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Astrocytic Dysfunction and Addiction: Consequences of Impaired Glutamate Homeostasis

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Abstract

Addiction is characterized as a chronic relapsing disorder whereby addicted individuals persistently engage in drug seeking and use despite profound negative consequences. The results of studies using animal models of addiction and relapse indicate that drug seeking is mediated by alterations in cortico-accumbal plasticity induced by chronic drug exposure. Among the maladaptive responses to drug exposure are long-lasting alterations in the expression of proteins localized to accumbal astrocytes, which are responsible for maintaining glutamate homeostasis. These alterations engender an aberrant potentiation of glutamate transmission in the cortico-accumbens circuit that is linked to the reinstatement of drug seeking. Accordingly, pharmacological restoration of glutamate homeostasis functions as an efficient method of reversing drug-induced plasticity and inhibiting drug seeking in both rodents and humans.

Keywords

glutamate; nucleus accumbens; reinstatement; GLT-1; xCT; astrocyte

The Nucleus Accumbens: A New Perspective on an Old Nucleus

The nucleus accumbens (NAc) is topographically interconnected with the ventral pallidum (VP) and the ventral tegmental area (VTA) (Fig. 1) and plays a central role in the neurobiological processes of reward learning, impulsivity, and addiction (Koob and Volkow 2010). More than 90% of the cells in the NAc are γ -aminobutyric acid releasing (GABAergic) medium spiny neurons (MSN) with a small portion of cholinergic aspiny cells and GABAergic interneurons (Smith and others 2013). MSNs in the accumbens are typically divided into two groups. The first group expresses D1 dopamine and M4 cholinergic receptors and also releases dynorphin and substance P and project to the ventral mesencephalon (Smith and others 2013). The second group expresses D2 dopamine and A2a adenosine receptors and also release enkephalin and neurotensin and project to the VP (Smith and others 2013) (Fig. 1). However, reports suggest that a substantial amount of heterogeneity in the system exists (for review, see Smith and others 2013). The NAc receives

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dopaminergic projections from the VTA as well as glutamatergic projections from a number of cortical, allocortical, and thalamic areas (Fig. 1). A wide body of literature details how drugs of abuse modulate dopamine release or uptake in the NAc to increase extracellular dopamine content and how these mechanisms contribute to reward and the reinforcement of drug seeking, which we will not discuss here (for review, see Baik 2013). Whereas dopamine mediates the acute reinforcing properties of drugs of abuse, long-lasting alterations in glutamatergic synaptic plasticity underlie the pathophysiology of relapse vulnerability (Kalivas 2009). Specifically, glutamatergic synaptic transmission from the prefrontal cortex (PFC) to the nucleus accumbens core (NAcore) has been shown to be required for the reinstatement of drug-seeking behavior in rodent models of relapse (Kalivas 2009). Emerging data from our lab indicate that the reinstatement of drug seeking is associated with rapid transient alterations in synaptic strength and increases in dendritic spine head diameter in NAcore MSNs (for review, see Gipson and others 2014). In this review, we focus on the cellular adaptations that occur in NAcore astrocytes following repeated exposure to drugs of abuse including cocaine, heroin, methamphetamine, nicotine, and ethanol. We also explore how these adaptations influence homeostatic regulation of extracellular glutamate levels and cause a pathological strengthening of the PFC-NAcore circuit underlying the reinstatement of drug seeking (Kalivas 2009). In addition, we present findings from rodent models and human clinical trials demonstrating that pharmacotherapies designed to correct glutamate homeostasis effectively inhibit drug seeking and relapse.

Astrocytes and Neurometabolic Coupling

The brain is composed of a complex network of neurons, glial cells, and blood vessels. Astrocytes, a subset of glial cells, preserve homeostasis of the extracellular space by buffering potassium and glutamate (Parpura and Verkhratsky 2013). Apart from their role in maintaining homeostasis, astrocytes also metabolically link neurons to the vascular glucose supply (Parpura and Verkhratsky 2013). Astrocyte metabolism operates via the generation of adenosine triphosphate (ATP) from glycolysis, the byproduct of which is lactate extrusion (Fig. 2) (Turner and Adamson 2011). Lactate serves as a key component of the neuronal metabolic cycle used to generate the ATP serving the energy demands of synaptic transmission (Turner and Adamson 2011). Astrocytes also play a central role in glutamatergic synaptic transmission by supplying the glutamate precursor glutamine to neurons (Albrecht and others 2010; Parpura and Verkhratsky 2013). Following an action potential, astrocytes act to terminate signaling by clearing glutamate from the synaptic cleft via the patterned expression the Na^+ -dependent glial glutamate transporter family, in particular GLT-1 (Williams and others 2005). Once removed from the synapse, glutamate is converted to glutamine, which is then released by astrocytes into the extracellular space where it can be taken up by neurons (Albrecht and others 2010). Following uptake, the enzyme glutaminase converts glutamine back to glutamate so that it can then be loaded into vesicles by the vesicular glutamate transporter (VGluT), restarting the cycle of glutamate synaptic transmission (Albrecht and others 2010).

Astrocytes Release Glutamate and Shape Neuronal Communication

Neuroglia (meaning nerve glue) were initially described by Rudolf Virchow in the 1850s as a substance providing support for neuronal elements, yet glial cells would not be recognized for their ability to directly communicate with neurons until the 1980s (Malarkey and Parpura 2008). The possibility of direct chemical communication between neurons and astrocytes was likely overlooked given that astrocytes lack axons and the ability to produce action potentials. However, these cells do indeed participate in bidirectional communication with neurons and release chemical transmitters (gliotransmission), including taurine, ATP, D-serine, and glutamate (Santello and others 2012). Glutamate gliotransmission has received particular attention as it has been linked to the regulation of excitatory synaptic transmission and plasticity (Santello and others 2012). Release of glutamate from astrocytes occurs through several mechanisms including through the reverse action of the glutamate transporter GLT-1, through unpaired gap junction pores on the cell surface (hemichannels), through swelling-induced opening of anion channels, through ionotropic purinergic receptors, through Ca^{2+} -dependent vesicular release, and also through glutamate exchange occurring via the cystine-glutamate antiporter (Xc-) (Malarkey and Parpura 2008) (Fig. 3).

Astrocytes extend thousands of fine membranous processes, many of which make contact with synapses to provide metabolic support and maintain the integrity of neuronal communication (Parpura and Verkhratsky 2013). Unlike neurons, astrocytes are connected to each other via gap junction pore proteins, forming functional ensembles of interconnected cells (Zorec and others 2012). As a result, Ca^{2+} and other small molecules like inositol-1,4,5-trisphosphate (IP3) can flow between adjacent cells in the reticular astrocyte network. This allows for the propagation of transient increases in internal calcium concentration ($[\text{Ca}^{2+}]_i$) across connected cells, termed calcium waves. Calcium waves are observed both in vitro (Cornell-Bell and others 1990) and in vivo (Dani and Smith 1995) and likely play a role in initiating organized gliotransmission in order to synchronize neuronal firing patterns (Poskanzer and Yuste 2011). Because increased $[\text{Ca}^{2+}]_i$ through direct calcium influx or release of calcium stores from the endoplasmic reticulum (ER) may induce vesicular release of glutamate from astrocytes (Zorec and others 2012), the mechanisms of calcium internalization and mobilization are of particular interest (Fig. 3). Direct calcium influx occurs through several mechanisms including through inward flow from adjacent cells, through activation of transient receptor potential canonical receptors (TRPC), ionotropic glutamate, and purine receptors, as well as through voltage-gated calcium channels (VGCC) (Ben Achour and Pascual 2012). G protein-coupled glutamate and purinergic receptors also mediate flux of calcium through the activation of IP3 receptors (IP3R2) located on the ER, initiating the release of calcium from internal stores and increasing $[\text{Ca}^{2+}]_i$, potentially leading to gliotransmitter release (Parpura and Verkhratsky 2013).

As discussed above, astrocytes regulate NAc synaptic plasticity through the release and uptake of glutamate into the extrasynaptic space (Kalivas 2009). Presynaptically, glial-glutamate release can activate Gi/Go-coupled group II metabotropic glutamate receptors (mGluR2/3) located on cortical glutamatergic neurons synapsing in the accumbens (Moussawi and Kalivas 2010). Stimulating glutamate autoreceptors attenuates synaptic

release through the activation of presynaptic potassium channels, the inhibition of presynaptic Ca^{2+} channels, and by directly inhibiting vesicular release (Moussawi and Kalivas 2010) (Fig. 4A). Glial-derived glutamate can also potentially activate mGluR5, a Gq coupled group I metabotropic glutamate receptor located postsynaptically on GABAergic MSNs in the NAc (Mitrano and Smith 2007). Activation of these receptors has been linked to synaptic plasticity (Simonyi and others 2005) and the induction of long-term potentiation (LTP) in the NAc (Schotanus and Chergui 2008).

In addition to metabotropic glutamate receptors, glial glutamate release can also activate nonsynaptic ionotropic GluN2B containing NMDA receptors (Fig. 4A). The mainly synaptic GluN2A containing NMDA receptors have been linked to the induction of LTP, whereas extrasynaptic GluN2B containing subtypes mediate the induction of long-term depression (LTD) (Liu and others 2004). Evidence suggests that these receptors play a role in mediating drug-related plasticity, as antagonizing GluN2B-containing NMDA receptors has been shown to inhibit opiate (Shen and others 2011), nicotine (Gipson and others 2013), and alcohol reinstatement (Wang and others 2010).

Drug-Induced Alterations in Glutamate Homeostasis

Glutamate homeostasis is defined as the balance between synaptic and nonsynaptic glutamate, with nonsynaptic glutamate acting to regulate neuronal communication (Kalivas 2009). As such, astrocytes tightly regulate synaptic and nonsynaptic glutamate levels through the coordinated release (discussed above) and uptake of glutamate (Moussawi and others 2011a; Parpura and Verkhratsky 2013) (Fig. 4A). In rodent models, decreased levels of basal extrasynaptic glutamate are observed in the NAc following chronic exposure to cocaine and methamphetamine, suggesting that a potential consequence of chronic drug exposure is the loss of extrasynaptic glutamate tone in the NAc (Kalivas 2009) (Fig. 4B; Table 1). A corollary of reduced glutamate tone is the lack of input for release regulating mGluR2/3 autoreceptors (Kalivas 2009) (Fig. 4B) and the dramatic enhancement of excitatory transmission at PFC-NAc synapses (Kalivas 2009; Kalivas and others 2003). Drug-induced enhancement of the cortico-accumbens circuit and the resulting increase in glutamate release from PFC terminals during drug seeking is a phenomenon observed following self-administration of nicotine, cocaine, heroin, and ethanol (Kalivas 2009) (Fig. 4C; Table 1). Therefore, the enhanced release of glutamate at PFC-NAc synapses during drug seeking appears to be a shared consequence of chronic drug exposure, making it an attractive target for the development of therapies to combat addiction (Kalivas 2009). Importantly, the results from preclinical models of addiction and relapse discussed above are consistent with results from human neuroimaging studies demonstrating that the presentation of drug-paired cues in addicted individuals causes metabolic activation of the PFC and NAc (Goldstein and Volkow 2002).

The cystine glutamate antiporter Xc-catalyzes the 1:1 stoichiometric release of glutamate in exchange for cystine and provides more than half of the total levels of glial-derived extrasynaptic glutamate in the NAc (Kalivas 2009). Chronic exposure to both cocaine and nicotine has been shown to reduce expression of xCT, the catalytic subunit of the cystine-glutamate exchanger Xc-, expressed predominantly on glial-cell membranes (Kalivas 2009;

Kalivas and others 2003). In contrast, unpublished data from our lab indicate that xCT expression is not affected by chronic exposure to heroin (Table 1). The down-regulation of xCT serves as plausible mechanistic explanation for the diminished levels of extrasynaptic glutamate observed after chronic cocaine exposure (Baker and others 2003; McFarland and others 2003) thought to contribute to potentiation of glutamate signaling during drug seeking. The basal levels of NAc core extrasynaptic glutamate have yet to be assayed following nicotine self-administration. Taken together, these data suggest that nicotine and cocaine exposure share similar consequences with respect to cysteine-glutamate exchange. This represents a potential mechanism for drug-induced strengthening of the PFC-NAc core circuit. However, enhanced levels of extrasynaptic glutamate are also observed during the reinstatement of cocaine, nicotine, heroin, ethanol, and methamphetamine seeking (Table 1). As such, drug-induced elevation of NAc core glutamate levels may occur due to reduced extrasynaptic NAc core glutamate tone (Kalivas 2009; Parsegian and See 2013), or additional mechanisms that augment glutamate clearance.

The excitatory amino acid transporter GLT-1 is responsible for 90% of glutamate uptake in the brain and is the primary mode of glutamate transport into astrocytes (Danbolt 2001). As such, GLT-1 is also required for the import of glutamate into astrocytes needed for subsequent release via Xc- or through other mechanisms (discussed above). Chronic exposure to cocaine, nicotine, ethanol, and heroin reduce expression of GLT-1 in the NAc core (Gipson and others 2013; Kalivas 2009; Sari and Sreemantula 2012), making the down-regulation of GLT-1 a remarkably consistent maladaptive response to drug exposure (Table 1). Interestingly, expression of GLT-1 is reduced immediately following cocaine self-administration, whereas extended withdrawal causes further down-regulation (Fischer-Smith and others 2012). The drug-induced inhibition of glutamate uptake slows the removal of transmitter from the synaptic cleft, potentially amplifying the magnitude of glutamatergic transmission. In addition, reduced expression of GLT-1 allows for synaptically released glutamate to gain access to non-synaptic compartments (Kalivas 2009). This spillover of glutamate could potentially activate mGluR5 and GluN2B-containing NMDA receptors (Kalivas and others 2003) yielding increased $[Ca^{2+}]_i$ and synaptic potentiation (Yashiro and Philpot 2008), as well as enhanced drug seeking behavior (Kalivas 2009) (Fig. 4B). The conservation of GLT-1 down-regulation in the NAc core following exposure to multiple classes of addictive substances points to a general glutamatergic dysfunction that contributes to the enhanced glutamate levels observed in the NAc core during the reinstatement of drug seeking (Kalivas 2009).

Apart from its effects on extrasynaptic glutamate and glutamate overflow, drug exposure can also directly inhibit signaling through mGluR2/3, possibly enhancing glutamate release at PFC-NAc synapses. Early withdrawal from nicotine has been shown to down-regulate expression and function of mGluR2/3 receptors in the NAc (Moussawi and Kalivas 2010). Similarly, down-regulation of mGluR2/3 is observed in PFC neurons following chronic exposure to ethanol (Meinhardt and others 2013). Moreover, withdrawal from chronic cocaine exposure inhibits the efficacy of signaling through mGluR2/3 receptors via phosphorylation and desensitization (Xi and others 2002) and also by enhancing the expression of the activator of G-protein signaling 3 (AGS3) in both the PFC and NAc core (Kalivas and others 2003). AGS3 inhibits mGluR2/3 function by binding to the inactive

form of the G_i coupled receptor, directly competing with $\beta\gamma$ in the reformation of the $\beta\gamma$ - $G_{i\alpha}$ heterotrimer (Kalivas and others 2003). Similar up-regulation of AGS3 and inhibition of mGluR2/3 function is observed following chronic exposure to ethanol (Moussawi and Kalivas 2010), and decreasing expression of AGS3 with an antisense strategy in the NAc core has been shown to inhibit the reinstatement of heroin seeking (Yao and others 2005). In a manner independent of AGS3, extended access to methamphetamine followed by a period of abstinence inhibits mGluR2/3 signaling in the accumbens via down-regulating mGluR2/3 surface expression in both the PFC and NAc core (Schwendt and others 2012). Reports indicate that these adaptations could be sensitive to environmental contexts as extinction training reversed the methamphetamine-induced alterations in mGluR2/3 expression observed in the NAc core but not in the PFC (Schwendt and others 2012).

Taken together, the effects of chronic drug exposure to many types of addictive substances share similar consequences with respect to glutamatergic signaling in the PFC-NAc circuit. Generally, drugs of abuse have been shown to potentiate glutamate release in the NAc core and also inhibit the removal of glutamate from the synaptic cleft (Table 1). Combined, these alterations facilitate the cue- and drug-induced glutamate spillover at NAc core synapses that has been shown in rodent models of addiction and relapse to underlie drug seeking (Kalivas 2009).

Glutamatergic Pharmacotherapies

mGluR2/3 Agonism

Systemic administration of the mGluR2/3 selective agonist LY379268 in animal models of addiction and relapse has been shown to inhibit cue-induced cocaine reinstatement, cue- and drug-primed methamphetamine reinstatement, cue- and context-induced nicotine reinstatement, as well as cue-induced heroin reinstatement (Table 1). In vivo NAc core microdialysis studies demonstrate that blockade of mGluR2/3 receptors increase glutamate release whereas activation of these receptors has the opposing effect, supporting a role for mGluR2/3 in the regulation of glutamate release in the NAc core (Moussawi and Kalivas 2010). Direct intracranial infusion of LY379268, an mGluR2/3 agonist, into the NAc core inhibited cocaine-primed reinstatement, cue-induced heroin seeking, as well as stress- and cue-induced reinstatement of ethanol seeking (Table 1). Taken together, results from numerous behavioral studies demonstrate that mGluR2/3 stimulation in the NAc core inhibits drug seeking by limiting the extent of glutamate release in the NAc core.

mGluR5 Antagonism

Studies in animal models of addiction indicate that in the NAc core the effect of activating postsynaptic mGluR5 receptors is diametrically opposed to that of the presynaptic mGluR2/3 receptors (Kalivas 2009; Moussawi and Kalivas 2010). Systemic blockade of mGluR5 with the antagonists 2-methyl-6-(phenylethynyl)pyridine (MPEP) or 3-((2-methyl-4-thiazolyl)ethynyl)pyridine (MTEP) inhibited cue- and drug-primed methamphetamine, cocaine, and nicotine reinstatement (Table 1). Moreover, blockade of mGluR5 signaling specifically in the core subcompartment of the NAc also inhibited the reinstatement of both cocaine and ethanol seeking (Table 1). These data suggest that

blockade of mGluR5 prevents synaptic potentiation of MSNs in response to glutamate overflow occurring during cue- and drug-primed drug seeking (Kalivas 2009).

Enhancing Xc- and GLT-1 Function and Expression

As regulation of glutamate synaptic transmission is exacted by extracellular glutamate, mechanisms of glial glutamate release and uptake are particularly relevant in treating addiction (Kalivas 2009). As discussed above, chronic drug exposure has been shown to affect synaptic plasticity through alterations in glial proteins that regulate glutamate homeostasis and through alterations in the function of nonsynaptic glutamate receptors. Accumulating evidence indicates that drug-related behaviors in rodents and humans can be inhibited by restoring glutamate homeostasis through the restoration of Xc- and GLT-1 function and expression.

Ceftriaxone, a third-generation cephalosporin β -lactam antibiotic, is commonly used in the treatment of bacterial meningitis (Knackstedt and others 2010). Apart from its action as an antibiotic, ceftriaxone has been shown to enhance GLT-1 and Xc-expression and function (Fischer and others 2013; Trantham-Davidson and others 2012). Given its capacity to increase glutamate uptake and maintain glutamate homeostasis, ceftriaxone has been evaluated for its ability to prevent excitotoxicity and neuronal damage, serving as a potential therapeutic for amyotrophic lateral sclerosis (ALS). Ceftriaxone was well tolerated by human patients but was halted in phase 3 of clinical trials of human ALS patients due to the possibility that it was not a sufficiently effective therapy (Kong and others 2012). The ability of ceftriaxone to enhance GLT-1 and xCT expression also make it an attractive candidate for the treatment of addiction, as multiple drugs of abuse reduce expression of these proteins (see above). Accordingly, repeated administration of ceftriaxone reduces ethanol consumption in alcohol-preferring rats and also inhibits both cue- and drug-primed cocaine reinstatement (Table 1). Ceftriaxone treatment has also been shown to inhibit the reinstatement of nicotine and methamphetamine seeking in rodents using the conditioned place preference paradigm (Table 1). Recent reports show that ceftriaxone-mediated inhibition of cocaine-seeking functions through the normalization of glutamate transmission (Trantham-Davidson and others 2012) and can be reversed by pharmacologically blocking GLT-1 in the NAc (Fischer and others 2013). Moreover, ceftriaxone treatment provides long-lasting cocaine relapse protection in rodent models when it is given weeks prior to the reinstatement trials (Sondheimer and Knackstedt 2011). Taken together, these data indicate that ceftriaxone-mediated inhibition of drug seeking occurs through the normalization of extrasynaptic glutamate levels and enhancement of glutamate uptake, countermanding drug-induced glutamate overflow in the NAc (Kalivas 2009). Unfortunately, ceftriaxone has not yet been evaluated for its efficacy in treating addiction in human patients.

Modafinil (2-diphenylmethyl-sulfinyl-2 acetamide aka Provigil) is a cognitive enhancing agent used in the treatment of narcolepsy (Mahler and others 2014). The mechanism of action for modafinil appears to be remarkably complicated as it has been reported to stimulate histamine, norepinephrine, serotonin, dopamine, and orexin systems in the brain (Gerrard and Malcolm 2007). Because it increases extracellular dopamine concentration, modafinil was considered an attractive candidate for a replacement therapy in treating

psychostimulant addiction (Mahler and others 2014). Paradoxically, modafinil does not induce a robust reinforcing effect either in humans or in rodent models (Mahler and others 2014). Apart from its stimulant-like properties, modafinil treatment also increases extrasynaptic glutamate concentration in the accumbens core and thereby inhibits cocaine reinstatement via activating mGluR2/3s (Mahler and others 2014). Moreover, inhibiting cocaine seeking by modafinil requires activity of Xc-, because blockade of cysteine glutamate exchange prevented modafinil-induced glutamate release (Mahler and others 2014). Modafinil treatment has also been shown to inhibit context-, cue-, and drug-primed reinstatement of methamphetamine seeking (Table 1). Furthermore, modafinil inhibits drug-primed reinstatement of morphine conditioned place preference, an effect that was also dependent on mGluR2/3 signaling (Tahsili-Fahadan and others 2010). In human patients, modafinil was not found to be an effective treatment for reducing methamphetamine relapse, although these results were inconclusive given a lack of medication compliance (Anderson and others 2012). In contrast, modafinil was effective in clinical trials for cocaine addiction with cocaine-dependent individuals reporting reduced craving and longer periods of abstinence (Anderson and others 2009).

N-acetylcysteine (NAC), a common dietary supplement, serves as an antioxidant precursor to glutathione and is commonly used in the treatment of acetaminophen poisoning (Murray and others 2012). Like modafinil, NAC's mechanism of action is multifaceted with studies reporting antioxidant activity, reduction of inflammatory cytokine release, modulation of dopamine release, as well as increased glial-glutamate release through activation of Xc- (Murray and others 2012). Because of the fact that NAC is a cystine prodrug, it serves as a substrate for cystine-glutamate exchange, as well as restores expression of GLT-1 and xCT in animals with a history of drug exposure (Knackstedt and others 2010). Given its positive effect on glial glutamate release, NAC could serve as a means for restoring inhibitory tone on presynaptic metabotropic glutamate receptors lost because of chronic drug exposure, possibly preventing glutamate overflow and the reinstatement of drug seeking (Kalivas 2009). Indeed, in preclinical models, systemic NAC administration reduces cue- and/or drug-primed reinstatement of cocaine, heroin, and nicotine seeking, an effect that was reversed by antagonizing NAc core mGluR2/3 receptors (Moussawi and others 2011b), as well as inhibits ethanol conditioned place preference (Table 1). Interestingly, NAC treatment restores the ability to induce LTP and LTD in the PFC-NAc core pathway in rats with a cocaine-induced deficit in the ability to induce both forms of synaptic plasticity when stimulating the PFC. This effect also depends on signaling through mGluR2/3 (Moussawi and others 2009). Restoration of GLT-1 expression by NAC in the NAc core is required for the inhibition of both cue- and cocaine-primed reinstatement (Reissner and others 2014b). As an additional potential therapeutic advantage, NAC treatment is effective not only when given during self-administration or prior to reinstatement (Madayag and others 2007; Murray and others 2012; Reichel and others 2011) but also facilitates extinction learning. In rodent models, chronic NAC treatment enhanced the rate of extinction of operant responding for both cocaine and heroin (Murray and others 2012). Much like ceftriaxone, administration of NAC provides a long-lasting protection from relapse. We have previously shown that the daily administration of 100 mg/kg NAC during abstinence was effective at inhibiting cocaine seeking even 2 weeks after the final injection of NAC (Reichel and others 2011). Human

clinical trials have supported a role for NAC in the treatment of drug addiction with cocaine-dependent individuals reporting lower rates of relapse and nicotine-dependent individuals reporting fewer cigarettes smoked (Murray and others 2012). Moreover, patients attempting marijuana cessation that received NAC treatment were twice as likely to produce negative toxicology results than placebo controls (Gray and others 2012). NAC has also shown promising effects in the treatment of pathological gambling, obsessive-compulsive disorder, skin picking, schizophrenia, and bipolar disorder (Murray and others 2012). Data from human magnetic resonance spectroscopy studies indicate that NAC normalizes levels of extracellular glutamate in the NAc of cocaine-dependent individuals with no effect observed in control subjects (Schmaal and others 2012). The combined conclusions of numerous rodent and human studies strongly support the ability of NAC to serve as an effective treatment for compulsive and addictive disorders. Both rodent and human studies are also consistent in supporting NAC's ability to inhibit drug seeking through the restoration of glutamate homeostasis in the NAc.

The atypical xanthine derivative propentofylline (PPF) has been shown to affect the physiology of glial cells by inhibiting phosphodiesterase (PDE) activity and adenosine uptake (Sweitzer and others 2001). Interestingly, PPF has also been shown to up-regulate GLT-1, making it a potential pharmacotherapy for addiction (Tawfik and others 2006). Indeed, preclinical studies support the ability of PPF to inhibit both cued- and drug-primed reinstatement to cocaine seeking in rodents (Reissner and others 2014a). Furthermore, as discussed above for NAC, the ability of PPF to inhibit cocaine seeking was dependent on its ability to enhance GLT-1 expression (Reissner and others 2014a). PPF has been used in clinical trials for its efficacy in treating Alzheimer's disease as well as cocaine dependence and was generally well tolerated (Reissner and others 2014a). PPF has not been approved for use in human patients, yet the structurally similar xanthine derivative pentoxifylline (Trental) is currently FDA approved for the treatment of chronic occlusive arterial disease (Reissner and others 2014a). Studies aimed at determining if pentoxifylline is an efficient method of treating cocaine dependence showed a nonsignificant trend toward decreased cocaine use in addicted individuals, yet no measure of medication compliance was taken (Ciraulo and others 2005).

Glial Modulators

In addition to PPF, other drugs classified as glial modulators have been tested for their efficacy in treating addiction-related behaviors. Ibudilast, a drug used in Japan for the treatment of asthma, has been shown to possess anti-inflammatory effects, promote release of GDNF, and, much like PPF, also inhibits PDE activity (Rolan and others 2009). In rodent models, administration of Ibudilast reduced overall methamphetamine (Snider and others 2013) and ethanol intake (Bell and others 2013) and also inhibited methamphetamine-induced locomotion and sensitization (Snider and others 2012). Furthermore, ibudilast treatment has been shown to inhibit stress- and drug-primed reinstatement of methamphetamine seeking (Beardsley and others 2010) and also inhibits morphine-induced DA release in the NAc as well as morphine withdrawal and conditioned place preference (Rolan and others 2009; Schwarz and Bilbo 2013). Given the multimodal action of ibudilast, it has yet to be determined which effect or combination of effects is required for inhibition

of drug seeking. Additional studies focusing on this class of drugs could provide exciting new avenues for the development of addiction pharmacotherapies that target specific functions of astroglial cells.

In summary, evidence from rodent and human studies supports the existence of a common drug-induced glutamatergic dysfunction of the cortico-accumbal circuit, responsible for craving and drug seeking underlying the pathophysiology of relapse. Though the precise alterations in specific proteins or measurements of glutamate levels in the NAc core differ slightly from drug to drug, human clinical studies using N-acetylcysteine illustrate the value of therapies aimed at the restoration of glutamate homeostasis in treating addiction and compulsive disorders. Additional study of drug-induced alterations of the mediators of glutamate homeostasis on astrocytes as well as the proteins that receive glutamate signals in the NAc core could potentially result in the development of additional pharmacotherapies for addiction.

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Figure 1.

Mesocorticolimbic circuit. Brain regions connected to the nucleus accumbens are shown in a simplified version of the mesocorticolimbic circuit. The prefrontal cortex (PFC) is shown in green. The nucleus accumbens (NAc) is shown in red. The ventral pallidum (VP) is shown in purple, and the ventral tegmental area (VTA) is shown in blue. Glutamate projections are shown in green, GABA projections are shown in red, and dopamine projections are shown in blue.

Figure 2.

Astrocytes provide metabolic support for neurons and regulate glutamate production and uptake. Represented above as a purple star, astrocytes are located in close proximity with both the neurovasculature (shown on the right) and synapses (shown on the left). In addition to providing lactate used to generate ATP in neurons, astrocytes also participate in the glutamate-glutamine cycle. Following glutamate efflux from the synaptic cleft glutamate (orange circles) is taken up by GLT-1 (green) on astrocytes and converted to glutamine. Glutamine is subsequently released by astrocytes and taken up by neurons where it is converted to glutamate and loaded into synapses to participate in the next round of synaptic transmission. System Xc- is also shown on the astrocytes cell as a blue circle.

Figure 3.

Mechanisms of glutamate release from astrocytes. Glutamate (orange) can be released from astrocytes via the reverse action of GLT-1 (green) via the action of cystine glutamate exchange (blue circle with red and blue arrows), through a swelling-induced release via volume regulated anion channels (VRAC) (pink), through purine activated ion channels (P2X7) (red), through gap-junctions or hemichannels (yellow), and through Ca^{2+} -dependent vesicular release (grey synaptic-like microvesicles [SLMV]). Potential sources for increased $[\text{Ca}^{2+}]_i$ are also shown above as these increases in Ca^{2+} concentration could result in vesicular glutamate release. Activation of transient receptor potential canonical receptors (TRPC) (green) causes direct calcium influx, as does the activation of inotropic glutamate receptors (iGluR) (purple), P2X7 purine receptors, and voltage-gated calcium channels (VGCC) (yellow). G-protein coupled receptors like metabotropic glutamate receptors (mGluR) (red) and metabotropic purine receptors (P2Y) (orange) activate phospholipase C (PLC) cleaving PIP2 into IP3 and DAG leading to the activation of IP3 receptors (IP3R2) (blue) located on the endoplasmic reticulum (gray). Once activated these receptors release Ca^{2+} into the cytosol from intracellular stores possibly enhancing $[\text{Ca}^{2+}]_i$ to levels that would influence Ca^{2+} -mediated vesicular release of glutamate from astrocytes.

Figure 4.

(A) Naive NAc core synapse. Shown here is a schematic of a tripartite synapse in the accumbens core with the pre- (green) and postsynaptic (orange) terminals as well as an astrocytic contact (blue). Glutamate is depicted as orange spheres and concentrations of glutamate in various compartments of the synaptic ultrastructure are also shown above. In the naïve state, glutamate tone activates presynaptic mGluR2/3 (green columns), which act as release regulating autoreceptors (red line). Astrocytic Xc- and GLT-1 are shown releasing and taking up glutamate, respectively. Ca^{2+} -mediated (blue) vesicular release of glutamate is also depicted above in the blue astrocyte cell. On the postsynaptic side mGluR5 receptors (red columns) are shown as well as GluN2B containing NMDA receptors (blue and gray). Glutamate concentration data are adapted from (Moussawi and others 2011a; Parpura and Verkhratsky 2013). (B) NAc core synapse following chronic drug exposure. Shown here is a schematic of a tripartite synapse in the accumbens core with the pre- (green) and postsynaptic (orange) terminals as well as an astrocytic contact (blue). Lack of tone on presynaptic mGluR2/3 (red cross) potentiates glutamate release leading to spillover and activation of mGluR5 and GluN2B containing NMDA receptors. Also listed here are the drugs that cause a decrease in extracellular glutamate and drugs that show potentiation of glutamate release in the NAc core during drug-seeking/reinstatement. (C) Restoration of glutamate homeostasis. Shown here is a schematic of a tripartite synapse in the accumbens core with the pre- (green) and postsynaptic (orange) terminals as well as an astrocytic contact (blue). Shown next to Xc- and GLT-1 are the drugs that affect these molecules that also inhibit drug seeking. Also depicted is the reduction in glutamate release due to the

restoration of glutamate homeostasis and lack of activation of mGluR5 and GluN2B containing NMDA receptors (red crosses).

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Table 1**Glutamatergic Signaling in Addiction.**

	GLT-1 Expression	xCT Expression	Decreased Basal Extrasynaptic Glutamate	Enhanced NAcore Glutamate During Drug Seeking
<i>Cocaine</i>	Down-regulated (Knackstedt and others 2010)	Down-regulated (Knackstedt and others 2010)	(Baker and others 2003a)	Drug-primed (McFarland and others 2003) Cue-primed (unpublished observation)
<i>Nicotine</i>	Down-regulated (Gipson and others 2013)	No change (Gipson and others 2013)	~	(Gipson and others 2013)
<i>Opiates</i>	Down-regulated (Shen and others Unpublished observation)	No change (Shen and others Unpublished observation)	~	Cue- and drug-primed (LaLumiere and others 2008)
<i>Ethanol</i>	Down-regulated (Sari and others 2013)	~	~	(Griffin Iii and others 2013)
<i>Meth</i>	~	~	(Parsegian and See 2013)	Cue- and drug-primed (Parsegian and See 2013)
	Activation of mGluR2/3 Inhibits Drug Seeking	Behavioral Paradigm	Blockade of mGluR5 Inhibits Drug Seeking	Behavioral Paradigm
<i>Cocaine</i>	Systemic (Cannella and others 2013)	Cue-primed reinstatement	Systemic (Kumaresan and others 2009)	Cue- and drug-primed reinstatement
	NAcore (Peters and Kalivas 2006)	Drug-primed reinstatement	NAcore (Knackstedt and others 2014)	Cue- and context-primed reinstatement
<i>Nicotine</i>	Systemic (Liechti and others 2007)	Cue- and context-primed reinstatement	Systemic (Dravolina and others 2007)	Cue- and drug-primed reinstatement
<i>Opiates</i>	Systemic (Bossert and others 2005)	Cue-primed reinstatement	Systemic (Popik and Wróbel 2002)	Conditioned place preference
	NAcore (Bossert and others 2006)	Cue-primed reinstatement		
<i>Ethanol</i>	Systemic (Zhao and others 2006)	Stress- and cue-primed reinstatement	NAcore (Sinclair and others 2012)	Cue-primed reinstatement
	NAcore (Griffin Iii and others 2013)	Stress and cue-primed reinstatement		
<i>Meth</i>	Systemic (Kufahl and others 2013)	Cue- and drug-primed reinstatement	Systemic (Watterson and others 2013)	Cue- and drug-primed reinstatement
	Ceftriaxone Inhibits Drug Seeking	Administration Regimen and Behavioral Paradigm	N-Acetylcysteine Inhibits Drug Seeking	Administration Regimen and Behavioral Paradigm
<i>Cocaine</i>	(Knackstedt and others 2010)	7 consecutive 200 mg/kg i.p. injections	(Baker and others 2003b)	2 weeks 100 mg/kg NAC during extinction
	(Sondheimer and Knackstedt 2011)	Cue- and drug-primed reinstatement	(Moussawi and others 2011)	Cue- and drug-primed reinstatement
<i>Nicotine</i>	(Alajaji and others 2013)	3 consecutive 200 mg/kg i.p. injections	(Ramirez-Niño and others 2013)	2 weeks 60 mg/kg NAC during extinction
		Nicotine-primed conditioned place preference		Cue-primed reinstatement
<i>Opiates</i>	(Shen and others Unpublished observation)	5 consecutive 100 mg/kg i.p. injections	(Zhou and Kalivas 2008)	2 weeks 100 mg/kg NAC during extinction
		Cue-primed reinstatement		Cue- and drug-primed reinstatement

	GLT-1 Expression	xCT Expression	Decreased Basal Extrasynaptic Glutamate	Enhanced NAc core Glutamate During Drug Seeking
<i>Ethanol</i>	(Sari and others 2013)	5 consecutive 100 mg/kg i.p. injections Reduced intake in ethanol preferring rats	(Ferreira Seiva and others 2009)	2 g/L NAC in drinking water Conditioned place preference
<i>Meth</i>	(Abulseoud and others 2012)	7 consecutive 200 mg/kg i.p. injections Conditioned place preference	Unpublished observation	2 weeks 100 mg/kg NAC during extinction Cue- and drug-primed reinstatement