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Using glutamate homeostasis as a target for treating addictive disorders

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Abstract

Well-developed cellular mechanisms exist to preserve glutamate homeostasis and regulate extrasynaptic glutamate levels. Accumulating evidence indicates that disruptions in glutamate homeostasis are associated with addictive disorders. The disruptions in glutamate concentrations observed following prolonged exposure to drugs of abuse are associated with changes in the function and activity of several key components within the homeostatic control mechanism, including the cystine/glutamate exchanger xc^- and the glial glutamate transporter EAAT2/GLT-1. Changes in the balance between synaptic and extrasynaptic glutamate levels in turn influence signaling through pre- and postsynaptic glutamate receptors, and thus affect synaptic plasticity and circuit-level activity. In this review we describe the evidence for impaired glutamate homeostasis as a critical mediator of long-term drug-seeking behaviors, how chronic neuroadaptations in xc^- and GLT-1 mediate a disruption in glutamate homeostasis, and how targeting these components restores glutamate levels and inhibits drug-seeking behaviors.

Keywords

Glutamate homeostasis; drug seeking; cystine/glutamate exchanger; glial glutamate transporter

Introduction

The influence of non-synaptic extracellular glutamate on synaptic glutamate release and signaling through glutamate receptors first became clear in the late 1990s and has since become increasingly appreciated as a major regulator of glutamatergic synaptic transmission (Haydon et al. 2009; Kalivas 2009). Not only is removal of glutamate from the synaptic cleft critical to prevent receptor desensitization and excitotoxicity, but stimulation of extrasynaptic mGluR receptors can affect synaptic release probability and postsynaptic responsiveness (Losonczy et al. 2003; Luscher and Huber 2010). Glutamate homeostasis refers to a tightly controlled range of extrasynaptic glutamate concentrations ($\sim 1\text{--}4\text{ }\mu\text{M}$ in the nucleus accumbens (NAc)), that are critical for maintaining the capacity of glutamatergic synapses to potentiate and depotentiate (i.e. undergo long-term potentiation [LTP] and depression [LTD]). Toward that end, considerable metabolic commitment is devoted to regulating glutamate metabolism, uptake, and release. Prolonged exposure to drugs of abuse induces enduring neuroadaptations affecting glutamate homeostasis in the NAc that in turn impairs synaptic plasticity in a manner promoting certain addictive behaviors, most notably relapse. In this review we discuss specific

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nodes in the regulation of glutamate homeostasis, how they are affected by drugs of abuse, and how specific pharmacological targeting of these nodes restores glutamate homeostasis and provides a new avenue for treating addictive disorders.

Unless specified otherwise, studies described herein have utilized a rodent self-administration/reinstatement model of addiction (Shaham et al. 2003; Epstein et al. 2006). In this model, animals are able to self-administer drugs of abuse, followed by a period of extinction in which access to drugs and drug-paired cues is removed. Drug-seeking behavior (most typically lever pressing, except in the case of alcohol) is then reinstated by the use of a drug prime, drug-paired cues, or stress. Reinstatement of drug-seeking is largely considered to provide a model of human relapse (however, see Katz and Higgins 2003), and use of this behavioral model has provided an valuable tool by which to understand how changes in glutamate homeostasis affect drug-seeking.

Glutamate Homeostasis Hypothesis of Addiction

Reward learning and hedonic effects of drugs of abuse are largely mediated by dopaminergic (DA) signaling (Hyman et al. 2006). Many drugs of abuse cause increases in dopamine transmission from the ventral tegmental area (VTA) to structures within the mesolimbic circuitry of the brain, particularly the amygdala, prefrontal cortex (PFC), and NAc. The glutamatergic projection from the PFC to the NAc has been proposed to be a common final pathway engaged in the reinstatement of drug seeking induced by stress, a drug prime, or drug-paired cues, highlighting the importance of this circuitry in the addiction process (Kalivas and Volkow 2005).

While DA is in large part responsible for reinforcing the acquisition of drug seeking behaviors, considerable evidence indicates that disruptions in corticostriatal glutamatergic neurotransmission are responsible for chronic, long-lasting drug seeking behaviors (Kalivas 2009). For example, the reinstatement of drug-seeking behavior in the self-administration rat model of addiction occurs concomitantly with an increase in PFC glutamate release into the NAc, suggesting that activation of glutamatergic transmission may be in part responsible for relapse-related behaviors (McFarland et al. 2003; LaLumiere and Kalivas 2008). Further, inhibition of AMPA receptors in the NAc(core) impairs drug-primed reinstatement for both cocaine and heroin (Cornish and Kalivas 2000; Di Ciano and Everitt 2001; LaLumiere and Kalivas 2008), as well as for alcohol reinstatement when administered systemically (Backstrom and Hyttia 2004; Sanchis-Segura et al. 2006). Increased surface expression of GluR1 AMPA receptor subunits has been identified following cocaine self-administration and withdrawal (Conrad et al. 2008), and correspondingly, potentiated postsynaptic prefrontal to NAc glutamate transmission has also been reported (Kourrich et al. 2007; Moussawi et al. 2009). These findings collectively illustrate the likely relevance of chronic disruptions in glutamatergic signaling to drug seeking behavior.

One possible source of these disruptions is a dysregulation of glutamate homeostasis. As described above, extracellular glutamate concentrations are tightly regulated for the purpose of preserving the integrity of synaptic function and plasticity. However, following chronic exposure to cocaine, a decrease in extrasynaptic glutamate concentrations has been reported in the NAc (Baker et al. 2003; McFarland et al. 2003; Madayag et al. 2007). This effect appears to be at least somewhat specific to the NAc, as no change was observed in the dorsal striatum or prefrontal cortex (PFC) (Baker et al. 2003). This decrease results in decreased tone on presynaptic inhibitory release-regulating group II metabotropic glutamate receptors (mGluR2/3). Because presynaptic group II mGluRs are inhibitory to neurotransmission, the decreased tone leads in turn to enhanced glutamate release when the PFC-NAc projection is activated during drug-seeking behavior (Kalivas 2009). Failure of the system to maintain levels

of extracellular glutamate outside the synaptic cleft correspondingly thus results in a non-physiological fluctuation from low basal extrasynaptic glutamate to excessive release and synaptic overflow during reinstatement (Fig 1, *left*). The left and right sides of Fig. 1 provide side-by-side comparisons of the four candidate targets illuminated by studies of glutamate homeostasis and how their impaired function by cocaine affects synaptic transmission at PFC-NAc synapses.

Together, these data indicate that allostatic stabilization of basal extracellular glutamate levels either above or below the physiological range can occur following exposure to drugs of abuse. It becomes of interest then, to identify the molecular mechanism(s) responsible for impairing glutamate homeostasis in the case of drugs such as cocaine and alcohol that appear to produce opposite directions of change. Along these lines, several long-lasting neuroadaptations in regulators of glutamate homeostasis have been identified following exposure to cocaine, heroin, and nicotine. Notably, a decrease has been reported in the NAc levels of two molecules critical to the release and uptake of extrasynaptic glutamate: the catalytic subunit of the cystine-glutamate exchanger, xCT, and the high-affinity glutamate transporter GLT-1 (Haowei Shen, personal communication; Madayag et al. 2007; Knackstedt et al. 2009, 2010b). Although, the molecular events underlying increased glutamate following exposure to ethanol remains less clear than for other drugs of abuse, particularly cocaine, reduced glutamate uptake through GLT-1 is likely a major contributor (Melendez et al. 2005).

Cystine-glutamate exchange

The finding that extracellular glutamate levels are reduced specifically in the NAc following chronic exposure and withdrawal from cocaine raised the possibility that neuroadaptations in the cystine-glutamate exchanger might contribute to the cellular mechanism of addiction. The cystine-glutamate exchanger, referred to also as system xc⁻, is predominantly expressed on glial cells and along with glial glutamate transport, is a critical regulator of nonsynaptic extracellular glutamate levels (Baker et al. 2002). The cystine-glutamate exchanger is composed of two subunits, a catalytic subunit light-chain xCT and a heavy-chain glycoprotein 4F2, which is common among several amino acid transporters. The cystine-glutamate exchanger is highly expressed in the brain and serves to import cystine as a precursor to glutathione biosynthesis, critical for cellular responses to oxidative stress and detoxification (Griffith 1999; Sato et al. 2002). Because the exchanger catalyzes a 1:1 stoichiometric release of glutamate in exchange for cystine uptake (McBean 2002), impaired function or expression of the exchanger in the NAc became a candidate underlying the observed decrease in extracellular glutamate produced in rodents by chronic cocaine administration (Baker et al. 2003; Szumlanski et al. 2004). Accordingly, both functional measurement of [³⁵S]cystine uptake and Western blot analysis of xCT protein expression in a membrane subfraction following 2–3 weeks of cocaine or nicotine self-administration reveal down-regulated cystine-glutamate exchange (Baker et al. 2003; Knackstedt et al. 2009, 2010b). The period of downregulation has not been directly determined; however the long-lasting effects of NAC suggest that downregulation may be enduring (see below).

The evidence for reduced expression and activity of xCT following exposure to chronic cocaine and nicotine suggests a possible target for therapeutic intervention. *N*-acetylcysteine (NAC) is an amino acid cysteine prodrug, effective in managing acetaminophen overdose by promoting the synthesis of the antioxidant glutathione (Flanagan and Meredith 1991). Systemic administration of NAC restores glutamate levels that have been reduced by chronic exposure to cocaine and prevents cocaine- and heroin-primed reinstatement in a rat self-administration model of relapse. Moreover, chronic NAC treatment following heroin self-administration can prevent reinstatement up to 40 days after cessation of NAC treatment (Zhou and Kalivas 2008). The NAC effect is blocked by the xc⁻ inhibitor (S)-4-carboxyphenylglycine (CPG)

microinjected directly into the NAc (Kau et al. 2008). NAC administered daily prior to self-administration impairs reinstatement 2–3 weeks after the last NAC injection, and also blocks cocaine-induced effects on [^{35}S]-cystine uptake and glutamate levels 3 weeks after the last NAC injection, illustrating the necessity of cocaine-induced changes on xc^- activity to the long-term effects of cocaine (Madayag et al. 2007). In addition to cocaine, rats trained to self-administer nicotine show reduced levels of xCT in the NAc and VTA, while levels are unchanged in the amygdala and PFC (Knackstedt et al. 2009). Interestingly, xCT levels are unaffected in rats receiving nicotine non-contingently by osmotic minipump, suggesting that the decrease in xCT may be related to the motivational aspect of contingently self-administered cocaine.

Other experiments have shown that the effects of NAC on glutamatergic synaptic transmission is indirect, via releasing glutamate through system xc^- to stimulate extrasynaptic metabotropic glutamate receptors (mGluR) (Fig 1, *right*). Perfusion of cystine to slices from NAc or PFC to activate xc^- increases glutamate release and decreases miniature excitatory postsynaptic current (mEPSC) frequency and evoked EPSC amplitudes, without effect on mEPSC amplitudes, indicating a likely presynaptic mechanism of action. This effect is blocked by inhibitors of both xc^- and group II mGluRs (Moran et al. 2005). Moreover, inhibitors of group II mGluRs block the capacity of NAC to inhibit cocaine-primed reinstatement, indicating that the impairment of reinstated drug-seeking by NAC occurs through its effects on presynaptic group II mGluRs (Moran et al. 2005). Also, withdrawal from self-administered cocaine is associated with a loss of LTD and LTP in the prefrontal to NAc synapses (Martin et al. 2006; Moussawi et al., 2009), and treatment with NAC restores impaired LTP and LTD (Moussawi et al. 2009). Restoration of LTP occurs through stimulation of presynaptic group II mGluRs, while restoration of LTD is mediated by stimulation of postsynaptic group I mGluR (specifically mGluR5), illustrating the regulation of both types of mGluRs by extracellular, nonsynaptic glutamate. N-acetylcysteine has also recently been shown to restore prepulse inhibition (PPI) in mGluR5 deficient mice, possibly by providing glutathione-mediated potentiation of NMDA receptor activity (Chen et al. 2010).

These findings provide intriguing preclinical evidence that NAC may reduce drug relapse via restoring glutamate homeostasis and glutamatergic synaptic plasticity in the NAc. Clinical trials of NAC in humans indicate safety and tolerability of oral administration and reduced responsiveness to cocaine-related cues (LaRowe et al. 2006, 2007; Mardikian et al. 2007). Further, in a double-blind clinical trial, smokers receiving NAC for 4 weeks used 25–30% fewer cigarettes, without affecting measures of craving or withdrawal (Knackstedt et al. 2009). However, continued research is necessary to determine the maximum potential use of NAC for treatment of addiction. For example, the bioavailability of NAC in the brain following oral administration is low (Sheffner et al. 1966; Farr et al. 2003). Specifically, studies in mice have found that following i.v. injection of NAC, the brain content of NAC reached 0.4 % injected NAC per gram of brain (Farr et al. 2003). Future medicinal chemistry studies will be required to prepare related compounds with greater blood-brain barrier permeability. Further, effectiveness of NAC seems largely limited to conditions in which there is a pathological reduction in glutathione levels (Flanagan and Meredith 1991), posing the possibility that NAC may more effectively increase cystine-glutamate exchange in situations such as in the accumbens of cocaine-treated animals where it is down-regulated. Indeed, reverse dialysis of cystine into the NAc elevates extracellular glutamate only in chronic cocaine-withdrawn animals showing reduced basal levels of glutamate and compromised cystine-glutamate exchange (Baker et al. 2003).

Interestingly, preliminary human studies also indicate that NAC treatment may be effective for treating psychiatric conditions beyond addiction, including trichotillomania, gambling, and schizophrenia (Grant et al. 2007; Berk et al. 2008a,b,c; Ng et al. 2008; Grant et al. 2009).

However, it is unclear if these effects are mediated through antioxidant effects of glutathione production, or through synaptic effects on glutamatergic signaling, as appears to be the case in addictive disorders. In particular, NAC has been shown to be effective both in case studies and in randomized, double-blind studies in schizophrenia (Berk et al. 2008a; Lavoie et al. 2008; Bulut et al. 2009). Also, in preclinical studies NAC treatment ameliorates social withdrawal and deficits in a T-maze task in a rodent phencyclidine (PCP) model of schizophrenia. These effects were blocked by inhibiting x_c^- , as well as by the mGluR2/3 antagonist LY341495, suggesting the effectiveness of NAC in this case may in fact be mediated through actions on glutamate signaling (Baker et al. 2008). Ongoing preclinical and clinical studies will further elucidate the mechanism of the therapeutic action of NAC and its effectiveness in the treatment of addiction.

Glutamate Transporters

Because excess extracellular glutamate can lead to excitoneurotoxicity, high-affinity glutamate transporters expressed on both glial cells and neurons serve to rapidly remove free glutamate from the synaptic space and control extracellular glutamate levels (Danbolt 2001). High affinity glutamate transport is performed by the solute carrier 1 (SLC1) glutamate transporter family, comprised of five members, EAAT1/GLAST, EAAT2/GLT-1, and EAAT3-5 (Danbolt 2001; Kanai and Hediger 2004; Beart and O'Shea 2007). In the brain, the majority of glutamate uptake is via GLT-1 (Haugseto et al. 1996). GLAST and GLT-1 are predominantly expressed on glial cells, while EAAT3-5 are expressed differentially among neurons (Amara and Fontana 2002). By maintaining tight control of glutamate in the extracellular space, glutamate transporters exert important effects on synaptic glutamatergic signaling, most importantly to limit the danger of excitotoxicity, but also on the kinetics of receptor activation (Bergles et al. 1999).

As discussed above, glutamate transporters can affect synaptic glutamate release by balancing glutamate release by system x_c^- . Thus, by removing glutamate from the perisynaptic space glutamate transporters control activation of pre- and post- extrasynaptic mGluRs that modulate glutamate release and synaptic plasticity (see above). Inhibition of glutamate transport leads to a decrease in synaptic glutamate release (Maki et al. 1994), and genetic deletion of GLT-1 leads to elevated extracellular glutamate levels, excitotoxicity, and impaired hippocampal LTP (Rothstein et al. 1996; Katagiri et al. 2001). Importantly, the regulation between glial and neuronal glutamate is bidirectional since neuronal activation of glial cells leads to increased expression of GLT-1 (Yang et al. 2009).

In 2005, Rothstein et al. identified the β -lactam class of antibiotics as effective pharmacological agents for upregulating GLT-1 expression and function (Rothstein et al. 2005). Specifically, the β -lactam antibiotic ceftriaxone exerted neuroprotection *in vitro* and was effective in an animal model of amyotrophic lateral sclerosis. Evidence suggests that ceftriaxone may also be effective in treating addictive disorders. Not only is GLT-1 expression significantly and specifically decreased in the NAc following self-administration of cocaine or nicotine (Knackstedt et al. 2009, 2010), but administration of ceftriaxone during extinction training after cocaine self-administration leads to reduced reinstatement of drug-seeking behavior (Sari et al. 2009; Knackstedt et al. 2010a). Interestingly, in addition to restoring GLT-1 levels in these animals, ceftriaxone also restores xCT levels, indicating possible co-regulation of these molecules (Knackstedt et al. 2010a). No studies have yet investigated the efficacy of ceftriaxone to reduce drug craving in human or primate models of addiction, or the capacity of ceftriaxone to reduce drug-seeking to other drugs of abuse.

mGluR2/3

A key component of the glutamate homeostasis hypothesis posits that decreased extrasynaptic glutamate results in a decreased tone on presynaptic inhibitory group II (mGluR2/3) receptors (Moran et al. 2005; Kalivas 2009). Group II mGluRs are well established as negative regulators of glutamate release (Conn and Pin 1997; Anwyl 1999; Cartmell and Schoepp 2000). Studies addressing changes in expression and function of mGluR2/3 receptors are consistent with impaired receptor signaling following exposure to cocaine. For example, cocaine-sensitized rats show reduced mGluR2/3 agonist-induced [³⁵S]GTPγS binding (Xi et al. 2002), probably resulting from an increase in levels of Activator of G-Protein Signaling3 (AGS3) which selectively inhibits the formation of Gi containing heterotrimer and thus ligand-induced Gi signaling (Bowers et al. 2004). Indeed, inhibition of AGS3 signaling reduces reinstated cocaine, opioid and alcohol seeking (Bowers et al. 2004, 2008; Yao et al. 2005). Moreover, tissue slices from cocaine-treated animals also exhibit reduced mGluR2/3 agonist-induced [³⁵S]-cystine uptake (Baker et al. 2003). Most importantly perhaps, *in vivo* studies to address the functionality of mGluR2/3 following cocaine sensitization indicate that 3 weeks following the last injection of cocaine, administration of an mGluR 2/3 agonist less effectively reduces extracellular glutamate (Xi et al. 2002).

The decreased tone on these receptors results in the excessive release of synaptic glutamate in response to PFC activation during reinstatement in a rodent model of drug abuse (Figure 1, *left*), and contributes to the impaired LTP observed in prefrontal synapses in the NAc of rats trained to self-administer cocaine. Restoring this tone with systemic NAC administration leads to decreased reinstatement and restored synaptic plasticity (Moussawi et al. 2009). Importantly, the involvement of group II mGluRs in dysregulated glutamate homeostasis indicates that pharmacological targeting of these receptors may represent an effective strategy for restoring glutamate homeostasis, and for treating addiction and other disorders of glutamatergic signaling (Fig 1, *right*). Substantial evidence supports this idea. For example, the mGluR2/3 antagonist LY341495 disrupts the ability of NAC to impair reinstatement (Moran et al. 2005), and prevents the ability of NAC to restore LTP (but not LTD) in cocaine self-administering animals (Moussawi et al. 2009). Specific genetic deletion of mGluR2 results in enhanced conditioned place preference with cocaine, supporting the evidence that disruption of mGluR2/3 signaling facilitates drug-related behaviors (Morishima et al. 2005). In contrast, administration of the mGluR2/3 agonist LY379268 in a cocaine self-administration paradigm decreases cocaine-induced reinstatement (Baptista et al. 2004; Adewale et al. 2006; Peters and Kalivas 2006; Lu et al. 2007b) and heroin-seeking behavior (Bossert et al. 2004, 2006).

While treatment with LY379268 resulted in a trend toward decrease in cocaine-primed reinstatement in a study on squirrel monkey, this effect was limited to a single dose of cocaine (Bauzo et al. 2009). Moreover, multiple studies have reported emesis caused by LY379268 in squirrel monkeys (Adewale et al. 2006; Bauzo et al. 2009), and some studies have shown that group II mGluR activation by LY379268 may exert undesirable inhibition of motivation to obtain natural rewards (Peters and Kalivas 2006; Baptista et al. 2004). These concerns should be considered in the development of mGluR2/3 agonists in the treatment of addiction. However, it is worth noting that although no human studies using mGluR2/3 agonists have been reported for treating addiction, a phase II clinical study found that LY2140023, a prodrug for a selective mGluR2/3 agonist, improves both positive and negative symptoms of schizophrenia (Patil et al. 2007). Use of this compound in humans is reported to be safe and well-tolerated, with reported adverse effects not significantly different from placebo controls or olanzapine (Zyprexa) (Patil et al. 2007).

mGluR5

In contrast to activation of presynaptic inhibitory group II mGluRs, considerable evidence exists to indicate that antagonism of postsynaptic mGluR5 attenuates self-administration and reinstatement of cocaine, methamphetamine, heroin, nicotine, and alcohol (Backstrom et al. 2004; Kenny et al. 2005; Paterson and Markou 2005; Backstrom and Hyttia 2006; Besheer et al. 2008; Platt et al. 2008; Gass et al. 2009; Kumaresan et al. 2009; for review, see Carroll 2008; Liechti and Markou 2008). Moreover, mGluR5 knockout mice demonstrate no cocaine-induced changes in locomotor activity, and do not self-administer cocaine (Chiamulera et al. 2001). Conversely, systemic activation of mGluR5 receptors with the positive allosteric modulator CDPPB prior to extinction sessions for conditioned place preference (CPP) results in facilitation of the extinction process (Gass and Olive 2009) and reverses the capacity of NAC to inhibit cocaine-induced reinstated drug-seeking (Moussawi et al. 2009). Finally, acamprosate is an FDA-approved drug for the treatment of alcoholism with, among other effects, efficacy as an antagonist of mGluR5 (Heilig and Egli 2006; Mann et al. 2008). Other effects of acamprosate include modulation of ionotropic glutamate receptors and GABA receptors, and it is therefore not specific to modulating metabotropic signaling. Nonetheless, the clinical effectiveness of acamprosate may be mediated, in part, by its ability to normalize glutamatergic transmission (Spanagel et al. 2005; Heilig and Egli 2006).

While inhibition of mGluR5 suppresses drug-seeking behaviors, the precise role of mGluR5 receptors in the addiction process is likely to be complex. Activation of mGluR5 elicits LTD in the NAc and hippocampus (Volk et al. 2006; Naie et al. 2007; Moussawi et al. 2009), and Brebner et al (2005) reported that injection of a Tat-conjugated peptide, which blocks clathrin-dependent endocytosis of GluR2 AMPA receptors into the NAc, prevented the expression of behavioral sensitization to amphetamine. Homer proteins provide a linkage between the postsynaptic density (PSD) and the endocytic zone (EZ), via protein interactions with dynamin 3 that is required for receptor recycling and AMPA-mediated synaptic transmission (Lu et al. 2007a). Since mGluR5 is also a Homer binding protein, it may be that blocking mGluR5 disrupts communication between the PSD and EZ, thereby preventing receptor mobilization required for behavioral responsiveness to a drug challenge (Fig. 2). However, this hypothesis has not yet been experimentally tested. Indeed, the ability of NAC to restore LTD at prefrontal to NAc synapses requires mGluR5 receptors, supporting a possible role for these receptors in this AMPA receptor internalization process (Moussawi et al. 2009). Moreover, infection of a Homer-expressing virus into the NAc impairs the induction of LTD *in vivo*, likely due to internal sequestration of mGluR5 receptors (Ronesi and Huber 2008; Knackstedt et al. 2010b).

Another potential mechanism whereby mGluR5 may contribute to reinstatement of drug-seeking relates to the potentiated state of glutamatergic synapses in the NAc following cocaine self-administration (Kourrich et al. 2007; Conrad et al. 2008; Moussawi et al. 2009). Group I mGluR stimulation can contribute to LTP in the NAc (Schotanus and Chergui 2008; Anwyl 2009). Thus, it is possible that blocking mGluR5 inhibits reinstated drug-seeking by impairing the potentiated state that exists prior to the reinstatement of drug-seeking. Taken together, these findings illustrate a paradox in the how mGluR5 antagonism may contribute to either the potentiation or depotentiation of glutamatergic synapses in the NAc, and thereby inhibit cocaine-seeking. Clearly, much work remains in order to characterize fully the pathobiology of the effects of addiction on synaptic plasticity in the NAc and the role played by mGluR5.

Conclusions

The studies described herein collectively point to disruptions in glutamate homeostasis as a mechanism for conferring vulnerability to drug-seeking behavior, and illustrate how restoring

glutamate homeostasis by directly targeting components of this system may provide effective treatment for an addictive disorder. Further studies will provide more mechanistic information about how other drugs of abuse affect extrasynaptic glutamate levels, why alcohol exposure leads to an increase in glutamate while cocaine leads to a decrease in glutamate, and how altered dynamics of glutamate receptors (metabotropic and ionotropic) affect the disruptions in synaptic plasticity that are believed to underlie the behavioral correlates of addictive disorders.

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Figure 1. A model for pharmacological targeting of glutamate homeostasis as a treatment for addiction

The left and right sides of the synapse compare synaptic dynamics in the pathology and the potential pharmacology amelioration of the pathology of glutamate homeostasis. Depicted are four components in the regulation of glutamate homeostasis: cystine/glutamate exchanger catalytic subunit xCT, glutamate transporter GLT-1, presynaptic mGluR2/3, and postsynaptic mGluR5. The left side of the synapse depicts the disruption in glutamate homeostasis following chronic exposure to cocaine. Decreased expression of xCT and GLT-1 results in decreased basal levels of extrasynaptic glutamate, which in turn leads to decreased tone on presynaptic inhibitory mGluR2/3. Decreased expression or function of GLT-1, xCT, and mGluR2/3

receptors are represented by outlined structures (compared to restored function of filled structures on right). Activation of PFC-NAc synapses during drug seeking thus results in excessive synaptic release of glutamate due to decreased tone on presynaptic inhibitory mGluR2/3, fueling activation of postsynaptic ionotropic glutamate receptors and mGluR5. However, restoration of glutamate homeostasis (shown on the right side of the synapse) normalizes the balance between synaptic and extrasynaptic glutamate levels. Agents that restore glutamate homeostasis (and impair drug seeking) are listed on right, with arrows to their target molecules. NAC treatment restores levels of xCT and GLT-1 (depicted by filled structures), correcting the depletion of extracellular glutamate and restoring tone on mGluR2/3. This restored tone aids in correction of synaptic glutamate release during reinstatement. Treatment with ceftriaxone also restores both GLT-1 and xCT levels, to similarly restore glutamate homeostasis. This model also includes how pharmacological stimulation of mGluR2/3, or antagonism of mGluR5 receptors, impairs relapse.

Figure 2. Homer-mediated protein interactions linking the PSD and EZ

Homer proteins are integral components of the vertebrate PSD, forming numerous protein interactions important for the cellular dynamics which occur following prolonged exposure to drugs of abuse. Homer proteins form homomeric multimers, thus allowing for complex interactions with a number of components within the vertebrate PSD. Interactions depicted here include Dynamamin 3 (dyn3), group I mGluR receptors (mGluR1/5), Shank, and the inositol trisphosphate receptor (IP3R), located on the endoplasmic reticulum (ER) within dendritic spines. It is important to note that this figure depicts only a subset of PSD components and Homer-mediated interactions (for more extensive detail, see Tu et al. 1998; Sheng and Hoogenraad 2007; Bayes and Grant 2009; Newpher and Ehlers 2009). The interaction between

Homer and Dynamin 3 is required for endocytosis of AMPA receptors in clathrin-coated pits (Lu et al. 2007a), a process shown to be required for expression of behavioral sensitization (Brebner et al. 2005). In addition, the interaction between Homer and mGluR5 receptors is required for LTD (Knackstedt et al. 2010a). Blockade of mGluR5 receptors provides an avenue for potential treatment of drugs of abuse; however the exact nature of mGluR5 activation and its relationship to Homer-binding proteins remains not fully resolved.