Psychostimulant-Induced Adaptations in Nucleus Accumbens Glutamatergic Transmission

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Carrying different aspects of emotional and motivational signals, glutamatergic synaptic projections from multiple limbic and paralimbic brain regions converge to the nucleus accumbens (NAc), in which these arousing signals are processed and prioritized for behavioral output. In animal models of drug addiction, some key drug-induced alterations at NAc glutamatergic synapses underlie important cellular and circuit mechanisms that promote subsequent drug taking, seeking, and relapse. With the focus of cocaine, we review changes at NAc glutamatergic synapses that occur after different drug procedures and abstinence durations, and the behavioral impact of these changes.

Drug addiction is an acquired, yet pathological, behavioral state that develops following repeated drug use and drug withdrawal. Similar to other adaptive and maladaptive behaviors, drug addiction shares many similarities with natural learning and memory processes. Indeed, the development of drug addiction involves the acquisition/learning of drug use and consolidation of this usage (Everitt and Robbins 2016). Furthermore, addictive behaviors can undergo extinction and reconsolidation, two hallmarks of natural memories (Torregrossa and Taylor 2013). As such, drug addiction is often conceptualized as a pathological form of memory that drives maladaptive behaviors. This has led to the neuroadaptation theory, which postulates that drugs of abuse harness cellular mechanisms that underlie general learning and

memory processes to form addiction-related memories (Hyman et al. 2006).

Over the past two decades, a major focus of the addiction research field has been to identify the neural adaptations drugs of abuse induce to alter the function of reward and motivation circuits that drive drug craving, seeking, and relapse. A key node within these circuits is the nucleus accumbens (NAc), which is anatomically positioned as an interface between limbic and motor systems to prioritize and translate motivational arousals into behavioral output (Mogenson et al. 1980). The NAc receives and integrates glutamatergic projections from multiple limbic and paralimbic regions, and transmits the processed information to downstream regions linked to behavioral output through principal medium spiny neurons (MSNs), the

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projection neurons of the NAc (Sesack and Grace 2010). Although various functional adaptations in NAc MSNs have been detected after exposure to drugs of abuse, drug-induced adaptations in glutamatergic projections to MSNs are particularly critical to the development and maintenance of many addiction-related behaviors. In this review, we provide a summary of the adaptations at glutamatergic synapses of NAc MSNs after exposure to psychostimulants, particularly cocaine, and how these adaptations contribute to addiction-related behaviors.

GLUTAMATERGIC TRANSMISSION IN THE NAc

A hallmark in vivo pharmacological effect of psychostimulants is the increase in the levels of dopamine within the NAc (Di Chiara and Imperato 1988). This, together with the strong link of the mesolimbic dopamine system to reward processing, positions dopamine as a predominant focus of addiction research for many years (Wise and Rompre 1989; Wise 2004; Volkow et al. 2017). Although dopaminergic signaling in the mesolimbic pathway is clearly important in psychostimulant addiction, NAc dopamine does not appear to be the sole player, and not even an essential player in some cases, in driving relapse after periods of withdrawal from drug use. For example, infusion of dopaminergic antagonists into the NAc of animals previously trained to self-administer cocaine does not affect the subsequent reinstatement of cocaine seeking (Cornish and Kalivas 2000; McFarland and Kalivas 2001). Instead, plenty of evidence establishes a critical role of NAc glutamatergic transmission in drug relapse after withdrawal.

The first wave of evidence comes from studies of locomotor sensitization, a phenomenon wherein repeated exposure to drugs of abuse results in a progressive enhancement of drug-induced locomotion. In cocaine-sensitized rats, inhibiting AMPA receptors (AMPA) in the NAc or lesioning the prefrontal glutamatergic input to the NAc decreases locomotor responding to basal levels, eliminating the sensitized component, whereas infusing AMPA into the NAc in rats with no challenge cocaine injection

is sufficient to induce the expression of locomotor sensitization (Pierce et al. 1996, 1998). In the second wave in which cocaine self-administration models are used, inhibiting NAc AMPARs decreases the reinstatement of cocaine seeking after drug withdrawal (Cornish and Kalivas 2000; McFarland and Kalivas 2001), whereas intra-NAc AMPA infusion is sufficient to reinstate cocaine seeking even without external triggers such as drug-associated cues, stress, and priming/challenge injection of cocaine (Cornish and Kalivas 2000). These results demonstrate that NAc glutamatergic signaling is both essential and sufficient in addiction-related behaviors after drug withdrawal, and guide the field toward examining NAc glutamatergic transmission in psychostimulant abuse.

The third wave of studies has started to delineate each component of the NAc glutamatergic circuits in addiction-related behaviors. The NAc receives glutamatergic projections from several other limbic and paralimbic regions, including the prelimbic (PL) and infralimbic (IL) subdivisions of the medial prefrontal cortex (mPFC), the basolateral amygdala (BLA), hippocampus (Hipp), paraventricular thalamus (PVT), and ventral tegmental area (VTA) (Sesack and Grace 2010). These projections are thought to convey different arousal signals to the NAc, where they are integrated for the output of NAc-based behaviors. For example, the BLA projection conveys information related to discrete cues to promote cue-induced reward seeking (Ambroggi et al., 2008), the ventral hippocampus (vHipp) projection conveys spatial information related to context to promote context-induced reward seeking (Ito et al. 2008; Lansink et al. 2009; Trouche et al. 2019), the mPFC projection is involved in encoding reward-associated discrete cues (Ishikawa et al. 2008), as well as spatial and social information (Murugan et al. 2017). Despite these differential aspects, all these projections promote reward seeking on direct optogenetic activation (Britt et al. 2012; Stuber et al. 2012). In addition, these projections are also critically involved in reinstatement of cocaine seeking after withdrawal (McFarland and Kalivas 2001; McFarland et al. 2003; Di Ciano 2004; Britt et al. 2012; Stefanik

and Kalivas 2013; Stefanik et al. 2013; Sjulson et al. 2018). It should be noted here that the PL and IL of mPFC have somewhat opposing effects on cocaine seeking, such that activation of the PL promotes, whereas activation of the IL suppresses, cocaine seeking (McFarland and Kalivas 2001; Peters et al. 2008; Stefanik et al. 2013; Cameron et al. 2019). Compared with other projections, the PVT projection to the NAc has been less studied, but emerging evidence suggests its involvement in multiple layers of emotional and motivational arousal (Kirouac 2015). For example, the PVT projection is not only involved in opioid withdrawal-associated aversive behaviors (Zhu et al. 2016), but also the incentive salience underlying the cues that predict rewards (Haight et al. 2015). Furthermore, disruption of the PVT transmission to the NAc compromises the acquisition of cocaine self-administration, but does not affect cue-induced cocaine seeking once the self-administration is acquired (Neumann et al. 2016).

Collectively, projection-specific glutamatergic synaptic transmission regulates NAc-based emotional and motivational responses related to psychostimulant-induced behaviors, especially behaviors associated with relapse after drug withdrawal. In the following sections, we will review psychostimulant-induced adaptations in NAc glutamatergic transmission and the resulting behavioral alterations.

PRESYNAPTIC ADAPTATIONS

In general, the strength of glutamatergic synapses can be modified through presynaptic (e.g., release probability) and/or postsynaptic mechanisms (e.g., number of receptors). Early studies report that rats behaviorally sensitized to cocaine show significantly increased levels of stimulation-evoked glutamate release (not basal levels) in the NAc (Pierce et al. 1996). Subsequent studies confirm that a similar up-regulation of NAc glutamate is also induced in rats after cocaine self-administration (McFarland et al. 2003). Importantly, such an increase is only detected in rats receiving cocaine through self-administration, but not through yoked infusion, suggesting that this presynaptic adapta-

tion is experience-dependent, and related to the learning process of drug taking.

A potential mechanism mediating the increased glutamate levels is cocaine-induced up-regulation of presynaptic release probability, for which early studies provide mixed results. For example, withdrawal from repeated exposure to cocaine increases the frequency of miniature excitatory postsynaptic currents (mEPSCs) in NAc MSNs (Kourrich et al. 2007; Moussawi et al. 2011), a change that can result from either increased presynaptic release or an increase in the number of synapses, but no change in the paired pulse ratio (PPR), an indicator of presynaptic release, is detected in parallel (Kourrich et al. 2007). It is worth noting that the PPR may not be sufficiently sensitive to detect small presynaptic changes, and these studies sampled synapses in a projection-nonspecific manner, although the increase in stimulation-evoked glutamate is primarily assessed by stimulating the mPFC projection (McFarland et al. 2003). Recent optogenetic studies with improved projection specificity demonstrate that repeated exposure to cocaine increases the presynaptic release probability mPFC- and PVT-to-NAc synapses (Suska et al. 2013; Neumann et al. 2016) but not BLA- and vHipp-to-NAc synapses (Suska et al. 2013; MacAskill et al. 2014). This presynaptic adaptation at mPFC- and PVT-to-NAc synapses occurs as early as after 1 day withdrawal from cocaine self-administration, and persists through long withdrawal periods (e.g., 45 days) (Suska et al. 2013; Neumann et al. 2016).

A potential contributor for this presynaptic adaptation is the dysregulation of glutamate homeostasis (Kalivas 2009). Although the evoked release of glutamate in the NAc is increased after withdrawal from cocaine self-administration, the basal level of glutamate is decreased compared with naive animals (McFarland et al. 2003). The decreased basal levels of glutamate may arise from astrocytes. Cocaine decreases the expression of the glutamate transporter-1 (GLT-1), a major glial transporter in the NAc that moves extracellular glutamate into astrocytes (Reissner et al. 2014). This alteration, in turn, decreases the function of the cysteine/

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glutamate exchanger that transports glutamate to the extracellular space (Baker et al. 2003). The decrease in extracellular glutamate then leads to a decrease in the basal activation of group II metabotropic glutamate receptors (mGluR2/3) (Moussawi et al. 2011). mGluR2/3 are G_i -coupled receptors primarily located on presynaptic terminals to suppress presynaptic release (Pomierny-Chamioło et al. 2014). As such, the decreased function of these receptors may disinhibit presynaptic terminals after cocaine withdrawal, resulting in increased levels of evoked glutamate release. Consistently, experimentally increasing the activity of mGluR2/3 normalizes the levels of stimulus-evoked glutamate release in the NAc after cocaine withdrawal (Smith et al. 2016). Importantly, experimental restoration of glutamate homeostasis by restoring basal glutamate levels in the NAc (Baker et al. 2003; Reissner et al. 2014) or increasing mGluR2/3 activities in the NAc (Peters and Kalivas 2006; Smith et al. 2016) attenuates the reinstatement of cocaine seeking after withdrawal.

Taken together, repeated exposure to cocaine and other psychostimulants (Roberts-Wolfe and Kalivas 2015) increases the release probability of glutamatergic synapses in specific NAc afferents, and this presynaptic adaptation contributes to drug seeking, relapse, and likely other drug-induced behaviors.

POSTSYNAPTIC ADAPTATIONS

Adaptations in Postsynaptic AMPARs

After withdrawal from noncontingent exposure (e.g., intraperitoneal [i.p.] injection) to cocaine, AMPAR-mediated glutamatergic synaptic strength in NAc MSNs is persistently increased (Boudreau and Wolf 2005; Kourrich et al. 2007), but this increase can be transiently normalized on reexposure to cocaine (Thomas et al. 2001). Subsequent studies show that this potentiation also occurs after withdrawal from contingent, self-administration of cocaine (Anderson et al. 2008; Conrad et al. 2008; Ortinski et al. 2012; Gipson et al. 2013), albeit with different cellular details between the two conditions (see below). Behaviorally, although com-

prising results link the NAc AMPAR up-regulation to the expression of cocaine-induced locomotor sensitization, the time courses of these cellular and behavioral alterations do not perfectly match (Boudreau and Wolf 2005; Pascoli et al. 2013). Specifically, the increase in postsynaptic strength reaches to a significant level only after prolonged withdrawal from the drug (Boudreau et al. 2007; Wolf and Tseng 2012), although locomotor sensitization is expressed right after repeated exposure to cocaine. Rather, the delayed up-regulation of synaptic AMPARs is likely mediated by withdrawal-associated mechanisms rather than an acute effect of cocaine and involved in withdrawal-associated behaviors (see below).

Exposure to cocaine not only quantitatively, but also qualitatively, changes postsynaptic AMPARs in NAc MSNs. In naive or saline-trained rats, the vast majority (~95%) of AMPARs in NAc MSNs contain GluA2 subunits and are calcium impermeable (CI-AMPA) (Conrad et al. 2008). However, following long-term withdrawal from cocaine self-administration, GluA2-lacking AMPARs, which are calcium permeable (CP-AMPA), are expressed and accumulate (Conrad et al. 2008; Wolf and Tseng 2012; Wang et al. 2018). These cocaine withdrawal-induced CP-AMPA are thought to primarily be homomeric GluA1-containing AMPARs, possibly also with a small portion of GluA1-GluA3 heteromers, as GluA1 subunit is preferentially up-regulated after long-term withdrawal from cocaine (Conrad et al. 2008). In general, accumulation of CP-AMPA is more reliably detected after more intensive cocaine procedures, such as after prolonged self-administration conditions that result in progressive intensification of cocaine seeking after withdrawal, a behavior phenomenon termed “incubation” of cocaine craving (Grimm et al. 2001) but not after noncontingent cocaine exposure or relatively short self-administration procedures that do not induce incubation (McCutcheon et al. 2011b; Purgianto et al. 2013). However, exceptions do exist for noncontingent procedures in which cue-cocaine association may play a key role (see below) (Pascoli et al. 2014; Terrier et al. 2016; Shukla et al. 2017).

Nonetheless, pharmacological inhibition (Conrad et al. 2008) or optogenetic removal of NAc CP-AMPA receptors (Lee et al. 2013; Ma et al. 2014) abolishes incubation of cocaine craving, demonstrating a critical role of CP-AMPA receptors in promoting the propensity for cocaine relapse after extended periods of withdrawal.

Mechanisms of Psychostimulant-Induced AMPAR Plasticity

Induction and expression are two relatively independent phases of long-term plasticity at glutamatergic synapses. A heavily studied form of long-term synaptic plasticity is *N*-methyl-D-aspartate receptor (NMDAR)-dependent long-term potentiation (LTP), which is induced by NMDAR activation and expressed, in many cases, through increased function of individual AMPARs or/and an increased number of functional AMPARs (Derkach et al. 2007; Huganir and Nicoll 2013). Similar to other brain regions, NMDAR-dependent LTP can be induced at NAc glutamatergic synapses (Yao et al. 2004; Pascoli et al. 2013). Inhibition of NAc NMDARs during the cocaine procedure prevents cocaine-induced up-regulation of synaptic AMPARs as well as the development of locomotor sensitization (MacAskill et al. 2014), suggestive of cocaine-induced AMPAR regulation as an LTP-like process. In addition to NMDARs, dopamine receptors may also be involved in NAc LTP. Stimulation of dopamine 1 (D1) receptors phosphorylates and promotes synaptic insertion of AMPARs in the NAc (Chao et al. 2002a,b; Mangiavacchi and Wolf 2004). Furthermore, self-stimulation of dopamine neurons is sufficient to up-regulate NAc AMPARs, mimicking the effect of cocaine (Pascoli et al. 2015). Given the substantially increased level of dopamine in the NAc after cocaine administration, it is possible that the dopamine signaling is a molecular bridge for cocaine to up-regulate synaptic AMPARs. This speculation is supported by the observation that the effect of cocaine on AMPARs and the magnitude of cocaine-induced dopamine increases are correlated (Brown et al. 2010). Furthermore, an enhanced VTA dopaminergic signaling to the NAc is es-

sential for AMPAR up-regulation in MSNs after repeated exposure to cocaine (Mameli et al. 2009). Thus, activation of NMDARs and dopamine receptors appears to be the first cellular step in the process of cocaine-induced up-regulation of NAc AMPARs.

Intracellular signaling pathways coupled to NMDARs and dopamine receptors may serve as the second step toward cocaine-induced up-regulation of NAc AMPARs. The carboxyl terminus of GluA1 subunit is enriched in modulatory sites (Derkach et al. 2007), among which the Ser831 is the phosphorylation site of calcium-calmodulin kinase II (CaMKII) (Lisman et al. 2012). Activation of synaptic NMDARs induces a calcium influx, which triggers CaMKII-mediated phosphorylation of GluA1, resulting in synaptic targeting and stabilization of GluA1-containing AMPA receptors, as well as enhancing their single-channel conduction (Barria et al. 1997; Hayashi et al. 2000; Poncer et al. 2002; Lee et al. 2003; Lu et al. 2010). In addition to GluA1, CaMKII also stabilizes newly inserted synaptic AMPARs through phosphorylation of transmembrane AMPAR regulatory proteins (TARPs) (Tomita et al. 2005; Opazo et al. 2010). Possibly through stabilization of AMPARs and other mechanisms, CaMKII activity also increases the head size of dendritic spines, thus structurally stabilizing the potentiated synapses (Anderson et al. 2008; Robison et al. 2013). These and other molecular processes link the induction to the expression of classic NMDAR-dependent LTP at glutamatergic synapses (Malenka et al. 1988, 1989; Malinow et al. 1989; Giese et al. 1998). After withdrawal from cocaine, the basal level of active CaMKII in the NAc is increased, corresponding with the increased level of synaptic AMPARs in rats (Boudreau et al. 2009; Ferrario et al. 2011), and likely also in human subjects (Robison et al. 2013). Conversely, inhibition of NAc CaMKII impairs the acquisition of cocaine and amphetamine self-administration as well as the reinstatement of drug seeking after withdrawal (Anderson et al. 2008; Loweth et al. 2013). Thus, CaMKII may be a key signaling component in the induction and expression of cocaine-induced LTP-like up-regulation of synaptic AMPARs in NAc MSNs.

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The cAMP-PKA signaling pathway coupled to D1 receptors is also implicated in cocaine-induced AMPAR plasticity. Exposure to cocaine, as well as cocaine-predicting cues, triggers a rapid surge of dopamine in the NAc, resulting in activation of D1 receptors and cAMP-PKA signaling pathway (Phillips et al. 2003; Stuber et al. 2005; Surmeier et al. 2007). Inhibition of the NAc D1 receptor-cAMP-PKA signaling pathway compromises the acquisition of cocaine self-administration and other cocaine-associated learning, suggesting the essential role of this pathway (Self et al. 1998; Caine et al. 2007; Anderson et al. 2008; Pisanu et al. 2015). Although the intracellular signaling is typically transient, accumulating evidence suggests that the NAc cAMP-PKA pathway undergoes persistent alteration after exposure to cocaine. Specifically, cocaine self-administration leads to an increase in the basal activity of PKA in the NAc, which persists through long periods of withdrawal (Lu et al. 2003), whereas inhibition of NAc PKA results in long-lasting impairment of cocaine seeking (Lynch and Taylor 2005) and consolidation of cocaine memories associated with conditioned place preference (CPP) (Cervo et al. 1997). These long-term behavioral effects may stem from cAMP-PKA-mediated up-regulation of GluA1-containing AMPARs, an up-regulation that has been shown to exist in the NAc (Esteban et al. 2003; Mangiavacchi and Wolf 2004). Interestingly, PKA-mediated trafficking of GluA1-containing AMPARs results in their insertion primarily to extrasynaptic sites, followed by translocation to the synaptic sites on activation of NMDAR-CaMKII signaling (Pas-safaro et al. 2001; Esteban et al. 2003; Sun et al. 2005; Gao et al. 2006), suggesting a cross talk between the NMDAR-CaMKII and D1-cAMP-PKA signaling pathways. This notion is further supported by the observation that the CaMKII activity is required for some of the D1 receptor-mediated effects on NAc AMPARs and cocaine seeking (Anderson et al. 2008).

In addition to the direct effects, the CaMKII and cAMP-PKA signaling may also incorporate other signaling pathways to regulate AMPARs. Exposure to cocaine activates ERK (Boudreau et al. 2007; Ferrario et al. 2011) and CREB

(Mattson et al. 2005), two signaling molecules implicated in transcriptional regulation of post-synaptic adaptations of NAc glutamatergic synapses after exposure to cocaine (Brown et al. 2011; Pascoli et al. 2013). The ERK and CREB signaling pathways, together with other signaling pathways, form a complex transcriptional and translational network involved in psychostimulant-induced cellular adaptations, but the content is beyond the scope of the current manuscript. Interested readers may find several in-depth reviews on this topic (Chao and Nestler 2004; Carlezon et al. 2005; Lu et al. 2006; Girault et al. 2007; Dong and Nestler 2014).

Although the adaptations discussed above primarily pertain to Hebbian-like plasticity, another important form of plasticity, namely homeostatic plasticity, should not be ignored. Indeed, it is thought that most molecular and cellular changes after exposure to drugs of abuse are homeostatic responses (Kalivas 2005). Homeostatic plasticity is the adjustment of synaptic strength or membrane excitability up or down to maintain a stable functional output of neurons in response to “unexpected” changes (Turrigiano 2008; Davis 2013). Homeostatic mechanisms regulating synaptic strength and membrane excitability often interact with each other to achieve an overall stability. In the NAc, changes in synaptic input induce changes in the membrane excitability of MSNs, and vice versa, which is termed “synapse-membrane homeostatic cross talk” (SMHC) (Ishikawa et al. 2009; Wang et al. 2018). Through SMHC, an increase or decrease in synaptic input lead to decreases or increases in membrane excitability, respectively. The SMHC “sensors” for synaptic strength are GluN2B-containing NMDARs, which convey a signal of synaptic strength through the coupled CaMKII signaling to regulate the membrane excitability (Wang et al. 2018). Following cocaine self-administration, synaptic levels of AMPARs are minimally altered initially (see above), but synaptic GluN2B-containing NMDARs are up-regulated (Huang et al. 2009), which generates a false signal of an increase in the glutamatergic synaptic strength and triggers the first round of synapse-to-membrane SMHC to decrease the membrane

excitability through up-regulation of SK2-type calcium-activated potassium channels (Wang et al. 2018). The decreased membrane excitability, and ultimately spiking output, triggers a second membrane-to-synapse SMHC, promoting synaptic accumulation of CP-AMPA after long-term withdrawal (Wang et al. 2018). Importantly, disrupting SMHC during cocaine self-administration, thus preventing subsequent CP-AMPA accumulation, disrupts incubation of cocaine craving after long-term withdrawal (Wang et al. 2018). These results provide an example that homeostatic dysregulation is induced by drug experience to participate in establishing pathophysiological changes at NAc glutamatergic synapses.

In many brain regions, early-stage expression of NMDAR-dependent LTP is partially mediated by synaptic insertion of CP-AMPA, which are replaced by CI-AMPA during the late stage (Shi et al. 2001; Plant et al. 2006; Guire et al. 2008; Morita et al. 2013; Park et al. 2016). The prolonged expression of synaptic CP-AMPA in the NAc after withdrawal from cocaine self-administration is partially mediated by dysregulated mechanisms underlying CP-AMPA trafficking. After withdrawal from cocaine self-administration, eukaryotic elongation factor 2 (eEF2) and eukaryotic initiation factor 2 α (eIF2 α) are dephosphorylated, effects that promote protein translation (Werner et al. 2018), and the eEF2- and eIF2 α -dependent protein translation is required for maintaining high levels of CP-AMPA in NAc MSNs during withdrawal from cocaine (Scheyer et al. 2014). However, the effects of cocaine on protein translation appear to be confined to GluA1 without affecting the overall protein translation (Stefanik et al. 2018). In addition to the potentially increased expression, synaptic maintenance of CP-AMPA is also altered after withdrawal from cocaine. In saline-trained animals, the tonic mGluR1 signaling promotes CP-AMPA internalization, contributing to low levels of CP-AMPA at glutamatergic synapses on NAc MSNs (Loweth et al. 2018). In animals after withdrawal from cocaine, experimental activation of mGluR1 reverses the accumulation of synaptic CP-AMPA (McCutcheon et al. 2011a; Loweth

et al. 2014). However, the basal level of NAc mGluR1 is decreased after withdrawal from cocaine, which, together with NMDAR and other signaling, may lead to insufficient removal, and thus accumulation, of CP-AMPA (Loweth et al. 2014; Stefanik et al. 2018).

Cell-Type and Pathway Specificity

The results discussed above were obtained by broad sampling of NAc synapses, which presumably arise from most NAc afferents. With optogenetics distinguishing different NAc afferents, recent studies reveal that after withdrawal from noncontingent exposure to cocaine, glutamatergic synapses in the mPFC (Pascoli et al. 2013), BLA (MacAskill et al. 2014), vHipp (Britt et al. 2012), and PVT (Joffe and Grueter 2016) projections to NAc MSNs are all potentiated, albeit with some degree of discrepancy after different cocaine procedures. Subsequent studies show a similar cross-projection potentiation after withdrawal from cocaine self-administration, but with unique features in each projection. Specifically, IL-to-NAc synapses are potentiated partially through up-regulation of CP-AMPA, although PL-to-NAc synapses are potentiated primarily through up-regulation of CI-AMPA (Pascoli et al. 2013, 2014; Ma et al. 2014). Similar to the IL projection, potentiation of BLA-to-NAc synapses is associated with synaptic incorporation of CP-AMPA (Lee et al. 2013; Ma et al. 2016; Terrier et al. 2016). In contrast, potentiation of neither vHipp-to-NAc synapses nor PVT-to-NAc synapses is associated with CP-AMPA (Pascoli et al. 2014; Neumann et al. 2016). Thus, although most examined glutamatergic projections to the NAc are potentiated after withdrawal from cocaine, the potentiation in each projection is likely achieved through different mechanisms.

In addition to the projection specificity, cocaine-induced synaptic adaptation is also differentially induced in different MSN subpopulations in the NAc, namely MSNs that express high levels of dopamine D1 receptors (D1-MSNs) versus MSNs that express high levels of dopamine D2 receptors (D2-MSNs) (Gerfen et al. 1990). D1- and D2-MSNs have overlap-

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ping, but also distinct projection patterns, and are thus thought to be involved in different aspects of motivated behaviors (Bocklisch et al. 2013; Kupchik et al. 2015; O'Connor et al. 2015; Creed et al. 2016). This notion is supported by observations that selective manipulation of NAc D1-MSNs versus D2-MSNs with optogenetics or chemogenetics often results in different or, on many occasions, opposing effects on reward/drug-elicited behaviors, with D1-MSNs promoting, whereas D2-MSNs suppressing these behaviors (Lobo et al. 2010; Bock et al. 2013; Cheng et al. 2016). However, the concept of behavioral separation between NAc D1- versus D2-MSNs should not be taken in its extreme term. In vivo recordings detect that both D1- and D2-MSNs are activated in reward-elicited behaviors, although differing in activation pattern (Calipari et al. 2016). Furthermore, D2-MSNs are recruited to establish cocaine CPP (Sjulson et al. 2018). Moreover, through different downstream projections, NAc D1-MSNs are simultaneously involved in two seemingly opposite behaviors, drug reinstatement and extinction (Gibson et al. 2018). Thus, although NAc D1- and D2-MSNs are capable of “opposing” each other, their activation is highly coordinated for successful accomplishment of naturally occurring behaviors.

After most commonly used drug procedures, cocaine-induced potentiation of glutamatergic synapses primarily occurs in D1-MSNs (Dobi et al. 2011; Bock et al. 2013; Pascoli et al. 2013, 2014), which is in concert to the role of D1 receptors in regulating AMPAR trafficking discussed above. However, synaptic strengthening can also be induced in D2-MSNs after robust cocaine self-administration procedures (Terrier et al. 2016). Given that experimentally strengthening glutamatergic synaptic inputs to D2-MSNs dampens cocaine-motivated behaviors (Bock et al. 2013), it is tempting to speculate that cocaine-induced synaptic strengthening in D2-MSNs functions as an endogenous mechanism to circumvent the development of drug addiction. Nonetheless, despite certain inconsistencies, most studies detect a reliable synaptic potentiation in the BLA, mPFC, vHipp, and PVT projections to NAc D1-MSNs after with-

drawal from noncontingent cocaine procedures (MacAskill et al. 2014; Pascoli et al. 2014; Joffe and Grueter 2016). After prolonged withdrawal from cocaine self-administration, the potentiation of mPFC-to-D1-MSN synapses (Pascoli et al. 2014; Terrier et al. 2016), and also likely BLA-to-D1-MSN synapses (Lee et al. 2013), involves synaptic incorporation of CP-AMPA. Compared with D1-MSNs, results related to D2-MSNs are mixed, with no changes (Pascoli et al. 2014), potential weakening (Kim et al. 2011), or strengthening (Bock et al. 2013; Terrier et al. 2016) all observed.

Cocaine-induced adaptations in different projections to the NAc differentially contribute to cocaine-associated behaviors. After withdrawal from cocaine, optogenetic induction of long-term depression (LTD) that selectively reverses cocaine-induced potentiation of mPFC-to-NAc synapses compromises the expression of locomotor sensitization and cue-induced cocaine seeking (Pascoli et al. 2013, 2014; Ma et al. 2014). However, projections from the PL and IL subdivisions of the mPFC have differential effects, with depotentiation of cocaine-potentiated PL-to-NAc synapses reducing cue-induced cocaine seeking, whereas depotentiation of IL-to-NAc synapses enhancing this behavior (Ma et al. 2014). For BLA-to-NAc synapses, reversing or preventing cocaine-induced potentiation also compromises locomotor sensitization and cue-induced cocaine seeking after drug withdrawal (Lee et al. 2013; MacAskill et al. 2014). For vHipp-to-NAc synapses, reversing cocaine-induced potentiation similarly decreases cue-induced cocaine seeking (Pascoli et al. 2014). For PVT-to-NAc synapses, however, disrupting their transmission does not affect cue-induced cocaine seeking after drug withdrawal (Neumann et al. 2016), raising the possibility that, rather than positive reinforcement, drug-induced adaptations at PVT-to-NAc synapses are preferentially involved in negative affective states, as demonstrated in a study of opioids (Zhu et al. 2016).

Silent Synapses and Synaptogenesis

Experience-dependent synaptic plasticity typically occurs as a strengthening and weakening

of preexisting synapses. However, under certain conditions, experience-dependent plasticity is also associated with generation of new synapses (Holtmaat and Svoboda 2009). Generation of new synaptic connections between neurons may create new pathways or patterns of information flow, which can be critical in forming memories of novel experiences that have never been confronted. This is particularly relevant to the development of drug addiction, during which new, multidimensional associative memories are established in drug-naïve subjects.

During the brain development, newly generated immature glutamatergic synapses often only contain NMDARs, whereas AMPARs are either absent or highly labile, thus AMPAR-silent synapses or, simply, silent synapses (Kerchner and Nicoll 2008). After development, synaptogenesis becomes less active and levels of silent synapses decline substantially (Durand et al. 1996; Petralia et al. 1999). However, synaptogenesis continues in adult brains for metabolic turnover as well as experience-induced synaptic remodeling (Maletic-Savatic et al. 1999; Holtmaat et al. 2006; Xu et al. 2009; Yang et al. 2009). Newly generated synapses in the adult brain are thought to be thin or filopodia-like, consistent with nascent silent synapses during development (Maletic-Savatic et al. 1999; Matsuzaki et al. 2001; Holtmaat et al. 2006; Knott et al. 2006; Fu et al. 2012). These nascent, immature synapses then gradually enlarge (Knott et al. 2006), corresponding to the functional maturation via AMPAR incorporation (Matsuzaki et al. 2004). Some of these experience-generated synapses persist over the lifetime of a memory and are critical for the behavioral expression of these memories (Yang et al. 2009; Attardo et al. 2015; Cichon and Gan 2015; Hayashi-Takagi et al. 2015). These results lead to a compelling possibility that experience-generated synapses encode specific memory traces of these experiences.

Exposure to cocaine and other psychostimulants increases the density of dendritic spines in the NAc, suggesting a synaptogenesis process (Robinson and Kolb 1999; Robinson et al. 2001; Russo et al. 2010). In concert, electrophysiological recordings reveal that either noncon-

tingent- or self-administration of cocaine increases the level of silent synapses in NAc MSNs (Huang et al. 2009; Wright et al. 2019). Cocaine-generated silent synapses show several features that are consistent with nascent, immature synapses: (1) they are enriched in GluN2B-containing NMDARs (Huang et al. 2009; Brown et al. 2011), a hallmark of nascent glutamatergic synapses (Monyer et al. 1994; Kirson and Yaari 1996; Tovar and Westbrook 1999); (2) blocking AMPAR internalization does not prevent cocaine-induced generation of silent synapses (Graziane et al. 2016); and (3) cocaine-induced increase in silent synapses is tightly correlated to a selective increase in the densities of thin and filopodia-like spines (Graziane et al. 2016). As such, these silent synapses may represent a distinct set of new synapses that are specifically generated for cocaine experience.

During withdrawal from cocaine, newly generated NAc silent synapses gradually mature by recruiting AMPARs, with a maturation process lasting 7–10 days (Huang et al. 2009; Lee et al. 2013; Shukla et al. 2017). If generation of silent synapses establishes new, cocaine-specific circuit patterns, maturation may consolidate these patterns and enhance the corresponding behavioral outputs. Consistent with this notion, experimentally resiliencing the already matured silent synapses or preventing the maturation process decreases the magnitude of cue-induced cocaine seeking and place preference (Lee et al. 2013; Shukla et al. 2017; Wright et al. 2019). In theory, high levels of cocaine seeking require intact cocaine-associated memories, successful reactivation of these memories, and mechanisms that support the expression of cocaine seeking. Recent results show that resiliencing cocaine-generated synapses before memory reactivation effectively decreases subsequent cocaine seeking, but during cocaine seeking once it is triggered, cocaine-generated synapses are in an AMPAR-silent state (Wright et al. 2019). These results tie cocaine-generated silent synapses to the storage or reactivation, instead of the expression of cocaine memories.

Cocaine-induced generation of silent synapses is detected in all three glutamatergic projections to the NAc that have been tested thus

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far, including projections from the BLA (Lee et al. 2013), both the IL and PL of the mPFC (Ma et al. 2014), and PVT (Neumann et al. 2016). However, how the synapses mature differs among these projections. In the BLA and IL projections, cocaine-generated silent synapses mature after drug withdrawal by recruiting CP-AMPA receptors (Lee et al. 2013; Ma et al. 2014), although in the PL and PVT projections, silent synapses mature by recruiting CI-AMPA receptors (Ma et al. 2014; Neumann et al. 2016). Thus, through silent synapse generation and maturation, these and possibly other glutamatergic projections to the NAc are remodeled, potentially resulting in projection-specific behavioral consequences. Indeed, after withdrawal from cocaine self-administration and maturation of silent synapses, experimentally resiliencing silent synapses selectively in the BLA or PL projection attenuates cue-induced cocaine seeking and thus incubation of cocaine craving (Lee et al. 2013; Ma et al. 2014), suggesting that silent synapse-mediated remodeling of the BLA and PL promotes drug relapse. In contrast, resiliencing silent synapses in the IL-to-NAc projection enhances cue-induced cocaine seeking (Ma et al. 2014), suggesting an antirelapse function of this remodeling. The behavioral consequence of silent synapse-mediated remodeling of the PVT-to-NAc projection has not been examined, but it has been shown that disrupting the entire projection does not affect cue-induced cocaine seeking after drug withdrawal (Neumann et al. 2016), a result that, to some extent, excludes the involvement of PVT-to-NAc projection in cocaine seeking.

The cell-type specificity of cocaine-induced generation of silent synapses remains underexplored. A recent study, however, observed that, after noncontingent exposure to cocaine, silent synapses are primarily generated on D1-MSNs (Graziane et al. 2016). After long-term withdrawal and maturation of silent synapses, the ratio of glutamatergic synaptic strength in D1-MSNs over D2-MSNs is increased, suggesting that, through generation and maturation of silent synapses selective on D1-MSNs, the balance of the NAc output is shifted in favor of D1-MSNs. Because noncontingent exposure and self-administration can induce different synap-

tic adaptations (Wolf 2016), it will be important to determine whether the D1-MSN-selective generation of silent synapses holds true after cocaine self-administration.

The molecular mechanisms underlying synaptogenesis during development and adulthood are complex and still insufficiently understood (Waites et al. 2005; Südhof 2018). In the context of cocaine-induced generation of silent synapses and potential synaptogenesis, several mechanisms are potentially involved (Russo et al. 2010; Dong and Nestler 2014), among which are CREB- and Δ FosB-mediated transcriptional mechanisms. CREB is a transcriptional factor downstream from the cAMP-PKA pathway, which is rapidly activated in the NAc after exposure to cocaine, resulting in multidimensional behavioral consequences (Carlezon et al. 1998, 2005; Terwilliger et al. 1991; Barrot et al. 2002). Experimental expression of an active form of CREB in hippocampal neurons induces silent synapses and spinogenesis (Murphy and Segal 1997; Marie et al. 2005), which may result from CREB-mediated transcription of synaptogenic proteins (McClung and Nestler 2003). In the NAc, mimicking cocaine-induced up-regulation of CREB activity increases the density of dendritic spines and triggers the generation of silent synapses in cocaine-naïve animals, although preventing CREB activation prevents generation of silent synapses and spinogenesis in cocaine-trained animals (Brown et al. 2011). These results suggest that cocaine-induced activation of CREB is one of the initial molecular processes leading to subsequent cellular changes in the NAc, such as generation of silent synapses and synaptogenesis. Similar to CREB, Δ FosB is also involved in transcriptional regulation of many synaptogenic proteins (McClung and Nestler 2003). Repeated exposure to cocaine induces repeated production of Δ FosB, which, because of its resistance to degradation, gradually accumulates and persists throughout the withdrawal periods (Hope et al. 1994; Damez-Werno et al. 2012; Lobo et al. 2013; Robison et al. 2013). Overexpression of Δ FosB selectively increases the density of immature spines in NAc D1-MSNs in cocaine-naïve mice, but not D2-MSNs, suggesting D1-MSNs-selective gen-

eration of silent synapses (Grueter et al. 2013; Robison et al. 2013). Thus, CREB and Δ FosB potentially regulate cocaine-induced generation of NAc silent synapses in a similar manner. Indeed, the acute genomic effects of CREB and Δ FosB are strikingly similar in the NAc (McClung and Nestler 2003), leading to an important question of how the CREB and Δ FosB transcriptional signaling pathways interact and coordinate to promote synaptogenesis and silent synapses generation after exposure to cocaine.

A prominent endogenous activator of CREB is the cAMP-PKA signaling pathway, which is coupled to D1 receptors and thus may result in D1-MSN-specific effects of CREB activation. This scenario provides a molecular mechanism for D1-MSN-selective generation of silent synapses after certain cocaine procedures (Graziane et al. 2016). Associated with early genes, Δ FosB can be induced by a variety of signaling pathways, among which a recent study shows that both CREB and serum response factor (SRF) are required for the cocaine-induced increase in Δ FosB in the NAc (Vialou et al. 2012), suggesting CREB as an upstream component to Δ FosB. Further supporting the upstream status of CREB, after certain cocaine procedures, Δ FosB and spinogenesis are selectively induced in NAc D1-MSNs (Lobo et al. 2013). It is important to note that other signaling pathways, such as the CaMKIV and TrkB-MAPK signaling, also regulate CREB activities (Carlezon et al. 2005; Muschamp and Carlezon 2013). Thus, through BDNF and NMDA receptors, CREB may also be activated in non-D1-MSNs after some cocaine procedures.

On activation of CREB, Δ FosB, and other synaptogenic signaling, the next critical step for cocaine-induced generation of silent synapses is the up-regulation of GluN2B-containing NMDARs. GluN2B-containing NMDARs are up-regulated by CREB and Δ FosB signaling in the NAc (Brown et al. 2011; Grueter et al. 2013), and have been critically implicated in synaptogenesis (Tovar and Westbrook 1999; Nakayama et al. 2005; Gambrill and Barria 2011). Repeated exposure to cocaine up-regulates GluN2B-containing NMDARs in the NAc, with a large portion residing at newly

generated silent synapses, whereas preventing CREB activation prevents cocaine-induced up-regulation of GluN2B-containing NMDARs (Huang et al. 2009; Brown et al. 2011).

Following initial cocaine-induced up-regulation, GluN2B-containing NMDARs are gradually replaced by non-GluN2B NMDAR subtypes during drug withdrawal (Wright et al. 2019), indicative of synaptic maturation and stabilization (Barria and Malinow 2002, 2005; Adesnik et al. 2008; Gray et al. 2011; Matta et al. 2011). This NMDAR subtype switch may involve Δ FosB signaling, which is persistently active after exposure to cocaine (Chao and Nestler 2004). Specifically, cyclin-dependent kinase-5 (Cdk5), a downstream gene of Δ FosB signaling, is triggered to be expressed at high levels in NAc MSNs after exposure to cocaine (Bibb et al. 2001). High levels of Cdk5 promote phosphorylation GluN2B subunits at the S1116 site, a posttranslational regulation that allows internalization of GluN2B-containing NMDARs for replacement and synapse maturation (Norrholm et al. 2003; Plattner et al. 2014). Another player that may participate in stabilizing cocaine-generated synapses is PSD-95, a synaptic scaffold protein regulating the maturation and stabilization of glutamatergic synapses (El-Husseini et al. 2000; Ehrlich et al. 2007; Hanse et al. 2013; Favaro et al. 2018). In mouse cortical neurons, genetic deletion or knockdown of PSD-95 prevents neonatal silent synapses from maturation (Favaro et al. 2018). In NAc MSNs, knockdown of PSD-95 prevents maturation of cocaine-generated silent synapses (Shukla et al. 2017). Both the GluN2B- and PSD-95-associated synaptic maturation and stabilization mechanisms are not unique to cocaine, but rather “generic” for most CNS glutamatergic synapses. What is unique for maturation of cocaine-generated silent synapses is the CP-AMPA insertion. In previous sections, we have discussed potential mechanisms related to the cross-board up-regulation of synaptic CP-AMPA. It remains to be examined whether these discussed mechanisms or, rather, some cocaine-specific mechanisms mediate the CP-AMPA insertion to cocaine-generated silent synapses, and whether these newly inserted

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CP-AMPA receptors are stable or subject to further modification.

Transient Synaptic Plasticity

Thus far, we have discussed long-term adaptations at NAc glutamatergic synapses that contribute to drug-induced behaviors. Several lines of recent studies show that transient plasticity may also play an important role in expression of drug-seeking and, likely, the dynamics of cocaine-associated memories.

One of the most studied forms of such transient plasticity is induced in animals after extinction from cocaine self-administration, after which cocaine seeking diminishes to low levels. At this time point, reexposure to the cues previously associated with cocaine self-administration reinstates strong cocaine seeking. This cue reexposure transiently increases the strength (measured by AMPAR/NMDAR ratio) of glutamatergic synaptic transmission to NAc MSNs, and this potentiation lasts ~2 hours (Gipson et al. 2013), whereas preventing this transient potentiation compromises cue-induced reinstatement of cocaine seeking (Smith et al. 2014, 2016). In the cocaine-seeking test, operant responses typically do not result in cocaine infusion (thus, seeking), but if cocaine infusion occurs, this transient potentiation is rapidly reversed (Spencer et al. 2017). In these cue reexposure tests, cocaine-trained animals are exposed to not only the cocaine-associated cues that may elicit cocaine memories, but also cues/contexts associated with the extinction procedure that may prevent cocaine seeking. Subsequent studies reveal that the transient potentiation is induced by both cocaine- and extinction-associated cues, but preferentially expressed in D1-MSNs versus D2-MSNs, respectively (Roberts-Wolfe et al. 2018, 2019). Thus, through NAc D1-MSNs versus D2-MSNs, this transient potentiation may promote both cocaine seeking and refraining simultaneously, with the final behavioral readout determined by the balance of these two processes.

Mechanisms underlying this transient potentiation have begun to be unveiled, involving a multistep regulation of glutamatergic signaling

in the NAc. Specifically, this transient potentiation is dependent on glutamate release from the mPFC projection, such that inhibiting the mPFC-to-NAc projection abolishes this potentiation (Gipson et al. 2013; Stefanik et al. 2016). Released glutamate is thought to subsequently activate mGluR5 on a subset of local inhibitory interneurons that express neuronal nitric oxide synthase (nNOS) (Smith et al. 2016). Activation of mGluR5, in turn, triggers the release of nitric oxide (NO) from these interneurons, which activates matrix metalloproteinase 9 (MMP-9), eventually leading to postsynaptic potentiation of glutamatergic synapses on MSNs (Smith et al. 2014, 2016). The signaling mechanisms downstream from MMP activation underlying the transient postsynaptic potentiation remain to be determined, but may involve cell-adhesion molecules such as integrin (Wiggins et al. 2011; Huntley 2012; Mulholland et al. 2016).

In contrast to cue-induced potentiation after extinction from cocaine self-administration, reexposure to cocaine after withdrawal from non-contingent cocaine administration triggers a transient depotentiation of NAc glutamatergic synapses (Boudreau et al. 2007; Kourrich et al. 2007), and this depotentiation contributes to cocaine-induced reinstatement of CPP (Bennetworth et al. 2019). Furthermore, this cocaine-induced depotentiation appears to occur specifically at synapses in the IL projection, a projection that suppresses cocaine-seeking behaviors (Peters et al. 2008; Ma et al. 2014). Thus, this depotentiation may contribute to cocaine seeking by removing the suppressive break.

Although the above-described transient plasticity directly influences ongoing behaviors, other forms of transient plasticity may function to regulate cocaine-associated memories. Similar to other memories, consolidated cocaine-associated memories can be transiently destabilized on cue-induced memory reactivation, and then reconsolidated approximately 6 hours later (Tronson and Taylor 2007; Torregrossa and Taylor 2013). During this 6-hour destabilization window, cocaine-associated memories become susceptible to disruption. To explore the synaptic underpinnings, a recent study examines the functional state of cocaine-

generated silent synapses (Wright et al. 2019). On reexposure to cocaine-associated cues after withdrawal from cocaine self-administration, cocaine-generated silent synapses become transiently resiled via internalization of CP-AMPA receptors, and then mature again by re-recruiting CP-AMPA receptors 6 hours later, defining the destabilization and reconsolidation of cocaine-associated memories. Furthermore, preventing the rematuration of cocaine-generated synapses during the destabilization window prevents memory reconsolidation and decreases subsequent cue-induced cocaine seeking, a behavioral readout of cue-associative cocaine memories. These results depict a synaptic mechanism dictating the dynamic states of cocaine-associated memories.

CONCLUDING REMARKS

We have attempted to provide a relatively thorough review of adaptive changes at NAc glutamatergic synapses that have clear implications in addiction-related behaviors. These findings position NAc glutamatergic transmission as a key cellular target through which cocaine and other psychostimulants reshape motivated behaviors. Although we are excited by these important findings, we would also like to raise two conceptual considerations for future studies. First, these findings represent an enormous number of drug-induced adaptations, each characterized from a reductionistic point of view. However, drug addiction is a behavioral consequence resulting from complex neuroadaptations crossing multiple domains. It might be the time to meta-analyze these findings from a holistic point of view for higher levels of understanding of the brain mechanisms underlying drug addiction. Second, most of these findings are obtained in tissues prepared from drug-trained animals. As such, the changes in synaptic compositions or structures may accurately predict how the functional capacity of these synapses is altered (e.g., a six-gear car upgraded to a nine-gear car), but how these synapses are operating during the behavior (e.g., whether the car is actually running in gear two, four, six, or nine) remains to be determined. It is our wishful thinking that some

of the results or viewpoints included in this manuscript may provide a stepping stone for future studies to address these and other challenging but exciting questions.

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