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Rapid, Transient Synaptic Plasticity in Addiction

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Abstract

Chronic use of addictive drugs produces enduring neuroadaptations in the corticostriatal glutamatergic brain circuitry. The nucleus accumbens (NAc), which integrates cortical information and regulates goal-directed behavior, undergoes long-term morphological and electrophysiological changes that may underlie the increased susceptibility for relapse in drug-experienced individuals even after long periods of withdrawal. Additionally, it has recently been shown that exposure to cues associated with drug use elicits rapid and transient morphological and electrophysiological changes in glutamatergic synapses in the NAc. This review highlights these dynamic drug-induced changes in this pathway that are specific to a drug seeking neuropathology, as well as how these changes impair normal information processing and thereby contribute to the uncontrollable motivation to relapse. Future directions for relapse prevention and pharmacotherapeutic targeting of the rapid, transient synaptic plasticity in relapse are discussed.

1.1 Introduction

Drug addiction is a leading cause of poor health and has enormous societal impact (Volkow et al., 2011). When investigating the neural mechanisms underlying various phenomena associated with drug addiction, glutamatergic input into the nucleus accumbens (NAc) emerges as a major regulator of addictive behavior. Long term changes in basal extracellular levels of glutamate (Baker et al., 2003; Peters et al., 2009b; Wydra et al., 2013) and synaptic strength at glutamatergic synapses in the NAc (Boudreau and Wolf, 2005; Conrad et al., 2008; Gipson et al., 2013; Kourrich et al., 2007; Martin et al., 2006; Moussawi et al., 2009) are induced by chronic drug use. Although these slow and persistent changes may render the individual more vulnerable to relapse, they are not the mechanism triggering the relapse event.

A relapse event is frequently triggered by environmental cues associated with drug use, which rapidly initiate an urge to use drugs. This rapid change in behavior is driven by rapid, transient increases in synaptic strength in glutamatergic synapses between prefrontal cortex (PFC) afferents and medium spiny neurons (MSNs) of the NAc. Moreover, while the rapid, transient relapse-associated changes in excitatory synapses on MSNs are shared between classes of addictive drugs including nicotine, cocaine and heroin (Gipson et al., 2012; Gipson et al., 2013; Shen et al., 2011), different classes of addictive drugs produce opposite long-term effects on excitatory transmission in the NAc. Specifically, repeated psychostimulant administration brings about an increase (Conrad et al., 2008; Gipson et al., 2012; Gipson et al., 2013; Kourrich et al., 2007), and opioids cause a decrease in synaptic strength in the NAc as measured electrophysiologically and by dendritic spine morphology

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(Robinson and Kolb, 1999a; Shen et al., 2011; Spiga et al., 2005; but see Wu et al., 2012 who showed synaptic potentiation in the nucleus accumbens shell (NAshell) after withdrawal from morphine). It should be noted, however, that functional relevance of structural changes in spines remains difficult to interpret, as is discussed below in section 3.1.1.

This review will focus on the glutamatergic input to the NAc and its involvement in drug relapse. We will discuss the sources of glutamatergic afferents to the NAc, as well as synaptic changes in glutamatergic input to the NAc. Special emphasis will be given to the newly discovered rapid, transient synaptic plasticity that underlies the initiation of relapse to drug seeking. Finally, we will discuss potential relevance to relapse prevention and pharmacotherapy development.

2.1 Glutamatergic Projections to the Nucleus Accumbens involved in Addiction and Relapse

Glutamate neurotransmission in the NAc has been shown to underlie drug-seeking behavior, and changes in NAc glutamatergic transmission are thought to encode the transition from occasional use of drugs to the pathological inability to control drug-seeking behavior (Kalivas and Volkow, 2011; Kasanetz et al., 2010; Peters et al., 2009b; Wolf and Ferrario, 2010). Neurons in the NAc receive convergent glutamatergic afferents from different cortical and subcortical regions (Figure 1), including innervation by projections from the prefrontal cortex (PFC) (Berendse et al., 1992; Fuller et al., 1987; Gorelova and Yang, 1997; Papp et al., 2012; Reynolds and Zahm, 2005; Stefanik et al., 2012), the basolateral amygdala (BLA) (Groenewegen et al., 1980; McDonald, 1991a, b; Papp et al., 2012; Stuber et al., 2011), the ventral hippocampus (vHipp) (Britt et al., 2012; DeFrance et al., 1985; Groenewegen et al., 1987; Papp et al., 2012; Thompson and Swanson, 2010), the midline/intralaminar thalamic nuclei (Berendse and Groenewegen, 1990; Kelley and Stinus, 1984; Smith et al., 2004; Vertes et al., 2012), and the recently described glutamatergic neurons in the ventral tegmental area (VTA) (Gorelova et al., 2012; Hnasko et al., 2012; Yamaguchi et al., 2007; Yamaguchi et al., 2011). Interestingly, the different inputs are topographically arranged, such that each projection innervates different regions in the NAc, rather than diffusely innervating the entire NAc (Voorn et al., 2004). For example, afferents from the prelimbic and infralimbic subcompartments of the medial PFC are mostly segregated and project mainly to the NAc core and NAshell, respectively (Groenewegen et al., 1999; Wright and Groenewegen, 1995; Zahm, 2000); the projections from the BLA are compartmentally organized and more densely innervate the NAshell than the NAc core (Papp et al., 2012; Wright et al., 1996); the vHipp projections are most concentrated in the medial NAshell (Britt et al., 2012); and the paraventricular nucleus of the thalamus projects mainly to the NAshell (Papp et al., 2012; Smith et al., 2004). Microstructural studies show that all of the above projections synapse on spine heads of the GABAergic MSNs (Kita and Kitai, 1990; Meredith et al., 1990; Papp et al., 2012; Sesack and Grace, 2010). It should be noted that other studies also showed that in spite of the topographical segregation between different inputs in the NAc, individual MSNs can be innervated by projections from two or more different regions (Britt et al., 2012; French and Totterdell, 2002, 2003; Sesack and Grace, 2010; Stuber et al., 2011), thus implying that the MSNs have a role in integrating glutamatergic information from multiple sources.

While most research we describe below focuses on the projection from the PFC to NAc, other glutamatergic inputs are also implicated to a greater or lesser extent in the modulation of drug-seeking behavior. For example, the BLA integrates information regarding conditioned associations and affective drive (Sesack and Grace, 2010). Thus, activating the BLA and its projection to the NAc induces self-stimulation behavior (Stuber et al., 2011),

while inhibiting this projection impairs drug-seeking induced by conditioned cues (Di Ciano and Everitt, 2004; Fuchs et al., 2007; McLaughlin and See, 2003; See et al., 2003). Similarly, activation of ventral hippocampal afferents to the NAc shell promotes addiction-like behavior (Grace et al., 2007; Vorel et al., 2001), while inhibiting them attenuates drug-induced locomotion (Britt et al., 2012; Lodge and Grace, 2008).

A major glutamatergic input to the NAc comes from the PFC. This cortical region regulates goal-directed behaviors by integrating information from numerous brain regions and “making a decision” to execute an adaptive behavioral response (Balleine and O’Doherty, 2010; Killcross and Coutureau, 2003; Sharpe and Killcross, 2012; Smith et al., 2012). The medial portion of the PFC, which sends extensive projections to the NAc, is divided to dorsal prefrontal (PL), and ventral infralimbic (IL) regions. Although not completely segregated, the IL projects to the NAc shell and has been associated with extinction of drug seeking, and the PL projects to the NAc core and is implicated in the execution of drug seeking (Capriles et al., 2003; Kalivas et al., 2005; LaLumiere et al., 2012; McFarland et al., 2004; McFarland and Kalivas, 2001; McLaughlin and See, 2003; Millan et al., 2011; Peters et al., 2009b; Peters et al., 2008; Rocha and Kalivas, 2010; Stefanik et al., 2012; Van den Oever et al., 2008). Thus, inactivation of the PL prevents reinstated drug seeking in various animal models, while inactivation of the IL increases cocaine seeking. Interestingly, it has been shown that without a period of extinction training, inactivation of the IL can inhibit drug-seeking behavior (Koya et al., 2009). The IL-NAc shell pathway appears to be involved in the learning of extinction rather than simply in the suppression of drug seeking behavior (LaLumiere et al., 2010); its activation reduces lever pressing by strengthening the extinction behavior (LaLumiere et al., 2012) when such behavior was learned. Thus, it is important to emphasize differences in various animal models when integrating mechanisms underlying relapse vulnerability.

Opposite roles for the PL and the IL, such as controlling drug seeking, have been reported for fear expression and extinction (Peters et al., 2009a) as well as cue-induced cocaine seeking (McLaughlin and See, 2003). In fear conditioning experiments, the PL promoted fear behavior and its inhibition reduced expression of fear to contextual stimuli (Corcoran and Quirk, 2007; Peters et al., 2009a; Sotres-Bayon and Quirk, 2010). The IL, on the other hand, is involved in fear extinction, and its inhibition decreases fear expression (Corcoran and Quirk, 2007; Peters et al., 2009a; Sotres-Bayon and Quirk, 2010). The anatomically segregated pathways of the PL-to-NAc core and IL-to-NAc shell projections, together with the results showing opposite involvement of PL and IL in the control of drug-seeking behavior, has led to a more simplified hypothesis of two parallel pathways in the control of drug-seeking behavior – the PL-to-NAc core pathway which promotes drug-seeking behavior and the IL-to-NAc shell pathway which is responsible for the extinction of drug-seeking behavior (Peters et al., 2009b). It should be noted, however, that studies examining the role of IL inactivation on reinstated drug seeking show inconsistent results, depending on the regimen used (Willcocks and McNally, 2013). Thus, IL inactivation has been shown to increase, decrease, or have no effect on reinstated drug seeking when using different behavioral paradigms, such as contextual renewal (Bossert et al., 2012; Willcocks and McNally, 2013), reinstatement after extinction (Peters et al., 2008), and cue-induced reinstatement after extinction from cocaine or methamphetamine self-administration (McLaughlin and See, 2003; Rocha and Kalivas, 2010).

The glutamatergic input from the PL to the NAc core is of particular interest when studying the mechanisms underlying the reinstatement of drug-seeking. The PL has been shown to be important for action-outcome contingencies and adjusting goal-directed behavior in response to changes in the environment or task conditions (Dalley et al., 2004; Sharpe and Killcross, 2012; Smith et al., 2012), such as those used in animal models of cue-induced reinstatement

of drug seeking. Thus, exposure to a drug-associated cue after extinction training, a manipulation known to induce PL-dependent reinstatement of drug-seeking behavior, is likely to involve changes in the PL-NAcore projections. In the next sections we review the alterations in glutamatergic neurotransmission in the NAcore that occur during various phases of the addiction cycle, with a focus on our recent findings showing rapid cue-induced changes induced by the presentation of a drug-associated cue to reinstate drug-seeking.

3.1 Enduring Drug-Induced Synaptic Plasticity: Alterations in Nucleus Accumbens Morphology and Synaptic Currents

Addictive drugs exert their reinforcing properties by targeting the mesocorticolimbic dopamine pathway, which includes the cell bodies in the VTA and axon terminals in the NAc, BLA and PFC. Although different drugs of abuse have specific targets (e.g., nicotine is an agonist for nicotinic acetylcholine receptors, cocaine is an inhibitor of the dopamine transporter, and heroin is an agonist at mu opioid receptors), they share a common ability to increase dopamine concentrations in efferents from the VTA to NAc, as well as within the VTA itself (Corrigall et al., 1994; Di Chiara and Imperato, 1988; Nestler, 2005). Addiction has been associated with altered neuroplasticity in this mesocorticolimbic brain circuitry, which is important in guiding goal-directed behavior (Everitt and Robbins, 2005; Peters et al., 2009b). Within a simplified PFC-NAc-VTA circuit, the NAc serves as a “gateway” through which information regarding the direction of behavioral output is processed from limbic cortex to motor subcircuits (Groenewegen et al., 1996; Yin and Knowlton, 2006). It is thought that the transition to compulsive drug seeking arises from an impaired ability of this subcircuit to effectively process information about negative environmental contingencies, leading to an inability to inhibit prepotent drug-associated responses; thereby the addict is rendered prone to relapse.

Due to its critical importance in governing behavior, it is important to examine the cellular changes induced by drugs of abuse within this circuit. Opposite changes in excitatory synaptic transmission have been found at early versus late withdrawal as well as with re-exposure to cocaine (Grueter et al., 2012). One surrogate measure commonly used to examine excitatory synaptic transmission is the ratio of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor- to N-methyl-d-aspartate (NMDA) receptor-mediated excitatory postsynaptic currents (EPSCs). At 24 hr after repeated cocaine injections, depression of synaptic transmission, quantified as a decrease in AMPA:NMDA ratio, was found in the NAc (Kourrich et al., 2007; Thomas et al., 2001). A current interpretation of this decrease is an increase in NMDA receptor-mediated currents typical in silent synapses, the number of which is increased in the NAcore after repeated cocaine treatment (Huang et al., 2009; Wolf and Ferrario, 2010). In contrast to the first 24 hr after discontinuing cocaine administration, excitatory synapses in NAc MSNs are potentiated following a protracted withdrawal phase (Boudreau and Wolf, 2005; Kourrich et al., 2007; Ortinski et al., 2012); consistent with an increase in dendritic spine head diameter (d_h) and spine density of NAc MSNs after three weeks withdrawal from daily cocaine injection (Shen et al., 2009) or an increase in density after one month withdrawal from cocaine self-administration (Robinson et al., 2001). Dendritic spines are highly plastic (Nimchinsky et al., 2002), and changes in their morphology are a structural correlate of alterations in synaptic strength (De Roo et al., 2008; Dietz et al., 2012; Dumitriu et al., 2012; Kasai et al., 2010). Indeed, parallel drug-induced increases in both spine d_h as well as AMPA:NMDA ratio have been observed in NAc following two weeks of withdrawal from cocaine self-administration (Gipson et al., 2013). It is hypothesized that the increased d_h results from increased actin cycling and trafficking of AMPA receptors to the cell surface (Dietz et al., 2012; Kopec et al., 2006; Shen et al., 2009), leading to an increase in synaptic strength. Based on these data with chronic cocaine, it is tempting to posit that increased synaptic

strength in NAc MSNs is an important mediator of relapse. However, extended withdrawal from heroin or morphine elicits an opposite, enduring reduction in d_h and AMPA:NMDA ratio (Robinson and Kolb, 1999b; Shen et al., 2011). Thus, the enduring increase or decrease in synaptic strength observed after withdrawal from addictive drugs is not a consistent neuroadaptation between addictive drugs and may therefore not mediate the shared characteristic of relapse vulnerability.

3.1.1 Functional Relevance of Changes in Spine Morphology

A question remains whether the changes in the spine's morphology per se are of functional importance or even a good marker for changes in synaptic strength. It is widely accepted that behavior is driven by neuronal activity determined by the sum of electrical signals generated by ionotropic receptors embedded in the postsynaptic membrane of the spine. In the frame of this notion the increase in spine head size might be a side effect of recruitment of AMPA receptors to the spine, a result of addition of membrane to the spine when AMPA-containing vesicles fuse with the spine membrane (Kopec and Malinow, 2006; Park et al., 2004; Park et al., 2006). Indeed, theoretical studies have shown that changes in spine morphology, while important for chemical compartmentalization within the spine, have a negligible effect on the size of the electrical signal in the soma (Gulledge et al., 2012; Jaslove, 1992; Kawato and Tsukahara, 1984; Koch and Zador, 1993; Segev et al., 1995; Wilson, 1984). However, recent studies reveal a more complicated scenario, reflecting a bidirectional interaction between structure (i.e spine morphology) and function (i.e. glutamate currents) in the spine (Hotulainen and Hoogenraad, 2010; Nimchinsky et al., 2002). In particular, a complicated interaction between glutamatergic ionotropic receptors (AMPA and NMDA) and actin, a main structural element in the spine (Fifkova and Delay, 1982; Matus et al., 1982), has been observed in a number of studies. Activation of AMPA receptors during LTP increases d_h (Fischer et al., 2000; Zhao et al., 2012a, b) and this increase is attributed to the stabilization of spines through actin-dependent mechanisms (Fischer et al., 2000) or to a change in the balance between the filament (F-actin) and monomer (G-actin) forms of actin (Zhao et al., 2012a). This would imply that changes in AMPA receptor activation drive the changes in spine morphology. However, the quantity of AMPA receptors embedded in the spine is itself affected by actin activation. Thus, pharmacological manipulation of F-actin activity was sufficient to change the amplitude and frequency of spontaneous AMPA currents in mature cultured hippocampal neurons (Ivanov et al., 2009). In addition, pharmacological inhibition of F-actin affected the movement of receptors into and out of the synapse (Charrier et al., 2006; Cingolani and Goda, 2008) and its activation drastically increased the levels of CaMKII in the postsynaptic compartment (Okamoto et al., 2004). Since CaMKII is essential for recruitment of AMPA receptors into the postsynaptic membrane, activation of F-actin per se could increase AMPA receptor density in the postsynaptic membrane. This would imply the morphological changes might themselves drive changes in synaptic AMPA receptor expression that underlie synaptic potentiation. Along these lines, during chemical LTP (LTP induced by chemical depolarization) it was shown that morphological enlargement of the spine occurs before the increase in synaptic AMPA expression (Kopec et al., 2006). It should be noted that in addition to the large amount of data linking changes in spine morphology and synaptic function, an emerging view notes that the signaling pathways that trigger structural and functional plasticity are, in some cases, dissociable (Cingolani and Goda, 2008). However, it has not yet been shown that spine morphological changes unaccompanied by changes in synaptic strength have an effect on behavior.

3.2 Alterations in Receptor Composition Following Drug Exposure: Return to Developmental Conditions?

Drug-induced alterations in AMPA and NMDA- receptor composition has been observed at various time-points after drug exposure, such as increased calcium permeable synaptic GluA2-lacking AMPA and extrasynaptic GluN2B-containing NMDA receptors (Bellone and Luscher, 2012; Conrad et al., 2008; Shen et al., 2011). These receptors are highly expressed during early postnatal synaptic development (Kumar et al., 2002; Monyer et al., 1994), and it is possible that drugs of abuse reopen this critical period of augmented synaptic plasticity by increasing GluN2B and GluA1 expression. This possibility is also consistent with an apparent increase in actin cycling in the NAc after discontinuing daily injections of either cocaine or morphine (Russo et al., 2010; Toda et al., 2006). Given that heroin reduces while cocaine increases synaptic strength, it is reasonable to speculate that the shared susceptibility to undergo synaptic plasticity is a more accurate correlate of addiction rather than the resting state of synaptic strength after discontinuing chronic drug treatment. How these alterations contribute to compulsive drug-seeking is not understood, but it is hypothesized that the increase in calcium permeable AMPA receptors may enhance learning to discriminate among different environmental stimuli to select the reward with the highest value in the decision making process (Bellone and Luscher, 2012). Accordingly, the enduring alterations in synaptic plasticity may provide a neural substrate for maladaptive processing of highly salient drug-paired stimuli in individuals with substance abuse disorders.

Following prolonged withdrawal from extended access to cocaine self-administration (but not experimenter-delivered cocaine), formation of Ca²⁺-permeable (CP) GluA2-lacking AMPA receptors in the NAc has been observed (McCutcheon et al., 2011b). Additionally, these CP-AMPA receptors have been implicated in the incubation of cocaine craving, in which greater withdrawal periods from cocaine lead to proportionally increased drug-seeking behavior (Conrad et al., 2008). Interestingly, the switch in AMPA receptor subunits occurs between day 25–30 of cocaine withdrawal and is maintained through day 70 (Wolf and Tseng, 2012). As well, accumulation of these receptors appears to take place under very specific conditions, only occurring after withdrawal from extended access to cocaine self-administration (Purgianto et al., 2013). Increased GluN2B NMDA receptors in the VTA has been observed after an acute cocaine injection (Schilstrom et al., 2006), as well as in the NAc after early (Huang et al., 2009) and extended withdrawal from experimenter-delivered cocaine (Schumann and Yaka, 2009) and self-administered heroin (Shen et al., 2011) and nicotine (Gipson et al., submitted). The increase in GluN2B-containing NMDA receptors has been linked to an increase in the generation of silent synapses after exposure to cocaine (Brown et al., 2011). Silent synapses are glutamatergic connections found during development as well as after exposure to cocaine, and defined by the presence NMDA receptor-mediated responses in the absence of stable AMPA receptor responses (Lee and Dong, 2011). Indeed, these silent excitatory synapses were found in the NAc shell at 24–48 hours after cocaine exposure, and it is thought that they allow NAc MSNs to more readily recruit AMPA receptors and thus increase synaptic transmission (Huang et al., 2009). Although this may be an underlying mechanism for the rapid, transient increases in synaptic plasticity we see in the NAc core during cue-induced cocaine seeking (Gipson et al., 2013), it is unclear if these silent synapses endure into periods of extended withdrawal and if they occur in the NAc core, as the NAc shell was examined at an early withdrawal time-point (Huang et al., 2009). Additionally, the paradigms used in these two studies differ between experimenter- and self-administered cocaine, extinction training versus abstinence, and two weeks of withdrawal versus two days. Finally, it is important to note that Gipson et al. (2013) used a short access (2-hr) self-administration condition, and it is unknown if the rapid

cue-induced changes in plasticity occur after withdrawal from conditions of extended cocaine access (e.g., 6-hr sessions).

Persistently impaired NAc synaptic plasticity is hypothesized to underlie the transition from goal-directed to habitual behavior in addiction. In the NAc drug-induced loss of both long-term potentiation (LTP) and long-term depression (LTD) occurs after withdrawal from chronic cocaine or heroin self-administration (Knackstedt et al., 2010b; Martin et al., 2006; Moussawi et al., 2009; Shen and Kalivas, 2012). A discrepancy exists in the literature, however, where one study found loss of LTD NAc core of cocaine-extinguished but not abstinent animals (Knackstedt et al., 2010b), and another study found that animals in 21 days abstinence from cocaine showed the loss of LTD (Martin et al., 2006). In the latter study, however, the loss of LTD is also not observed in non-contingent yoked cocaine or in sucrose trained animals (Martin et al., 2006), indicating that this deficit is specific to the pathological state induced by a history of voluntary cocaine self-administration (Madsen et al., 2012). In contrast, LTD can be induced both 24 hr after 50–72 days of cocaine self-administration (Kasanez et al., 2010) and after abstinence from extended access to cocaine self-administration (McCutcheon et al., 2011b). Taken together, these data suggest that loss of LTD may be paradigm-specific. Also as discussed in section 4.1, it is possible that while the NAc is in an enduring potentiated or depotentiated state after extended withdrawal from cocaine or heroin, respectively (Gipson et al., 2013; Kourrich et al., 2007; Shen et al., 2011; Shen et al., 2009), these cells do not have great flexibility to undergo experimenter-induced synaptic plasticity, but perhaps have capacity to undergo rapid synaptic plasticity induced by a motivated behavior.

3.3 Relationship Between Synaptic Plasticity and Glutamate Homeostasis

Some types of long term plasticity depend on the activity of extrasynaptic glutamatergic receptors, such as extrasynaptic NMDA receptors or metabotropic glutamate receptors (Asrar and Jia, 2013; Liu et al., 2012a; Oh et al., 2012; Papouin et al., 2012), and it has been hypothesized that changes in the extracellular basal levels of glutamate may contribute to the loss of synaptic plasticity in MSNs after cocaine or heroin self-administration (Peters et al., 2009b). Indeed, basal extracellular glutamate levels in the NAc are decreased after extinction from cocaine self-administration, a result of downregulated catalytic subunit (xCT) of the glial cystine-glutamate exchanger (system xc⁻). The relative paucity of glutamate prevents activation of extrasynaptic mGluRs necessary for the expression of long-term plasticity (Moussawi et al., 2009). In this way, it is possible that cocaine-induced loss of metaplasticity at cortico-accumbens synapses after withdrawal from cocaine underlies the failure of the PFC to regulate drug-seeking behavior. However, neither the reduction in xCT nor a reduction in basal extracellular glutamate is measured in the NAc after withdrawal from heroin self-administration (Shen et al., unpublished), indicating that this effect of cocaine is not central to relapse in addiction to all drugs of abuse.

In contrast with xCT, self-administration of all addictive drugs studied thus far induces an enduring reduction of the glial glutamate transporter GLT-1 in the NAc, including cocaine, heroin and nicotine (Gipson et al., 2012; Knackstedt et al., 2010a; Shen et al., unpublished data). The enduring reduction in glutamate uptake from the vicinity of the synapse would be predicted to increase the overflow of glutamate from the synapse during periods of high synaptic activity, as might occur during a relapse event. Indeed, the reinstatement of heroin or cocaine seeking is associated with a transient increase in extracellular glutamate that is prevented by inhibiting the glutamatergic projection from PFC to NAc (LaLumiere and Kalivas, 2008; McFarland et al., 2003). Given that this transient rise in extracellular glutamate could stimulate extrasynaptic GluN2B-containing NMDA receptors and dysregulate postsynaptic plasticity (Papouin et al., 2012; Petralia, 2012), we recently used

the reinstatement model of relapse to demonstrate that relapse is associated with the rapid and transient induction of LTP-like changes in synaptic strength (Gipson et al., 2013).

4.1 Rapid, Transient Plasticity during Relapse to Drug-Seeking

Although alterations in synaptic plasticity have been examined during withdrawal from drugs of abuse, it has remained unclear until recently if synaptic changes are initiated by and contribute to relapse. Cues associated with cocaine use can precipitate relapse, and using a rat model of cue-induced cocaine reinstatement, two measures of synaptic plasticity in the NAc were recently quantified – spine head diameter (d_h) and AMPA- to-NMDA ratio (A/N) ((Gipson et al., 2013); see Figure 2). The presentation of cocaine-conditioned cues elicited rapid (within 15 min of initiation of contingent cue reinstatement) and transient increases in both d_h and A/N. The magnitude of synaptic potentiation was positively correlated with the intensity of 5 or 15 min of reinstated cocaine seeking, and inhibiting PL glutamatergic inputs to the NAc prevented both synaptic potentiation and reinstatement. These results show that rapid cue-evoked synaptic potentiation in the NAc may underpin relapse to cocaine use. Further supporting the possibility that the induction of synaptic potentiation may mediate the initiation of reinstated behavior, active lever presses were significantly correlated with d_h and A/N only during the first 5 min bin after initiating the reinstatement session, and not during the second and third 5 min bins (Figure 3). Similar results, although with a somewhat slower timescale, were found in another recent study with d-amphetamine, where re-exposure to the drug-paired context elicited rapid (within 30 min) NAc d_h enlargement in FosB (+) cells (Vezina et al., 2012). Also, heroin-induced reinstatement of heroin seeking was associated with a short-term (45 min) increase in d_h and LTP measured *in vivo* by electrically stimulating the PFC and recording field potentials in the NAc (Shen et al., 2011). Thus, in contrast with opposite changes in resting synaptic strength in NAc MSNs by cocaine and nicotine versus heroin, a rapid, reversible synaptic potentiation occurs during drug or cue induced reinstatement for both drugs (Figure 4); indicating that reinstatement-associated synaptic potentiation might be a better correlate of relapse vulnerability than enduring drug-induced synaptic plasticity in the NAc. This possibility is supported by the fact that operant reinstatement after withdrawal from sucrose self-administration did not result in rapid synaptic plasticity in NAc MSNs (Gipson et al., 2013).

The biochemical mechanisms underlying the rapid plasticity associated with drug seeking are unknown, although recent evidence indicates this may be mediated by CaMKII. Indeed, both L-type Ca²⁺ channels (linked to NAc GluA1 receptor plasticity in cocaine sensitization (Schierberl et al., 2011)) and CaMKII (important in transporting AMPA receptors to synapses (Boehm and Malinow, 2005)), were shown to mediate interaction between glutamatergic and dopaminergic signaling in the NAc during initiation of cocaine-induced cocaine seeking (Anderson et al., 2008). Interestingly, increased CaMKII phosphorylation was found in the NAc shell but not core during reinstatement of morphine seeking (Liu et al., 2012b), indicating that this mechanism may underlie relapse vulnerability across different drug classes.

An intriguing finding in the cue-induced drug-seeking results presented above is the strikingly similar changes in synaptic strength and spine morphology. This similarity suggests that spine morphology is intimately linked with synaptic strength. Indeed, although still somewhat controversial (see Cingolani and Goda, 2008), it is generally accepted that spine head enlargement reflects strengthening of the synapse (Alvarez and Sabatini, 2007; Holtmaat and Svoboda, 2009; Hoogenraad and Akhmanova, 2010). Larger spine volumes are positively correlated with the area covered by the postsynaptic density (PSD) (Harris et al., 1992; Schikorski and Stevens, 1999), which in turn is proportional to synaptic AMPA

receptors expression (Cingolani and Goda, 2008; Kharazia and Weinberg, 1999; Nusser et al., 1998; Takumi et al., 1999) and sensitivity to glutamate (Matsuzaki et al., 2001) (although see Beique et al., 2006; Elias and Nicoll, 2007 who show that spines of the same size can show very different AMPA receptor function). Also, electrically driving LTP or LTD is known to cause an increase (Allison et al., 1998; Goldin et al., 2001) or a decrease (Nagerl et al., 2004; Okamoto et al., 2004; Zhou et al., 2004) in d_h , respectively.

It is noteworthy that the rapid synaptic potentiation observed after reinstatement of drug seeking is seemingly contradictory to the lack of ability to induce either LTP or LTD following withdrawal discussed above. However, an essential difference between these two sets of findings is that while the loss of LTP or LTD is revealed using artificial electrical stimulation of NAc glutamatergic afferents, the presentation of a drug-associated cue induces specific, physiological activation of the relevant NAc afferents. This indicates that while MSNs have become relatively refractory to the induction of synaptic plasticity by stimuli unrelated to the experience of drug use, stimuli associated with drug use (i.e. conditioned cues or the drug itself) efficiently induce LTP-like synaptic plasticity. We propose that the loss of LTP or LTD in response to a stimulus unrelated to drug use combined with the selective induction of synaptic plasticity related to drug associated stimuli may contribute to two key characteristics of relapse vulnerabilities: 1) the difficulty addicts have in developing behavior that competes with relapse to drug use (i.e. reduced plasticity by nondrug-associated stimuli), and 2) the overwhelming desire to obtain drug (i.e. the robust LTP induced by drug-associated stimuli).

5.1 Clinical Implications and Future Directions

Drug-paired environmental cues abnormally affect the morphology and physiology of synapses in the accumbens, and this may mediate the uncontrollable effect cues have in initiating relapse to drug use. As mentioned above, the rapid plasticity associated with initiating relapse to drug seeking may be linked to alterations in glutamate homeostasis, and supports the following sequence of events: 1) Following chronic cocaine or heroin, reduced basal glutamate levels result in lower binding to presynaptic mGluR2/3 and increased levels of activator of G protein signaling 3 (AGS3) (Bowers et al., 2004; Yao et al., 2005), thereby decreasing inhibitory tone on presynaptic glutamate release (Xi et al., 2002); 2) withdrawal from addictive drug use is associated with downregulated glial glutamate uptake (GLT-1) which allows glutamate to spill over from the synapse; 3) drug-associated stimulus increases activity at glutamatergic synapses resulting in excessive glutamate spillover from the synapse and stimulating extrasynaptic receptors such as GluN2B-containing NMDA receptors and mGluR5; 4) activation of GluN2B and mGluR5 (Cosgrove et al., 2011) signals rapid increases in d_h and A/N which drive and perhaps perpetuate drug seeking behavior, likely via increasing calcium influx or release from internal stores, respectively (Figure 5). Based on this sequence of events, targeting key proteins involved in synaptic plasticity may be crucial in the development of drug relapse prevention pharmacotherapies.

Because impaired glutamate homeostasis has been associated with reinstated drug-seeking, repairing glutamate levels via various drugs that target dysregulated proteins of the tripartite synapse (presynapse, postsynapse and glia; see Figure 5) has been of pharmacotherapeutic interest. Of these pharmacotherapies, one is the commonly prescribed antibiotic ceftriaxone, and another is the antioxidant N-acetylcysteine (NAC), both of which restore levels of GLT1 and extracellular glutamate in the NAc of rats trained to self-administer cocaine, nicotine or heroin (Knackstedt et al., 2010a; Moussawi et al., 2011; Shen et al., submitted). NAC also restores the ability to electrically induce LTP and LTD in cocaine-withdrawn animals (Moussawi et al., 2009). In humans, NAC decreases cigarette use (Knackstedt et al., 2009), marijuana use (Gray et al., 2010), and cocaine craving and symptoms of withdrawal,

as well as restores glutamate levels in cocaine-dependent individuals (Amen et al., 2011; Schmaal et al., 2012). Although NAC holds promise as a pharmacotherapy, in some cases data in various disorders including autism, schizophrenia, depression, cocaine, marijuana, smoking, bipolar disorder, gambling, among others remain preliminary and require replication (Berk et al., 2013). Indeed, as NAC continues to be tested in various disorders, it is likely to show relatively higher efficacy in some disorders.

In addition to targeting glial proteins involved in glutamate homeostasis, both presynaptic and postsynaptic metabotropic and ionotropic glutamate receptors have been targeted in animal models of relapse. Given that the overflow of glutamate would produce excessive stimulation of extrasynaptic GluN2B-containing NMDA receptors and metabotropic glutamate receptors, antagonists to these glutamate receptors would be postulated to reduce reinstated drug seeking. Pharmacological inhibition of mGluR5 and stimulation of mGluR2/3 receptors reduces cue- and cocaine-induced reinstatement of cocaine-seeking behavior, as well as nicotine self-administration (Kenny et al., 2003; Peters and Kalivas, 2006; Wang et al., 2013). Stimulation of mGluR1 under conditions of increased CP-AMPA receptor accumulation may also represent a novel pharmacotherapeutic approach (Loweth et al., 2013; McCutcheon et al., 2011a), as activation of these receptors inhibits CP-AMPA receptor mediated synaptic transmission. As well, targeting GluN2B-containing NMDA receptors inhibits heroin seeking (Shen et al., 2011). Interestingly, the effects of NAC on metaplasticity (Moussawi et al., 2009) and glutamate transmission in the PFC-NAC synapse (Kupchik et al., 2012) are themselves mediated by mGluR2/3 and mGluR5.

5.2 Conclusions

The successes to date of targeting drug-induced changes in proteins and physiology in the tripartite synapse shown in Figure 5 are encouraging. However, with the exception of NAC, all studies have been conducted in the reinstatement animal model of relapse. While this model possesses face validity, and the NAC studies lend some criterion validity to the model (Epstein et al., 2006), more fully translating these findings into clinical trials is necessary. Within the animal model additional future studies are needed to determine if these treatments induced temporary antagonism of the vulnerability to reinstate, or if chronic treatment can provide enduring protection. While encouraging data in this regard has been obtained with daily NAC treatments during extinction training after cocaine or heroin self-administration (Moussawi et al., 2011; Reichel et al., 2011; Zhou et al., 2009), substantial additional work into the mechanisms of not only relapse associated changes in synaptic transmission but how to target these changes to provide enduring protection from relapse remains to be conducted.

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Highlights

- Glutamatergic input to the NA and its involvement in drug relapse is discussed.
- Cue-induced relapse to cocaine requires rapid, transient plasticity in accumbens.
- Future directions for relapse prevention are discussed.

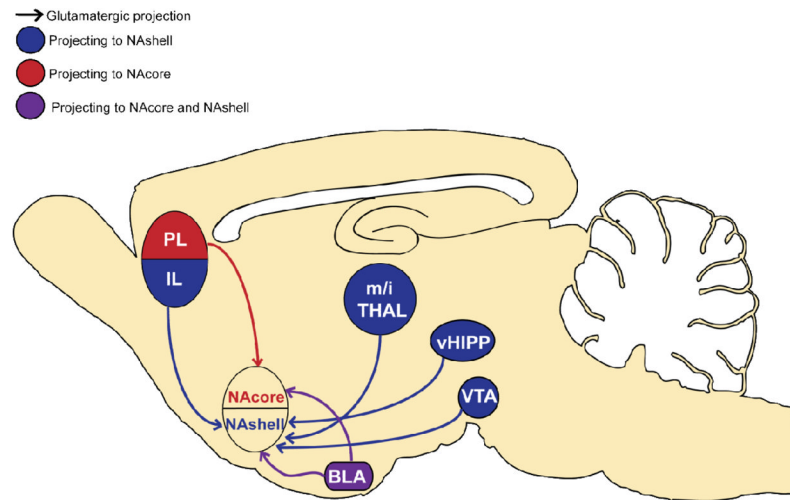


Figure 1. Glutamatergic afferents to the nucleus accumbens involved in addictive behavior
 While both nucleus accumbens subregions (NAcore and NAshell) receive input from all cortical regions, there is strong topographic bias. The NAcore receives glutamatergic input mainly from the prelimbic cortex (PL) and the basolateral amygdala (BLA), whereas the NAshell receives strong glutamatergic input from a larger number of sources, including the infralimbic cortex (IL), the ventral hippocampus (vHIPP), glutamatergic neurons in the ventral tegmental area (VTA), the midline/intralaminar thalamus nuclei (m/i THAL), and the BLA.

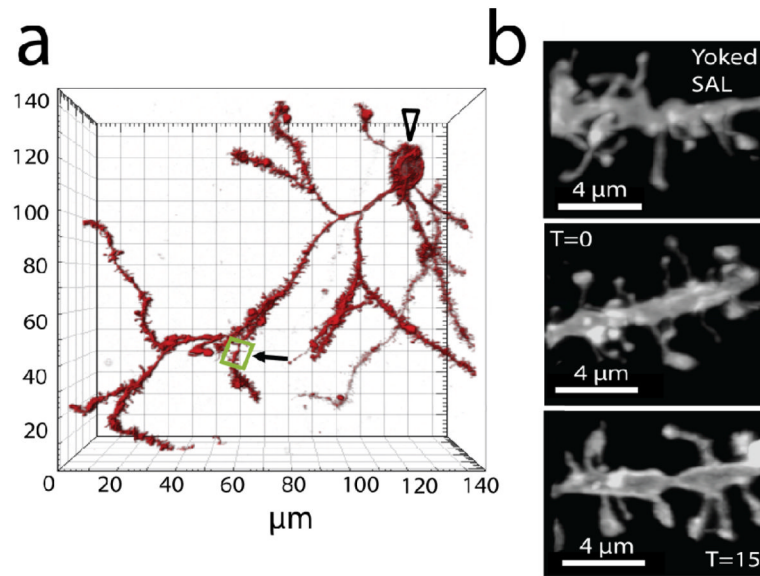


Figure 2. Spine enlargement after 15 min of cue-induced cocaine reinstatement in NAc core medium spiny neurons

(a) Example of NAc core medium spiny neuron. Clear arrow - location of soma; boxed region - segment from yoked saline animal shown in (b). **(b)** Sample dendrites from NAc core spiny cells in yoked saline or cocaine-trained rats at 0 min (no reinstatement; T=0) and 15 min after initiating cue-induced reinstatement (T=15).

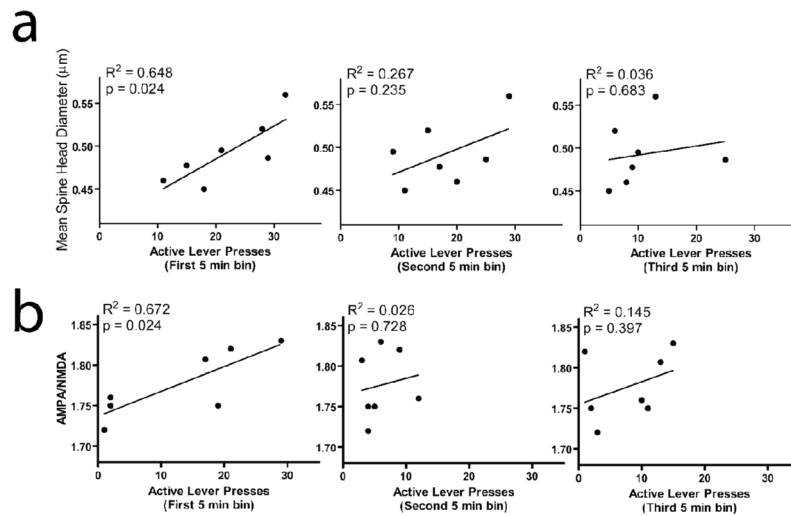


Figure 3. Synaptic potentiation is correlated with behavior in the first 5 min after initiating relapse

Linear regressions of either **(a)** mean spine head diameter or **(b)** AMPA/NMDA ratio and active lever presses in either the first (0–5 min), second (6–10 min), or third (11–15 min) 5 min bin of the 15 min cue relapse session, indicating that only the initiation (first 5 min bin) of relapse is significantly correlated with synaptic potentiation.

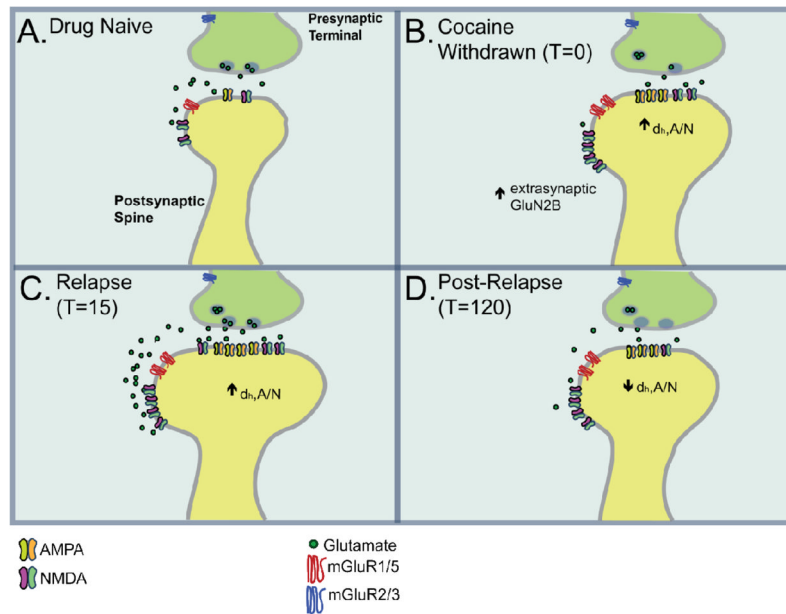


Figure 4. Timeline of postsynaptic changes in NAc core MSNs during withdrawal from and relapse of cocaine seeking

(a) A drug naïve state. (b) In cocaine-withdrawn animals (T=0), d_h is enlarged compared to drug-naïve animals, with increased AMPA and GluN2B-containing NMDA receptors, resulting in an increased A/N. (c) Fifteen minutes into a relapse event (T=15) more AMPA receptors are inserted into the postsynaptic membrane; the result is a further increase in d_h and A/N. (d) The increased d_h and A/N rapidly reverses, and 120 minutes after the initiation of the relapse event (T=120), both measures return to pre-relapse levels.

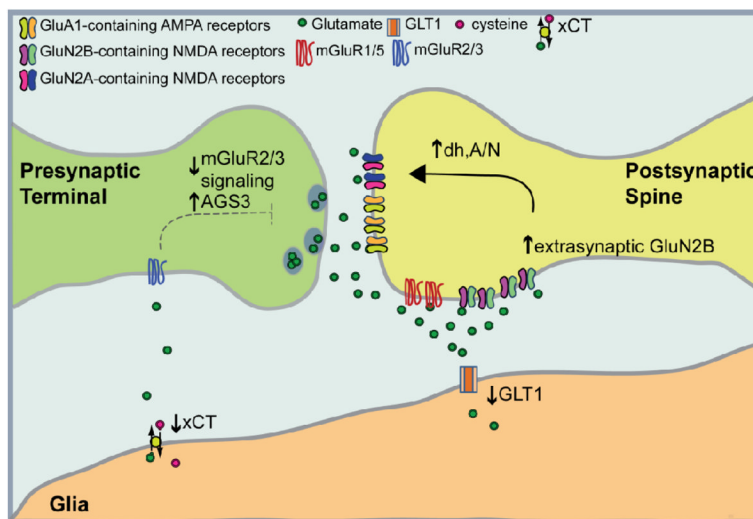


Figure 5. Alterations in glutamate homeostasis and synaptic plasticity in addiction and relapse
 Impaired glutamate homeostasis after withdrawal from chronic use of an addictive drug. Expression of both xCT and GLT-1 is decreased, which results in decreased basal levels of extrasynaptic glutamate. This results in decreased glutamatergic tone on presynaptic inhibitory mGluR2/3 receptors and upregulation of activator of G protein signaling 3 (AGS3), which in turn disinhibits glutamatergic transmission. Upon activation of the presynaptic terminal (for example, by presentation of a drug-associated cue) an abnormally high amount of glutamate is released, which, together with the decreased GLT-1 expression, causes glutamate spillover; the net result is enhanced activation of synaptic and extrasynaptic ionotropic glutamate (i.e., AMPA, NMDA, and kainite receptors) and mGluR5 receptors. This in turn signals the rapid increase in dendritic spine head diameter (d_h) and AMPA:NMDA ratio (A/N).