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Group II metabotropic glutamate receptors (mGlu_{2/3}) in drug addiction

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Abstract

Drug addiction is characterized by maladaptive decision-making and dysfunctional brain circuitry regulating motivated behaviors, resulting in loss of the behavioral flexibility needed to abstain from drug seeking. Hence, addicts face high risk of relapse even after prolonged periods of abstinence from drug use. This is thought to result from long-lasting drug-induced neuroadaptations of glutamate and dopaminergic transmission in the mesocorticolimbic and corticostriatal circuits where group II metabotropic glutamate receptors (mGlu_{2/3} receptors) are densely expressed. mGlu_{2/3} receptors presynaptically control glutamate as well as dopamine release throughout the mesocorticolimbic structures involved in reward processing and drug seeking, and their function is reduced after prolonged exposure to drugs of abuse. In pre-clinical models, mGlu_{2/3} receptors have been shown to regulate both reward processing and drug seeking, in part through the capacity to control release of dopamine and glutamate respectively. Specifically, mGlu_{2/3} receptor agonists administered systemically or locally into certain brain structures reduce the rewarding value of commonly abused drugs and inhibit the reinstatement of drug seeking. Given the ability of mGlu_{2/3} receptor agonists to compensate for and possibly reverse drug-induced neuroadaptations in mesocorticolimbic circuitry, this class of receptors emerges as a new therapeutic target for reducing relapse in drug addiction.

Keywords

addiction; glutamate; group II metabotropic glutamate receptors (mGlu_{2/3} receptors); LY379268; LY341495

1) Addiction as a cognitive disorder

Drug addiction is often described as a cognitive disorder that is characterized by maladaptive decision-making and dysfunctional motivational circuits (Koob and Le Moal 2001; Kalivas and Volkow 2005; Schoenbaum, Roesch et al. 2006). Addicts lose interest in obtaining natural reward and choose to seek drugs of abuse despite their insights into the adverse outcomes of their decision. Thus, addicts lack the necessary behavioral flexibility required to implement their stated desire to abstain from drug seeking. Instead, they engage in repeated drug seeking and exhibit increased vulnerability to relapse even after prolonged periods of withdrawal (Kalivas and O'Brien 2008). This is thought to result from long-

lasting neuroadaptations in the brain circuitry regulating motivated behaviors caused by repeated exposure to drugs of abuse (Kalivas and Volkow 2005; Graybiel 2008). Emerging research studies over the past few years illustrate the role of glutamate neurotransmission in the neurobiology of addiction (Kalivas 2009). In particular, this review will describe the physiology and drug-induced pathologies in group II metabotropic glutamate receptors (mGlu_{2/3} receptors) supporting therapeutic interventions targeting this receptor class in treating drug addiction.

2) Neurocircuitry of motivated behavior and relapse

It is well established that increased vulnerability to relapse after chronic exposure to drugs of abuse is rooted in the long term neuroadaptations in the neural circuitry of normal goal oriented behavior (Kalivas and Volkow 2005). The prefrontal cortex (PFC) glutamatergic projection to the ventral striatum (nucleus accumbens; NAc) is a key component of the circuit involved in initiating and learning adaptive behaviors (Hyman, Malenka et al. 2006; Graybiel 2008), and this projection is in turn regulated by mesocorticolimbic dopaminergic projections from the ventral tegmental area (VTA), signaling the salience and facilitating learning of the relevant experience (Schultz and Dickinson 2000; Redgrave and Gurney 2006). Projections into PFC and NAc from other brain areas like hippocampus and basolateral amygdala are thought to provide previously learned, relevant contextual and emotional information associated with the experience at hand (Swanson and Petrovich 1998; Bast, Zhang et al. 2001; Phelps and LeDoux 2005; Rudy and Matus-Amat 2005). As well, other areas like the extended amygdala (bed Nucleus of stria terminalis, central amygdala, and NAc shell) sending projections into PFC/NAc convey signals about the organism's internal state that contribute to ongoing information processing (Swanson and Petrovich 1998; Kelly and Strick 2004; Reynolds and Zahm 2005). Importantly, in addition to regulating adaptive behavioral responses, the PFC-NAc glutamatergic pathway is involved in addiction related behaviors, and is necessary and sufficient for reinstating drug seeking behavior in some animal models of relapse (Figure 1) (Kalivas and Volkow 2005).

Lesion or inactivation of the prelimbic PFC or NAc prevents reinstatement of drug seeking in extinguished animals, while stimulation of either promotes drug seeking in the absence of a drug- or cue-prime (Cornish, Duffy et al. 1999; Cornish and Kalivas 2000; Di Ciano and Everitt 2001; McFarland and Kalivas 2001; Capriles, Rodaros et al. 2003; McFarland, Lapish et al. 2003; McLaughlin and See 2003; McFarland, Davidge et al. 2004; Peters, LaLumiere et al. 2008). Moreover, behavioral electrophysiological data indicate an increase in firing rate of PFC pyramidal neurons (Sun and Rebec 2006), as well as subpopulations of NAc medium spiny neurons (MSN) (Carelli and Ijames 2000) during reinstatement of cocaine seeking. Human imaging studies have also identified correlations between craving and increased activity in the ventral orbital cortex, cingulate cortex, and ventral striatum upon drug or cue exposure (Breiter, Gollub et al. 1997; Breiter and Rosen 1999; Wilson, Sayette et al. 2004; Kufahl, Li et al. 2005; Risinger, Salmeron et al. 2005).

In addition, other brain regions are compulsory depending on the stimulus used to elicit drug seeking (Figure 1). For example, cue primed relapse requires basolateral amygdala while stress induced relapse requires the extended amygdala (Shaham, Erb et al. 2000; See 2002;

McFarland, Davidge et al. 2004). Corresponding to the discovery of this circuitry, many laboratories have focused on identifying and reversing enduring neuroadaptations in the relapse circuitry encompassing protein biochemistry, gene expression, spine morphology, and electrophysiology (Hyman, Malenka et al. 2006; Kauer and Malenka 2007; Kalivas 2009). Different animal models are used to examine aspects of drug reward, including intracranial self stimulation, conditioned place preference, or self-administration of the relevant substance, while other models are thought to reflect enduring brain changes associated with increased reinforcing value and/or vulnerability to relapse, including locomotor sensitization and reinstatement of drug seeking (Epstein, Preston et al. 2006; Sanchis-Segura and Spanagel 2006). Using these animal models, mGlu_{2/3} receptors have emerged as an important substrate for drug-induced neuroadaptations and one that may have utility in regulating drug seeking and other addiction related behaviors.

3) mGlu_{2/3} receptors and regulation of neurotransmitter release

Group II metabotropic receptor (mGlu_{2/3} receptors) family includes 2 subtypes both coupled to Gi proteins; mGlu2 receptors are expressed outside the active zone on presynaptic axon terminals to negatively regulate neurotransmitter release, while mGlu3 receptors are localized pre- and post-synaptically as well as on glia with a less clear overall function, but including negative regulation of transmitter release (Ohishi, Shigemoto et al. 1993; Testa, Friberg et al. 1998; Schoepp 2001; Tamaru, Nomura et al. 2001; Richards, Messer et al. 2005). mGlu_{2/3} receptors can be homosynaptic, regulating glutamate release, or heterosynaptic regulating release of dopamine and γ -aminobutyric acid (GABA) (Hu, Duffy et al. 1999; Schoepp 2001; Karasawa, Yoshimizu et al. 2006; Xi, Kiyatkin et al. 2010). Gi coupling of mGlu_{2/3} receptors controls release through different mechanisms including activation of presynaptic K⁺ channels, inhibition of presynaptic Ca²⁺ channels, or direct interference with vesicular release (Anwyl 1999).

In the PFC, mGlu_{2/3} receptors appear to be tonically activated by endogenous glutamate. Microdialysis studies reveal an increase in PFC glutamate levels upon infusion of a selective mGlu_{2/3} receptor antagonist (LY341495) (Melendez, Vuthiganon et al. 2005; Xie and Steketee 2008). However, perfusion of a selective agonist ((2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (APDC)) was without effect, suggesting the presence of ceiling-like glutamatergic tone on mGlu_{2/3} receptors (Melendez, Vuthiganon et al. 2005). In addition, infusion of the antagonist LY341495 in the prefrontal cortex increased glutamate levels in subcortical regions of the reward circuitry including the nucleus accumbens and ventral tegmental area (Xie and Steketee 2008). This is possibly due to reduced inhibition resulting in facilitated excitatory output from the PFC.

In the nucleus accumbens, data support the presence of endogenous glutamatergic tone on mGlu_{2/3} receptors regulating both glutamate and dopamine levels. Electrophysiological recordings from NAc slices reveal presynaptic autoregulation of glutamate release by mGlu_{2/3} receptors. Bath application of the selective agonists (S)-4-carboxy-3-hydroxyphenylglycine ((1S,3S)-ACPD) and (2S,1'S,2'S)-2-(2'-carboxycyclopropyl)glycine (L-CCG1) increased paired pulse ratios and reduced miniature excitatory post synaptic currents (mEPSC) frequency without affecting their amplitude, pointing to a presynaptic

mode of action (Manzoni, Michel et al. 1997). In addition, in vivo microdialysis studies reveal glutamatergic tone on mGlu_{2/3} receptors as indicated by increased glutamate release upon selective antagonist LY143495 perfusion into NAc, while agonist (APDC) reduced extracellular glutamate levels (Xi, Baker et al. 2002). mGlu_{2/3} receptors regulate synaptic release in addition to glutamate efflux through Na⁺ independent cystine-glutamate antiporter through Ca²⁺ and protein kinase A (PKA) dependent cellular mechanisms (Xi, Baker et al. 2002).

Dopamine release in NAc is also controlled by mGlu_{2/3} receptors. Intra-accumbens infusion of direct (LY354740; (2S, 1'R,2'R,3'R)-2-(2,3-dicarboxycyclopropyl) glycine (DCG-4); LY379268) or indirect agonists (2-(phosphonomethyl)-pentanedioic acid [2-PMPA], inhibitor of N-acetylaspartylglutamate [NAAG] peptidase, thereby increasing NAAG levels, an endogenous mGlu₃ receptor agonist) reduce, while antagonists (MGS0039; α-methyl-4-phosphonophenylglycine (MPPG)) increase basal dopamine levels measured with microdialysis probes (Hu, Duffy et al. 1999; Greenslade and Mitchell 2004; Karasawa, Yoshimizu et al. 2006; Xi, Kiyatkin et al. 2010). While this regulation depends on activation of voltage-dependent Ca²⁺ channels (Hu, Duffy et al. 1999) pointing to vesicular release, it is not clear if it is mediated directly via heterosynaptic mGlu_{2/3} receptors on dopaminergic terminals, especially since some studies failed to identify significant mGlu_{2/3} receptor mRNA levels in midbrain neurons projecting to the ventral striatum (Ohishi, Shigemoto et al. 1993). Another possibility is that mGlu_{2/3} receptors regulate glutamatergic terminals on accumbens medium spiny neurons which in turn project onto dopaminergic cells in the ventral tegmental area (VTA) (Kalivas, Churchill et al. 1993). Furthermore, mGlu_{2/3} receptors regulate glutamate release in VTA (Manzoni and Williams 1999), hippocampus (Marco 2004), bed nucleus of stria terminalis (BNST) (Grueter and Winder 2005) and other regions within the motivational circuit (Poisik, Raju et al. 2005).

4) Addiction causes neuroadaptations in mGlu_{2/3} receptors

Repeated exposure to drugs of abuse alters mGlu_{2/3} receptors function. mGlu_{2/3} receptors inhibitory effects on excitatory transmission in VTA and NAc are enhanced after early withdrawal from chronic morphine (Manzoni and Williams 1999; Martin, Przewlocki et al. 1999). Different conclusions are drawn from some nicotine studies. Compared to control subjects, a higher dose of mGlu_{2/3} receptor agonist is required to elevate the threshold of intracranial self-stimulation after acute withdrawal from nicotine self-administration, suggesting a functional down-regulation of these receptors in early withdrawal from nicotine (Harrison, Gasparini et al. 2002; Kenny, Gasparini et al. 2003; Kenny and Markou 2004). Furthermore, using [³⁵S] GTPγS binding assay, Liechti et al. recently found that acute withdrawal from nicotine self administration reduces mGlu_{2/3} receptor function by blunting coupling to G proteins throughout the corticolimbic system (PFC, NAc, VTA, amygdala, hippocampus, and hypothalamus) (Liechti, Lhuillier et al. 2007). Acute withdrawal from cocaine also resulted in reduced mGlu_{2/3} receptor function in central amygdala neurons as measured with electrophysiological markers (Neugebauer, Zinebi et al. 2000). Furthermore, PFC and NAc mGlu_{2/3} receptor function is reduced after prolonged withdrawal from chronic cocaine (Xi, Ramamoorthy et al. 2002; Bowers, McFarland et al. 2004; Xie and Steketee 2008; Ghasemzadeh, Mueller et al. 2009; Xie and Steketee 2009). In the PFC and NAc,

activator of G-protein signaling 3 (AGS3) protein which uncouples Gi subunits from their receptors (De Vries, Fischer et al. 2000) is overexpressed after chronic cocaine (Bowers, McFarland et al. 2004). Accordingly, mGlu_{2/3} receptor coupling to G protein is reduced in NAc after chronic cocaine or ethanol (Xi, Ramamoorthy et al. 2002; Bowers, Hopf et al. 2008; Ghasemzadeh, Mueller et al. 2009).

In addition to deficits in receptor density and/or Gi signaling, mGlu_{2/3} receptor-dependent plasticity is impaired after exposure to drugs of abuse. For example, chronic cocaine impairs mGlu_{2/3} receptor-dependent long term depression (LTD) in PFC pyramidal cells (Huang, Yang et al. 2007), and chronic morphine impairs mGlu_{2/3} receptor induced LTD at excitatory synapses in NAc medium spiny neurons (Robbe, Bockaert et al. 2002). This form of plasticity is pharmacologically induced by the bath application of a selective mGlu_{2/3} receptor agonist onto acute slices (Robbe, Alonso et al. 2002; Robbe, Bockaert et al. 2002). Therefore, the impaired LTD could be explained by reduced receptor function as discussed previously. More recently it was shown that LTP induced in the PFC by high frequency stimulation of the PFC was abolished after withdrawal from self-administered cocaine, and this resulted from a reduction in mGlu_{2/3} receptor stimulation (Moussawi et al., 2009). Thus, in the absence of endogenous stimulation of mGlu_{2/3} autoreceptors, the PFC to NAc synapses were already potentiated, thereby masking the induction of further LTP. Given the importance of neuroplasticity in learning and updating behaviors following changes in environmental contingencies (Malenka and Bear 2004; Whitlock, Heynen et al. 2006; De Roo, Klauser et al. 2008), impaired plasticity after chronic drugs of abuse (Robbe, Bockaert et al. 2002; Martin, Chen et al. 2006; Huang, Lin et al. 2007; Moussawi, Pacchioni et al. 2009) could reflect the inability of addicts to modify or stop compulsive drug seeking despite the detrimental results of this maladaptive behavior. Thus, reduced function of mGlu_{2/3} receptors may be related to behavioral inflexibility observed in drug addicts.

It is possible that dysfunctional negative feedback of mGlu_{2/3} autoreceptors could underlie enhanced glutamate release in NAc after prolonged withdrawal from drugs of abuse in response to the drug itself or associated cues (Pierce, Bell et al. 1996; Bell, Duffy et al. 2000; Hotsenpiller, Giorgetti et al. 2001; Baker, McFarland et al. 2003; Madayag, Lobner et al. 2007; LaLumiere and Kalivas 2008). Along these lines, mGlu_{2/3} receptor agonists were shown to prevent glutamate and dopamine overflow in NAc of rats sensitized to amphetamine (Kim, Austin et al. 2005), and mGlu_{2/3} receptor antagonists facilitate drug induced glutamate release in NAc after chronic cocaine self-administration (Xi, Gilbert et al. 2006). Enhanced glutamate release in NAc after cue or drug presentation in cocaine or heroin trained animals is a hallmark and prerequisite of relapse to drug seeking in some animal models (Kalivas 2009). Accordingly, by facilitating glutamate release, chronic drug-induced defects in mGlu_{2/3} receptor signaling could contribute to drug seeking and relapse. A corollary of these findings is that stimulating mGlu_{2/3} receptors may be a potential therapeutic strategy for drug addiction.

5) mGlu_{2/3} receptors regulate reward processing and drug seeking

a) Regulation of reward function

Animal studies show that mGlu_{2/3} receptors regulate both reward processing and drug seeking. While mGlu₂ receptor knock-out mice show no gross behavioral abnormalities, they express higher cocaine-induced locomotor sensitization and stronger conditioned place preference, suggesting an increased rewarding value of cocaine in absence of mGlu₂ receptor signaling (Morishima, Miyakawa et al. 2005). In addition, these mice reveal increased dopamine and glutamate release in NAc in response to a cocaine injection (Morishima, Miyakawa et al. 2005) that could possibly underlie the enhanced reinforcing value of cocaine. Consistent with these findings, direct or indirect systemic mGlu_{2/3} receptor agonists (LY379268; 2-PMPA) reduce cocaine-induced release of dopamine in rat NAc and attenuate rewarding effects of cocaine as measured by cocaine self-administration and intracranial self-stimulation in squirrel monkeys as well as rats (Baptista, Martin-Fardon et al. 2004; Adewale, Platt et al. 2006; Xi, Kiyatkin et al. 2010). Similar conclusions can be drawn from alcohol and nicotine studies. mGlu_{2/3} receptor agonists (LY314582; LY379268) reduce nicotine self-administration (Liechti, Lhuillier et al. 2007) and precipitate elevations in intracranial self-stimulation threshold (Harrison, Gasparini et al. 2002; Kenny, Gasparini et al. 2003), implying negative regulation of reward function by mGlu_{2/3} receptors (Harrison, Gasparini et al. 2002; Kenny, Gasparini et al. 2003; Kenny and Markou 2004; Liechti and Markou 2007). On the other hand, 1 and 3 mg/kg doses of systemic LY379268 show no effects on heroin self-administration (Bossert, Busch et al. 2005) and only a higher systemic dose of LY379268 (5mg/kg dose) reduces alcohol self-administration (Bäckström and Hyytiä 2005). However, these latter results are complicated by the evidence that LY379268 suppresses locomotor activity at higher doses (Bäckström and Hyytiä 2005). While the mGlu_{2/3} receptor agonist dose used in most studies (3 mg/kg) was reported to suppress basal locomotor activity (Cartmell, Monn et al. 2000), the same dose showed no effect on rotarod activity (Cartmell, Monn et al. 2000), suggesting a relatively mild effect on locomotion. In addition, this 3 mg/kg dose revealed no effect on the ability of animals to respond for natural reinforcers (Baptista, Martin-Fardon et al. 2004; Bossert, Poles et al. 2006; Liechti, Lhuillier et al. 2007) or some drugs of abuse (Bäckström and Hyytiä 2005; Bossert, Busch et al. 2005). Finally, consistent with the effects of mGlu_{2/3} receptors on drug reinforcement, mGlu_{2/3} receptors antagonist LY341495 increases behavioral sensitization in cocaine treated rats (Yoon, Jang et al. 2008), while mGlu_{2/3} receptor agonists reduce amphetamine-induced locomotor sensitization (Kim and Vezina 2002). However, it is important to note that the latter study lacks a necessary control group for the effects of the mGlu_{2/3} receptors agonist LY379268 on locomotor activity in saline treated rats.

b) Regulation of drug seeking

mGlu_{2/3} receptors regulate drug seeking across different species. Systemic injections of the mGlu_{2/3} receptor agonist LY379268 blocks drug primed relapse in squirrel monkeys (Adewale, Platt et al. 2006) and rats (Peters and Kalivas 2006) after cocaine self-administration. Baptista *et al.* also showed a dose dependent reduction of cue-induced reinstatement of cocaine seeking (Baptista, Martin-Fardon et al. 2004). In addition, systemic mGlu_{2/3} receptor agonists prevent cue and/or context induced relapse to nicotine (Liechti,

Lhuillier et al. 2007), alcohol (Bäckström and Hyytiä 2005; Rodd, McKinzie et al. 2006; Zhao, Dayas et al. 2006), heroin (Bossert, Liu et al. 2004; Bossert, Busch et al. 2005), and cocaine (Lu, Uejima et al. 2007).

The ability of mGlu_{2/3} receptors to control drug seeking is not limited to one brain region. Microinjections of mGlu_{2/3} receptor agonist LY379268 into NAc core block drug primed reinstatement of cocaine seeking (Peters and Kalivas 2006), while microinjections of LY379268 into VTA or NAc shell produced a dose-dependent antagonism of context induced reinstatement of heroin seeking (Bossert, Liu et al. 2004; Bossert, Gray et al. 2005), with only high doses showing an effect in NAc core. Substantia nigra and dorsal striatum microinjections were without effect (Bossert, Liu et al. 2004; Bossert, Gray et al. 2005). In addition, Lu *et al.* showed that LY379268 microinjection into the central but not basolateral amygdala nucleus reduced the incubation of cocaine craving and blocked cue induced relapse (Lu, Uejima et al. 2007).

Taken together, these behavioral studies support a conclusion that mGlu_{2/3} receptor stimulation negatively regulates drug-seeking. The site of action in the brain varies between studies, perhaps in part as a function of the drug being examined or the stimulus used to reinstate drug-seeking. Thus, while activation of mGlu_{2/3} receptors in the VTA or NAc shell inhibits context-induced reinstatement in heroin-trained animals, reinstatement to cocaine in cocaine-trained animals was blocked by mGlu_{2/3} receptor agonists into the core of the NAc. The difference between the neural substrates underlying the effects of mGlu_{2/3} receptor agonists on drug seeking could be explained by the different circuitry underlying contextual vs. cue or drug primed reinstatement. NAc shell is required for context induced reinstatement (Vorel, Liu et al. 2001; Taepavarapruk and Phillips 2003; Ito, Robbins et al. 2008), corresponding to the hippocampus projecting substantially to NAc shell as compared to core (Groenewegen, Vermeulen-Van der Zee et al. 1987). Moreover, the role of the VTA in context-induced drug seeking is consistent with the known role of dopamine agonists in the shell, but not the core, to promote drug seeking (Schmidt, Anderson et al. 2006), and dopamine antagonists to prevent relapse (Ciccocioppo, Sanna et al. 2001; Crombag, Grimm et al. 2002). Given that mGlu_{2/3} receptor agonists reduce both glutamate and dopamine levels in NAc (Hu, Duffy et al. 1999; Greenslade and Mitchell 2004; Karasawa, Yoshimizu et al. 2006; Xi, Kiyatkin et al. 2010), it is possible that LY379268 blockade of context-induced drug-seeking is caused by reducing extracellular levels of both glutamate and dopamine in NAc shell.

It is important to note that several studies reveal an effect by mGlu_{2/3} receptors on natural reward vs. drug seeking. For example, systemic or locally microinjected LY379268 blocked reinstatement to conventional reinforcers (food, sweet milk, sucrose) (Baptista, Martin-Fardon et al. 2004; Bossert, Poles et al. 2006; Peters and Kalivas 2006; Uejima, Bossert et al. 2007), without affecting their primary rewarding value (Baptista, Martin-Fardon et al. 2004; Bossert, Poles et al. 2006; Liechti, Lhuillier et al. 2007). Hence, drugs of abuse and natural reinforcers possibly share a common glutamatergic neurocircuitry in regulating behavior. This conclusion is corroborated by human imaging studies showing that natural and drug reinforcers activate overlapping cortico-striatal circuits (Daglish, Weinstein et al. 2003). However, the overlap may in part result from relatively poor resolution of

neuroimaging since behavioral electrophysiological recordings support the idea of separate subcircuits for drugs of abuse and natural rewards within the larger motivational circuit (Carelli, Ijames et al. 2000; Carelli 2002; Carelli and Wondolowski 2003; Donita and Regina 2008).

6) Solving the puzzle: mGlu_{2/3} receptor agonists functionally compensate for long term drug induced neuroadaptations

mGlu_{2/3} receptor agonists proved to be effective in preventing relapse to different drugs of abuse when administered systemically or locally into certain brain regions (see above). While it is well established that these agonists reduce glutamatergic transmission in the relevant areas of the reward circuitry, the bigger picture relating this effect to long-term drug induced neuroadaptations underlying relapse and compulsive drug seeking remains obscure. In the following section, we will discuss possible mechanisms relating mGlu_{2/3} receptors and glutamate transmission to long lasting drug induced neural changes, derived primarily from studies in the NAc after chronic cocaine treatment.

As discussed in the beginning of this article, glutamatergic transmission in the NAc is essential for addiction related behaviors. Glutamate homeostasis in the NAc, defined here as the balance between synaptic and nonsynaptic extracellular glutamate release and elimination (Figure 2 A), plays an intricate role in regulating synaptic transmission and plasticity by altering ionotropic and metabotropic glutamate receptor stimulation (Warr, Takahashi et al. 1999; Moran, McFarland et al. 2005; Jourdain, Bergersen et al. 2007; Mulholland, Carpenter-Hyland et al. 2008). This includes glutamate transporter regulation of extracellular glutamate levels arising from both synaptic and glial release (Danbolt 2001). In NAc, extracellular nonsynaptic glutamate is primarily released from glial Na⁺ independent cystine-glutamate antiporter (Xc⁻), which exchanges extracellular cystine for intracellular glutamate (Baker, Xi et al. 2002; McBean 2002).

Microdialysis measurements reveal reduced basal extracellular glutamate levels in NAc after withdrawal from chronic cocaine (Hotsenpiller, Giorgetti et al. 2001; Baker, McFarland et al. 2003; Madayag, Lobner et al. 2007; Berglind, Whitfield et al. 2009). This is associated with reduced Xc⁻ system function (Baker, McFarland et al. 2003; Madayag, Lobner et al. 2007) and downregulation in the protein level of its catalytic subunit (Knackstedt, Melendez et al. 2010). In parallel with reduced basal levels of extracellular glutamate, microdialysis studies show that glutamate release from PFC afferents in the NAc is increased during reinstatement of drug seeking (McFarland, Lapish et al. 2003; Madayag, Lobner et al. 2007) (Figure 2 B-D). This latter change likely results in part from the marked down-regulation of glial glutamate transport after self-administered cocaine, and a corresponding escape of synaptically released glutamate from uptake into glia (Knackstedt, Melendez et al. 2010). Also, nonsynaptic extracellular glutamate derived from system Xc⁻ activity normally modulates glutamate release from presynaptic prefrontal projections into NAc by providing tone on presynaptic inhibitory mGlu_{2/3} receptors (Xi, Baker et al. 2002; Losonczy, Somogyi et al. 2003; Moran, Melendez et al. 2003; Grueter and Winder 2005; Moran, McFarland et al. 2005), and hence regulates impulse flow from the PFC to NAc (Figure 2 D). Therefore, by reducing glutamatergic tone on mGlu_{2/3} receptors, withdrawal from chronic cocaine

potentiates basal excitatory transmission at PFC-NAc synapses and increases glutamate release from PFC terminals during relapse to drug seeking (Pierce, Bell et al. 1996; Baker, McFarland et al. 2003; Kourrich, Rothwell et al. 2007; Madayag, Lobner et al. 2007; Conrad, Tseng et al. 2008; Berglind, Whitfield et al. 2009; Moussawi, Pacchioni et al. 2009).

Given the important role played by mGlu_{2/3} receptors in the regulation of synaptic glutamate release by nonsynaptic glutamate derived from system Xc- (figure 2), it follows that stimulation of mGlu_{2/3} receptors in NAc prevents reinstatement to cocaine seeking (Baptista, Martin-Fardon et al. 2004; Adewale, Platt et al. 2006; Peters and Kalivas 2006); likely by interfering with glutamatergic synaptic transmission and interrupting potentiated impulse flow from the PFC to NAc. This mechanism is supported by several studies using N-acetylcysteine (NAC) that acts as an indirect mGlu_{2/3} receptor agonist. NAC is a cystine prodrug currently approved for clinical use as an antioxidant (glutathione precursor) for acetaminophen toxicity and cystic fibrosis treatment. It has been shown to reduce compulsive gambling behavior (Grant, Kim et al. 2007), desire for cocaine use (LaRowe, Myrick et al. 2007), and number of cigarettes smoked (Knackstedt, LaRowe et al. 2009) in humans. In animal models of drug addiction, NAC prevents relapse to drug seeking (Baker, McFarland et al. 2003; Moran, McFarland et al. 2005; Madayag, Lobner et al. 2007; Kau, Madayag et al. 2008; Zhou and Kalivas 2008; Moussawi, Pacchioni et al. 2009). Acute administration of NAC reverses cocaine induced neuroadaptations related to glutamate homeostasis and synaptic transmission in NAc. By providing cystine and driving reduced Xc- transporter activity (Kau, Madayag et al. 2008), NAC normalizes extracellular glutamate levels in NAc after chronic cocaine (Baker, McFarland et al. 2003; Madayag, Lobner et al. 2007), reduces synaptic glutamate release and excitatory drive from the PFC after cue or drug exposure (Baker, McFarland et al. 2003; Madayag, Lobner et al. 2007; Zhou and Kalivas 2008), thereby preventing reinstatement of drug seeking. NAC was also shown to normalize PFC-NAc synaptic transmission by depotentiating these synapses, and restoring impaired plasticity (long term potentiation and long term depression, associated with learning and memory) in NAc after chronic cocaine (Moussawi, Pacchioni et al. 2009).

Akin to NAC, CB1 endocannabinoid receptor antagonist AM251 blocks relapse after cocaine self-administration and prevents increases in glutamate release in the NAc during reinstated cocaine seeking (Xi, Gilbert et al. 2006). AM251 inhibition of relapse was blocked by mGlu_{2/3} receptor antagonists suggesting a similar mechanism to NAC (Xi, Gilbert et al. 2006). Although the link between CB1 receptor and mGlu_{2/3} receptors remains to be clarified, it is interesting to note that NAC restores LTD by indirectly stimulating mGlu₅ receptors, which is known to regulate LTD in the striatum via postsynaptic retrograde release of endocannabinoids (Robbe, Kopf et al. 2002; Sergeeva, Doreulee et al. 2007). Thus, the inhibition of drug seeking by NAC is associated with the simultaneous stimulation of mGlu_{2/3} and CB1 receptors.

7) Conclusions

mGlu_{2/3} receptors have been shown to regulate both reward function and drug seeking, in part through the capacity to control release of dopamine and glutamate respectively in

mesocorticolimbic motivational circuitry. This interpretation is in agreement with the hypothesis that dopamine signaling controls drug reinforcement during early stages of drug addiction, while glutamate neurotransmission controls drug seeking at later stages (Kalivas and Volkow 2005). Given the effectiveness at reducing drug seeking after chronic exposure to different drugs of abuse, mGlu_{2/3} receptor agonists emerge as a promising potential treatment for relapse in drug addiction. The efficacy stems from an ability of mGlu_{2/3} receptor agonists to exert presynaptic inhibitory tone on glutamatergic terminals, which functionally compensates for drug-induced impaired glutamate homeostasis (Kalivas 2009), and normalizes excitatory synaptic transmission (Moussawi, Pacchioni et al. 2009). Furthermore, the modulatory nature of mGlu_{2/3} receptors allows them to selectively target extreme, pathological behaviors (compulsive drug seeking) without or minimally affecting normal responses to natural rewards. Taken together, these data indicate that mGlu_{2/3} receptor agonists may be therapeutically relevant ligands for reducing relapse in drug addiction.

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Figure 1.

The neurocircuitry of relapse. Drug, cue, and stress induced relapse after cocaine self-administration require the projections from prefrontal cortex (PFC) to nucleus accumbens (NAc) to ventral pallidum (VP) (red pathway), commonly referred to as the final common pathway. In addition, cue induced relapse depends on basolateral amygdala (BLA) projections to PFC, and stress induced relapse requires activation of the extended amygdala (Ext Amyg) – ventral tegmental area (VTA) pathway, which in turn feeds into PFC and NAc. PFC is not involved in context induced relapse after abstinence; instead, projections from hippocampus (Hipp) to dorsal striatum (DS) (Fuchs, Evans et al. 2005; Fuchs, Branham et al. 2006) and NAc shell are thought to be involved (Bossert, Gray et al. 2005).

Figure 2.

(A) Glutamate homeostasis in a PFC-NAc excitatory synapse in a yoked saline rat. Extracellular glutamate regulates synaptic release from PFC terminals by stimulating mGlu_{2/3} receptors. (B) After chronic cocaine, basal extracellular glutamate is reduced and PFC-NAc synapses are potentiated pre- and post-synaptically as indicated by arrows (see text for details). (C) Cartoon of PFC-NAc pathway in a rat brain. (D) Stress, cues, or drug primes induce reinstatement of drug seeking by activating the potentiated PFC-NAc pathway. (E) Interfering with impulse flow pre- (N-Acetylcysteine, mGlu_{2/3} receptor agonists) or post-synaptically (blocking ionotropic GluRs or mGlu₅ receptors in NAc) prevents relapse.