraph, many prior studies have shown that cocaine exposure blunts or eliminates mGluR5-LTD in the nucleus accumbens. More strikingly, mGluR1, which has very little effect on excitatory synaptic transmission in control animals, acquires the ability to regulate AMPA receptor transmission after incubation. Thus, bath application of DHPG, in slices from the cocaine-exposed animals, rapidly eliminated the postsynaptic CP-AMPAR contribution to accumbens synaptic transmission, but enhanced the CI-AMPAR contribution (McCutcheon et al. 2011a). These effects were blocked by an mGluR1 (but not an mGluR5) antagonist and a PKC inhibitor (McCutcheon et al. 2011a). The most straightforward interpretation of these results is that in cocaine-experienced rats administration of the mGluR1/5 agonist DHPG to the nucleus accumbens resulted in the mGluR1-dependent endocytosis of CP-AMPARs and synaptic insertion of CI-AMPARs. Consistent with the first part of this interpretation, when administered to cultured accumbens neurons DHPG promoted the rapid internalization of GluA1-containing AMPA receptors (Mangiavacchi and Wolf 2004b). The latter part may seem inconsistent with a role for PKC signaling in promoting internalization of CI-AMPARs (Famous et al. 2008), but it must be recalled that events downstream from PKC (e.g., changes in association between GluA2, GRIP1, and PICK1) are very complex and can be associated with AMPA receptor insertion as well as removal (see Anggono and Huganir 2012).

It is notable that an mGluR1-mediated exchange of CP-AMPARs for CI-AMPARs has been reported previously in VTA and cerebellar synapses that contain CP-AMPARs (Bellone and Lüscher 2006; Mameli et al. 2007; Kelly et al. 2009; for a review, see Wolf and Tseng 2012). In all brain regions, including the nucleus accumbens, this exchange results in LTD, because a high conductance CP-AMPAR is being exchanged for a lower conductance CI-AMPAR. Presumably in these situations, the inhibitory effect of removing CP-AMPARs is dominant over any other postsynaptic effects produced by mGluR1 stimulation, so the net effect is attenuation of excitatory synaptic transmission and thus reduced cocaine seeking.

The suggestion that mGluR1 stimulation might blunt cocaine craving (McCutcheon et al. 2011a) appears to be at odds with a substantial literature indicating that group I mGluR antagonists attenuate the reinstatement of cocaine seeking (Olive 2009). However, the majority of these studies implicated mGluR5. In contrast, DHPG-induced reversal of cocaine-mediated accumulation of CP-AMPARs in the nucleus accumbens was solely owing to activation of mGluR1 (McCutcheon et al. 2011a). More importantly, none of these studies tested cocaine seeking in animals that experienced both extended access cocaine self-administration and a prolonged period of withdrawal (i.e., the circumstances that lead to CP-AMPAR accumulation in nucleus accumbens synapses). Once CP-AMPARs are present in nucleus accumbens synapses, stimulation of mGluR1, as opposed to blockade of mGluR5, may be a more effective way to decrease excitatory transmission in the accumbens and reduce craving. Indeed, our preliminary results suggest that mGluR1 stimulation reduces the expression of incubated cue-induced cocaine seeking (JA Loweth and ME Wolf, unpubl.).

CONCLUSIONS

AMPA receptor plasticity occurs in the nucleus accumbens during cocaine withdrawal as well as in conjunction with the reinstatement of cocaine-seeking behavior. During withdrawal, AMPA receptor levels in nucleus accumbens synapses are increased, but the time course of AMPA receptor up-regulation and the type of AMPA receptor affected depend on the cocaine regimen. Noncontingent cocaine exposure leads to a relatively rapid up-regulation of CI-AMPARs that is evident by withdrawal day 7, whereas limited access cocaine self-administration
increases synaptic AMPA receptor levels, but these appear to be CI-AMPARs rather than CP-AMPARs. Extended access cocaine self-administration followed by prolonged withdrawal (>1 mo) leads to a persistent increase in accumbens levels of CP-AMPARs that mediate the expression of incubated cue-induced cocaine craving. Superimposed on withdrawal-dependent changes, cocaine-primed reinstatement after limited access cocaine self-administration involves removal of GluA2-containing AMPA receptors (Famous et al. 2008; Wiggins et al. 2011) and increases in GluA1-mediated excitatory transmission in the accumbens shell (Anderson et al. 2008).

The mechanisms that control AMPA receptor levels and subtype over the long term, as well as mechanisms that regulate rapid AMPA receptor plasticity in response to cocaine reexposure, are potential targets for anticausing medications. Given the serious side effects associated with direct AMPA receptor blockade, it will be most useful to target mechanisms that indirectly regulate synaptic AMPA receptor transmission. Recently acquired information about the subtypes of AMPA receptors and the regulatory mechanisms that predominate after different types of cocaine exposure can be used to target therapeutic approaches to specific clinical situations. For example, N-acetyl-cysteine, now in clinical trials, works by targeting adaptations that are produced even by noncontingent cocaine exposure (Kalivas 2009) and may, therefore, have utility in many situations. However, mGluR1 agonists, which normalize a change in synaptic transmission associated with prolonged withdrawal from extended access cocaine self-administration (i.e., CP-AMPAR accumulation), may be useful for users who have achieved abstinence and hope to minimize the likelihood of cue-induced relapse. The signaling mechanisms altered by repeated cocaine exposure are complex and involve many effectors. As reviewed above, L-type calcium channel antagonists and their associated signaling systems link D1 dopamine receptors to GluA1-containing AMPA receptors during the reinstatement of cocaine seeking. Thus, L-type calcium channel antagonists, which have long been used in the treatment of hypertension, might also prove to be efficacious in the treatment of cocaine craving and relapse. A more complete knowledge of the precise mechanisms underlying cocaine-induced changes in AMPA receptor transmission in the nucleus accumbens and other brain regions holds promise for identifying novel targets for the development of pharmacotherapies for cocaine addiction, which thus far remain elusive.

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