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Review

AMPA Receptor Synaptic Plasticity Induced by Psychostimulants: The Past, Present, and Therapeutic Future

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Experience-dependent plasticity at excitatory synapses of the mesocorticolimbic system is a fundamental brain mechanism that enables adaptation to an ever-changing environment. These synaptic responses are critical for the planning and execution of adaptive behaviors that maximize survival. The mesocorticolimbic system mediates procurement of positive reinforcers such as food and sex; however, drugs of abuse resculpt this crucial circuitry to promote compulsive drug-seeking behavior. This review will discuss the long-term changes in glutamatergic neurotransmission that occur within the mesolimbic system following cocaine exposure. In addition, we will examine how these long-lasting neuroadaptations may drive the pathology of psychostimulant addiction. Finally, we review clinical trials that highlight antagonists at excitatory AMPA receptors as promising targets against cocaine abuse.

Psychostimulant Abuse: An Overview

In the past few decades, psychostimulant addiction has become increasingly appreciated as a neuropathological disorder marked by chronic and compulsive relapse episodes during which the drive to seek and use drugs cannot be controlled (O'Brien, 1996). This may be due to genetic and socioeconomic conditions combined with pharmacologically induced effects that, upon continued drug use, favor the execution of rigid, drug-associated behaviors in lieu of more adaptive and flexible responding (Kalivas and Volkow, 2005; Kalivas and O'Brien, 2008; Koob et al., 1998). The persistence of drug-induced alterations in brain function has been hypothesized to exacerbate the recidivistic and compulsive nature of drug addiction (Hyman et al., 2006). Thus, addiction is increasingly regarded as an aberrant form of learning (Hyman and Malenka, 2001; Jones and Bonci, 2005). Efforts to understand the molecular basis of this complex disease must therefore rely upon an integrated understanding of how commonly abused drugs alter the synaptic plasticity, neurophysiology, and behavior of model organisms.

Mesocorticolimbic System: General Concepts

The mesocorticolimbic system comprises several interconnected brain regions, including the ventral tegmental area (VTA) and substantia nigra, dorsal striatum, ventral striatum (nucleus accumbens, NAcb), and the amygdala, as well as the frontal cortical regions that correspond to rat prefrontal cortex or human anterior cingulate (Goldstein and Volkow, 2002; Ongür and Price, 2000). The VTA, NAcb, and frontal cortex comprise an integral part of the motivational circuit (Figure 1) (Mogenson et al., 1993). The major source of dopamine (DA) to forebrain structures, such as the prefrontal cortex and NAcb, arises from cell bodies in the VTA of the midbrain (Fields et al., 2007). The important and complex role of DA in motivated behavior and learning has been previously reviewed (Berke and Hyman, 2000; El-Ghundi et al., 2007; Nicola et al., 2000), and previous work supports the hypothesis that the NAcb, a primary target of the VTA, serves as a limbic-motor interface that processes reward valence and modulates motivational drives in order to execute both novel and more habitual responding (Kelley, 2004; Koob and Le Moal, 2001; Mogenson et al., 1993; Nestler, 2005; Nicola et al., 2000; Pierce and Kumaresan, 2006; Smith, 2004). The NAcb has two main regions, with the NAcb core important for control of motivated behavior by conditioned cues and the NAcb shell most often implicated in processing of primary reward and novelty.

Increased extracellular DA concentrations, such as that elicited by abused drugs, facilitate learning (Jay, 2003; Kelley, 2004), including relationships between the behavioral response to drug-related stimuli and drug-mediated reinforcement (Berke and Hyman, 2000; Nestler, 2001). For example, dorsal striatal DA release from the nigrostriatal pathway is necessary for habit learning (Faure et al., 2005), and repeated amphetamine exposure, which enhances DA levels, augments subsequent habit formation (Nelson and Killcross, 2006). Moreover, in addition to shaping learning about drug reinforcement, DA may also modulate the motivation to seek drugs independent from their perceived hedonic value (Berridge and Robinson, 1998). Intriguingly, upon repeated pairing of a natural reinforcer like sucrose and a cue that predicts that reinforcer, midbrain DA neurons no longer exhibit phasic firing for the reinforcer and only fire for the predictive cue (Schultz, 1998, 2004). Thus, DA neuronal

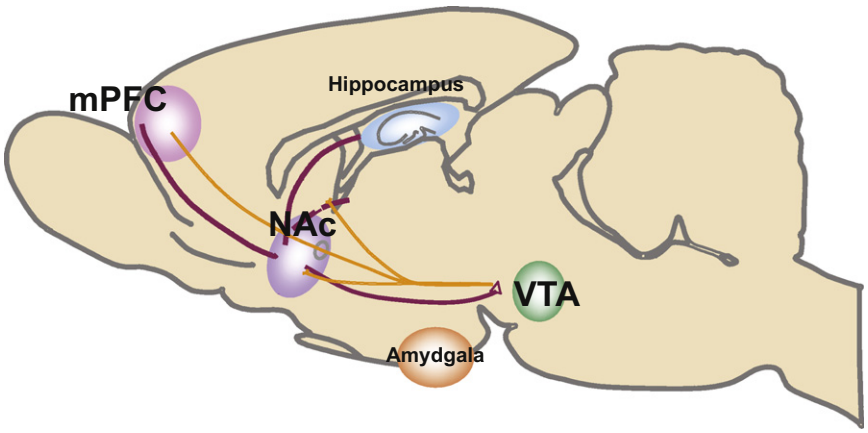

Figure 1. Motivational Circuit
The major reward centers implicated in drug addiction. Dopaminergic projections from the ventral tegmental area (VTA) provide the major source of dopamine to prefrontal cortex (PFC) and nucleus accumbens (NAcb).

activation for a natural reinforcer does not occur if learned cues fulfill predicted valence expectations, which is hypothesized to facilitate adaptive responding (Schultz, 2004). In contrast, DA release following presentation of drug rewards and drug-associated cues persists (Ito et al., 2002; Kalivas and O'Brien, 2008; Volkow et al., 2006).

Increased DA release with repeated drug exposure supports theories suggesting that drugs of abuse modify normally adaptive circuitry to be more responsive to drug stimuli and thus less flexible (Berridge and Robinson, 1998; Everitt and Robbins, 2005; Goldstein and Volkow, 2002; Kalivas, 2008). Drug-seeking behavior following repeated drug use is thought to be driven by a persistent, maladaptive allostatic state (Koob and Le Moal, 1997) and/or by altered attribution of incentive salience (Berridge and Robinson, 1998) rather than by drug-associated positive reinforcement. Additional work is required to determine how these addiction model interpretations map onto humans, and congruence across species remains a largely unaddressed, but increasingly recognized, chasm between clinical and preclinical data sets. The molecular mechanisms central to rodent synaptic plasticity following psychostimulant exposure highlighted in this review may also be predictive of clinically relevant and pharmacologically tractable targets for treatment of human psychostimulant addiction.

While much of the addiction literature has focused on the dopaminergic system, other neurotransmitter systems are relevant to psychostimulant-induced plasticity and pharmacological and pharmacogenetic interventions for addiction has been addressed, including important distinctions between glutamatergic response of the mesocorticolimbic system to repeated cocaine or amphetamine exposure (Cobos et al., 2008; Haile et al., 2009; Kalivas and O'Brien, 2008; Knackstedt et al., 2010; Wolf, 1998; Xi and Gardner, 2008; Yahyavi-Firouz-Abadi and See, 2009). This review will focus on drug-related changes in the glutamatergic system. Thus, there is an anatomical basis for a close association between dopaminergic and glutamatergic molecular plasticity due to the synaptic triad ultrastructure, where DA and glutamate afferents converge on the same neuron, with DA receptors preferentially on the neck of the spine and glutamate receptors on the spine head (Sesack et al., 2003). Thus, ascending dopaminergic input can shape synaptic integration of cortical and allocortical glutamatergic afferents.

Operant Models of Psychostimulant Abuse: The Role of Glutamate

Animal models of drug addiction, specifically operant self-administration (Davis and Smith, 1976; de Wit and Stewart, 1981), facilitate a mechanistic dissection of the neurophysiology and molecular plasticity that could support human drug addiction. In such experiments, laboratory rodents and nonhuman primates are trained to manipulate an operandum, such as a lever or nose-poke, which delivers a reinforcer in a contingent fashion. This method of operant, drug self-administration has been utilized for nearly all drugs abused by humans. Importantly, these models involve voluntary drug intake, in contrast to other commonly used models where animals experience passive drug exposure.

Operant models of self-administration can be extended to study the mechanisms thought to underlie craving and relapse by establishing a prolonged drug-free period after self-administration sessions (forced abstinence) or by initiating extinction training. During extinction, operant responding no longer delivers drug, thus responding significantly declines (Davis and Smith, 1976). After forced abstinence or extinction, an animal can be exposed to stimuli to precipitate drug-seeking behavior ("relapse"). Such stimuli include situations that approximate stressful events, cues predictive of drug reinforcement, or drug re-exposure. A number of studies have suggested that these models of drug relapse are useful for pharmacotherapeutic screening (Epstein et al., 2006).

This review will refer to studies employing either operant or passive drug-exposure models to probe AMPAR-mediated plasticity. Importantly, the extinction-reinstatement model has been used to demonstrate a central role of NAcb AMPAR (Cornish et al., 1999; Cornish and Kalivas, 2000; Di Ciano and Everitt, 2001; McFarland and Kalivas, 2001; McFarland et al., 2004) and glutamate released from prefrontal afferents into the NAcb (McFarland et al., 2003; Park et al., 2002) for cue-primed (Bäckström and Hyytiä, 2007; Di Ciano and Everitt, 2001), stress-primed (McFarland et al., 2004), and cocaine-primed (Bachtell et al., 2008; Cornish and Kalivas, 2000; Ping et al., 2008) reinstatement. In general, striatal AMPAR antagonism prevents relapse while AMPAR activation promotes it (Cornish et al., 1999; Cornish and Kalivas, 2000; Di Ciano and Everitt, 2001; McFarland et al., 2004; Suto et al., 2004; Vanderschuren et al., 2005), but this may be an oversimplified hypothesis (Bachtell et al., 2008).

There is general agreement that the glutamatergic projection from the prefrontal cortex to the NAcb core is critical for the reinstatement of cocaine-seeking behavior (Bachtell et al., 2008; Bäckström and Hyytiä, 2007; Cornish et al., 1999; Cornish

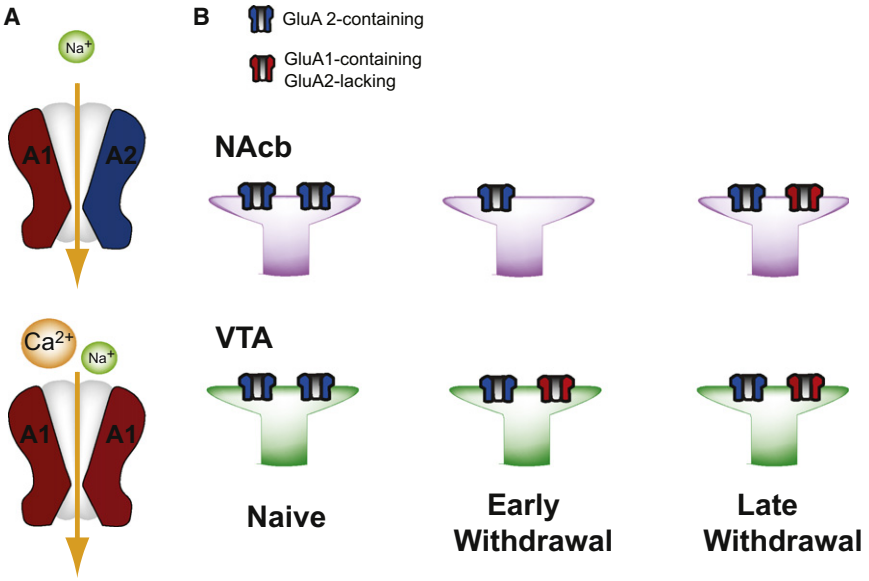

Figure 2. AMPA Receptor Plasticity
(A) Tetrameric AMPA receptors in control (top) and potentiated (bottom) state. In control conditions, AMPA receptors typically contain the GluA2 subunit. Following cocaine exposure (either non-contingently or through self-administration), there is an increase in GluA2-lacking AMPA receptors. GluA2-lacking AMPARs have greater channel conductance and are permeable to Ca^{2+}.
(B) Changes in AMPAR subunit composition during naive, early withdrawal, and late withdrawal stages of cocaine addiction in the NAcb (top) and VTA (bottom). AMPAR subunit composition is altered at each of these three stages of cocaine addiction.

and Kalivas, 2000; Di Ciano and Everitt, 2001; McFarland et al., 2003, 2004; Park et al., 2002; Ping et al., 2008). Importantly, upon repeated performance, drug-seeking behavior becomes less adaptive and less receptive to shaping via anterior cingulate, prefrontal, and orbital frontal executive oversight (Everitt and Robbins, 2005; Goldstein and Volkow, 2002; Kalivas, 2008; Kalivas and Volkow, 2005), with greater control exerted by sensory-motor cortical input into the dorsal striatum (Everitt and Robbins, 2005). Importantly, recent evidence also suggests that the ventral and dorsal striatum interact to control habitual behavior (Belin and Everitt, 2008). Together, these data suggest that repeated psychostimulant use reduces cortical interaction with habit circuitry. However, during drug abstinence, relapse can be precipitated by increased cortical activity that may feed forward into what now may be habitual, drug-directed responses.

It is important to recognize both the strengths and possible limitations of the animal models used to investigate the neural mechanisms of drug relapse. Recent work has addressed the brain circuits important for relapse in rodents after forced abstinence without extinction training. These studies have shown a critical role for the dorsal striatum and midbrain, but not a number of other mesocorticolimbic structures that mediate reinstatement after extinction (Fuchs et al., 2006; See et al., 2007). Extinction experiments in rodents appear to more closely parallel imaging data generated from human psychostimulant addicts (Fuchs et al., 2006; Kalivas, 2008; Kalivas and O'Brien, 2008; Shalev et al., 2002), and extinction efforts have yielded some clinical success (O'Brien et al., 1992). Thus, while these data may be particularly relevant to human addiction, additional temporary inactivation experiments with the abstinence model and more complex choice and devaluation paradigms are needed to provide more thorough insight into human addiction.

Psychostimulant-Induced Synaptic Plasticity

Rapid, excitatory neuronal transmission is primarily mediated through the activation of ionotropic glutamate receptors. Ionotropic glutamate receptors are present in two distinct classes: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and N-methyl-D-aspartate receptors (NMDARs). AMPARs are typically composed of four subunit proteins (GluA1-A4), which can form hetero or homomeric complexes. Under basal conditions, the tetrameric AMPAR is often composed of GluA2 subunits in complex with either GluA1 or GluA3 (Dingledine et al., 1999) (Figure 2A).

Increased AMPAR function is observed after exposure to psychostimulants, which can significantly modulate reward-directed behavior. Synapses can be strengthened or weakened in response to changing neuronal activity, a mechanism that is thought to underlie learning and memory. Following induction of long-term potentiation (LTP), synaptic strengthening can be achieved through active insertion of GluA2-lacking AMPARs (i.e., GluA1/A1 or GluA1A/3 receptors). Compared with GluA2-containing AMPARs, GluA2-lacking AMPARs have greater channel conductance, are calcium permeable, and can therefore trigger calcium-dependent signaling cascades (Figure 2A) (Kauer and Malenka, 2007). Conversely, long-term depression (LTD) is associated with removal of AMPARs from synapses (Malinow and Malenka, 2002); thus, AMPAR trafficking is a powerful and rapid mechanism by which synapses can be strengthened and weakened to affect behavior. Furthermore, changes in phosphorylation state or splice variants can also regulate AMPAR-mediated synaptic transmission (Braithwaite et al., 2000; Kessels and Malinow, 2009; Wang et al., 2005). In general, GluA1 phosphorylation increases AMPAR currents (Derkach et al., 1999; Roche et al., 1996) and can also drive insertion of AMPARs into synapses (Esteban et al., 2003), which can strengthen synapses and lead to LTP.

Cocaine-Induced Synaptic Plasticity: VTA

Phasic VTA DA neuron activity is induced by reward-predictive cues (Schultz, 1998), implicating a critical role for DA neurons in responding to positive reinforcement. This transition from a tonic spike firing mode to phasic firing can be modulated by glutamatergic afferents onto DA neurons (Mathon et al., 2003; White, 1996). Thus, alterations in glutamatergic input onto VTA DA neurons could significantly alter DA release in terminal regions. Glutamatergic synapses onto VTA DA neurons and

NAcb medium spiny neurons (MSNs) are capable of expressing LTP and LTD of evoked AMPAR-mediated synaptic responses (Bellone and Lüscher, 2005; Bonci and Malenka, 1999; Robbe et al., 2002). Interestingly, following reward-related learning, an NMDA-dependent potentiation of AMPAR-mediated synaptic response of VTA DA neurons is observed (Stuber et al., 2008). Since drug exposure can also enhance AMPAR function in the VTA, these data collectively support the hypothesis that drugs of abuse can co-opt brain circuitry that processes motivationally relevant non-drug stimuli.

Potentiation of AMPAR-mediated responses in VTA DA neurons is observed 24 hr following single or multiple noncontingent cocaine injection (Argilli et al., 2008; Borgland et al., 2004; Ungless et al., 2001). Cocaine-induced AMPAR potentiation is mediated through enhanced trafficking of GluA2-lacking AMPA receptors into the synapse (Figure 2B; Argilli et al., 2008; Bellone and Lüscher, 2006). In addition, this increase in synaptic AMPARs is indicative of synapses in a potentiated state, which can prevent further synaptic plasticity (Argilli et al., 2008). Importantly, activation of mGlu1 reverses cocaine-induced potentiation through the exchange of GluA2-lacking AMPARs with GluA2-containing AMPARs (Bellone and Lüscher, 2006; Mameli et al., 2007), restoring these synapses back to their pre-drug states.

Potentiation of AMPAR function is not limited to cocaine, as noncontingent injections of nicotine, alcohol, amphetamine, or morphine can also elicit a LTP-like potentiation of glutamate transmission onto VTA DA neurons (Saal et al., 2003). Thus, glutamatergic synapses onto VTA DA neurons are equally enhanced following reward-related learning and after exposure to drugs of abuse; however, the potentiation of glutamatergic input onto VTA DA neurons is transient. Following non-drug reward-related learning, synaptic potentiation persists for 2 to 7 days depending on the behavioral task (Chen et al., 2008; Stuber et al., 2008), but is absent by 14 days after the last reward-learning training session (Chen et al., 2008). Similarly, a short-lasting potentiation is also observed following a single intraperitoneal (i.p.) cocaine injection, with enhanced AMPAR function evident after 1 and 5 but not 10 days of abstinence (Ungless et al., 2001). Because relapse to cocaine-seeking behavior can occur even after a prolonged period of abstinence, one wonders whether repeated cocaine exposures would induce a longer-lasting potentiation of VTA DA neurons. Surprisingly, even when rats were administered noncontingent cocaine injections across for 7 consecutive days (Borgland et al., 2004), the duration of LTP onto VTA DA neurons was not increased and returned to baseline levels after 10 days of abstinence. Thus, despite repeated cocaine exposure, the short-lived potentiation of glutamatergic synapses suggests that cocaine-induced synaptic changes in VTA DA neurons represent a transient neuroadaptation to cocaine exposure.

In sharp contrast to the effect of noncontingent cocaine injections, voluntary cocaine self-administration induced LTP at VTA DA neurons that persisted for up to 3 months of abstinence (Chen et al., 2008). This did not reflect the pharmacological effects of cocaine, as repeated administration of noncontingent i.v. cocaine in a similar pattern and concentration resulted in only a short-lasting potentiation of AMPAR function. These results suggest that the voluntary intake of cocaine plays a critical role in the long-lasting potentiation of AMPAR function on VTA DA neurons that extends beyond the primary mechanism of drug action itself. We speculate that the requirement for voluntary intake may reflect the contribution of an active learning mechanism, so that persistent AMPAR potentiation only develops when the animal undergoes learning in relation to the voluntary intake of cocaine. Furthermore, LTP at VTA DA neurons induced by voluntary cocaine self-administration remained potentiated even after drug-seeking behavior was extinguished, and AMPAR function was not further enhanced following cue-induced reinstatement (Chen et al., 2008). Together these data suggest that glutamate function at VTA DA neurons is maximally potentiated following cocaine self-administration; more importantly, this potentiation is unchanged even after cocaine-seeking behavior is extinguished. The intractability of cocaine-induced potentiation at DA neurons is in sharp contrast to plasticity induced by natural-reward learning. For example, extinction of behaviors associated with natural-reward learning also reverses the synaptic potentiation induced during the initial acquisition of these tasks (Pan et al., 2008). This suggests that glutamate synapses onto VTA DA neurons are capable of expressing bidirectional plasticity to support both learning and unlearning. Thus, the persistent potentiation at VTA DA neuron synapses following cocaine self-administration may be instrumental in the maintenance of a drug "memory" despite years of abstinence that may facilitate the reinstatement of drug-seeking behaviors (Nestler, 2001).

In summary, the pharmacological effect of cocaine and other drugs of abuse induce a transient potentiation of glutamatergic projections onto VTA DA neurons. Importantly, synaptic neuroadaptations induced through voluntary cocaine self-administration sessions are persistent, and remain potentiated despite extinction of cocaine-seeking behavior. Several important questions remain unanswered. Numerous brain regions are activated by drugs of abuse (Pierce and Kumaresan, 2006), many of which provide extensive excitatory projections onto VTA DA neurons (Colussi-Mas et al., 2007; Fields et al., 2007; Geisler et al., 2008). Traditional ex vivo electrophysiology techniques lack the precision to isolate region-specific afferents synapsing onto VTA DA neurons. Fortunately, with the development of optogenic approaches (Zhang et al., 2007), it is now possible to identify region-specific glutamatergic projections that may be differentially modulated by cocaine and other drugs of abuse. In addition, in vivo electrophysiological techniques (Lee et al., 2006) offer another promising tool in which drug-induced alterations in synaptic function can be examined in the intact animal. This technique will be especially useful to study drug-mediated changes in synaptic function between interconnected brain regions, which is not possible using classic slice electrophysiology. Development and implementation of these new technologies by addiction researchers will greatly aid our understanding of the neurophysiological consequences of drug abuse.

Cocaine-Induced Synaptic Plasticity: NAcb

NAcb AMPAR activation is implicated in many cocaine-seeking behaviors (Conrad et al., 2008; Cornish and Kalivas, 2000; Di Ciano and Everitt, 2001; Ping et al., 2008; Suto et al., 2004). In addition, a number of studies have suggested that NAcb

AMPAR function is persistently elevated during abstinence from cocaine self-administration (Conrad et al., 2008; Famous et al., 2008) and during abstinence following repeated passive exposure to cocaine (Kourrich et al., 2007; Thomas et al., 2001). Thus, there is considerable interest in understanding the molecular basis for changes in NAcb AMPAR function, since this could facilitate the development of novel pharmacotherapies for psychostimulant addiction.

Passive cocaine exposure can alter NAcb AMPAR function, but on a different time course than in the VTA. While potentiation of AMPAR-mediated activity in VTA DA neurons was observed as early as 3 hr after a single cocaine exposure (Argilli et al., 2008); modulation of NAcb AMPAR function was unaffected by a single cocaine injection. Instead, changes in Nacb glutamate function occur only following repeated cocaine injections (Kourrich et al., 2007; Thomas et al., 2001). In sharp contrast to the VTA, alterations in glutamatergic transmission in the NAcb exhibited a biphasic effect. Ex vivo electrophysiological analysis reveals depressed AMPAR function in the shell but not the core of the NAcb in early withdrawal from repeated non-contingent cocaine injections (24 hr after last exposure) (Kourrich et al., 2007), consistent with a decreased AMPAR-mediated response of NAcb neurons observed in vivo (White et al., 1995) and in biochemical experiments (Boudreau et al., 2007). However, after a longer abstinence period (>10 days), AMPAR function is enhanced (Boudreau et al., 2007; Kourrich et al., 2007). Interestingly, re-exposure to cocaine during abstinence reverses the potentiated AMPAR function to a decreased AMPAR function (Kourrich et al., 2007). This rapid, cocaine-induced reversal in AMPAR function is mirrored by a decrease in AMPAR surface expression (Boudreau et al., 2007) and decreased efficacy of intra-NAcb AMPAR to modulate locomotion (Bachtell et al., 2008) following cocaine exposure. In addition, repeated amphetamine administration did not alter GluA1 or GluR2 surface expression in the NAcb (Nelson and Killcross, 2006), but did upregulate the flip isoform of GluA2 (Yu et al., 2005), which can dramatically alter fast channel kinetics (Mosbacher et al., 1994).

Unlike the effects of noncontingent infusions of cocaine, the effects of voluntary cocaine self-administration on glutamatergic function in the NAcb are generally similar to that observed in the VTA. One difference from the VTA is that self-administration of cocaine also elicits a biphasic response in AMPAR function during abstinence. In early abstinence, a depression of AMPAR function was observed in NAcb shell (Schramm-Sapyta et al., 2006), but after a longer period of abstinence, an increase in AMPAR-mediated response was observed in both the shell (Anderson et al., 2008) and the core (Conrad et al., 2008). In these studies, enhanced AMPA function was attributed to a shift in AMPAR subunit composition, leading to greater channel conductance. Anderson et al. (2008) observed an increase in cell-surface expression of GluA1-containing AMPARs, while Conrad et al. (2008) saw an increase in GluA2-lacking AMPARs (Conrad et al., 2008). The increase in GluA2-lacking AMPAR appears to play an important role in facilitating the incubation of cocaine craving (Figure 2B; Conrad et al., 2008), and promoting GluA2 surface expression in either the NAcb core or shell attenuated the capacity of cocaine to reinstate extinguished drug-seeking behavior (Famous et al., 2008). Moreover, GluA1 and GluA2 trafficking increased during the extinction of cocaine-seeking behavior (Ghasemzadeh et al., 2009), and the extent of extinction was correlated with the upregulation of GluA1 (Sutton et al., 2003).

Cocaine self-administration can also alter regulation of glutamate release in the NAcb. Decreased basal extracellular glutamate concentration is observed in the NAcb in animals abstinent from cocaine self-administration (Baker et al., 2003; Kalivas and Hu, 2006; Pierce et al., 1996) due to impaired function of the glial cysteine-glutamate exchanger, which transports glial glutamate into the extracellular space. The amelioration of this deficit may, in part, explain the efficacy of glutamate transport modulators to decrease cocaine seeking (Knackstedt et al., 2010; Baker et al., 2003; Martínez-Raga et al., 2008). Decreased basal glutamate levels impair the ability for synapses to undergo LTP and/or LTD in glutamatergic transmission, and indeed, NAcb core neurons failed to express LTD or LTP in animals withdrawn or extinguished from voluntary cocaine self-administration, respectively (Martin et al., 2006; Moussawi et al., 2009).

Thus, protracted abstinence from cocaine self-administration can induce at least two separate alterations in glutamatergic function in the NAcb. As the period of abstinence proceeds, AMPAR-mediated responses are potentiated due to an increase in synaptic GluA2-lacking AMPARs. These GluA2-lacking AMPARs in the NAcb may be critical for the enduring drive to seek cocaine. The second effect of cocaine is its ability to alter the induction of synaptic plasticity. The persistent neuroadaptations that occur during abstinence from cocaine self-administration (Martin et al., 2006; Moussawi et al., 2009), especially the inability to produce further plastic changes, are an intriguing parallel to the inflexible responding of individuals repeatedly exposed to psychostimulants. Thus, AMPAR-selective pharmacotherapeutics could reduce the recidivistic and compulsive nature of cocaine and amphetamine addiction.

A recent study shows that cocaine-induced potentiation of glutamatergic transmission in the NAcb requires persistent VTA potentiation (Mameli et al., 2009). Reversal of cocaine-induced potentiation in the VTA through activation of mGlu1 prevents enhanced glutamate function in the NAcb and attenuates reinstatement of cocaine-seeking behaviors. While the mechanism linking the VTA and NAcb is unclear, this study establishes a clear serial effect of cocaine on glutamate function in the VTA and NAcb. Thus, voluntary cocaine self-administration induces a long-lasting potentiation of glutamate function in the VTA and the NAcb and this persistent synaptic potentiation may be critical in the continued expression of drug craving. Moreover, inasmuch as dopamine signaling originating within the VTA plays an important role in signaling saliency about the environment (Schultz, 1998), the long-lasting potentiation onto VTA DA neurons following cocaine self-administration could act to selectively accentuate drug-related cues while de-emphasizing all other non-drug stimuli or cues. This is hypothesized to bias the animal's behavior toward drug-related stimuli while precluding expression of other behaviors. In essence, behavior flexibility is lost as the animal becomes increasingly focused on performing drug-associated behaviors (Kalivas and O'Brien, 2008). In the NAcb, similar drug-induced changes in these neurons can facilitate a preferential excitation of neurons that

respond to drug-associated cues that could also promote execution of drug-associated behaviors.

Second Messenger Pathways that Can Modulate AMPAR Function

A number of studies has shown that signaling through the cAMP response element binding protein (CREB)-mediated pathway is utilized by various forms of reinforcing stimuli, including drugs of abuse (Carlezon et al., 1998; Nestler, 2001) and non-drug stimuli (Jin et al., 2005). Both cocaine and amphetamine can activate the CREB transcriptional machinery via increased CREB phosphorylation (Carlezon et al., 2005), leading to altered expression patterns of several transcription factors downstream of CREB, such as c-*fos*, *zif268*, and *fosB* (Harlan and Garcia, 1998; McGinty et al., 2008), and altered mRNA splicing of Fos family members that enable accumulation of ΔFosB (McClung et al., 2004). Here, we will review CREB-related signaling mechanisms that can interface with AMPA receptor plasticity and perhaps modulate responding for drugs of abuse.

Increased CREB phosphorylation appears to regulate cocaine reinforcement, as NAcb CREB overexpression reduced the reinforcing properties of cocaine while also increasing aversion to low cocaine doses (Carlezon et al., 1998). Conversely, NAcb CREB dominant-negative overexpression *increased* apparent cocaine-mediated reinforcement (Carlezon et al., 1998). However, CREB knockdown *reduced* the reinforcing efficacy of cocaine when measured via contingent cocaine delivery after instrumental responding (Choi et al., 2006) rather than if measured via Pavlovian conditioning following noncontingent cocaine exposure (Carlezon et al., 1998). While these data are themselves very intriguing, the diverse signaling pathways that impinge onto CREB (Shaywitz and Greenberg, 1999) are perhaps of even greater interest because phosphorylated CREB can promote the expression of transcription factors and other gene products that have also been implicated in addiction, e.g., preprodynorphin, NAC-1, and the various Homer isoforms (Hurd and Herkenham, 1993; Nestler, 2001). Thus, CREB may represent a molecular integrator of second messenger signaling systems that are common substrates of abused drugs.

Another downstream CREB target, ΔFosB, is also quite interesting, in part due to a unique, accumulating expression pattern in DA terminal fields of the mesocorticolimbic circuit following repeated administration of commonly abused drugs, including cocaine and amphetamine, as well as following repeated, non-drug reinforcement (McClung et al., 2004; McClung and Nestler, 2003). ΔFosB is a transcription factor that acts to upregulate GluA2 in the NAcb (Kelz et al., 1999) and cyclin-dependent kinase 5 (Cdk5) in the striatal complex (Bibb et al., 2001) and hippocampus (Chen et al., 2000). Overexpression of GluA2 in the NAcb shell decreases intracranial self-stimulation thresholds (Todtenkopf et al., 2006), suggesting that ΔFosB accumulation might augment drug-mediated reinforcement. It has been shown that ΔFosB overexpression increases the incentive motivation to seek both drug and non-drug reinforcement, while ΔFosB dominant-negative overexpression reduces motivation to seek these reinforcers (Colby et al., 2003; Nestler, 2005).

Analysis of postmortem midbrain (Tang et al., 2003) and NAcb (Hemby et al., 2005) tissue collected from human cocaine-overdose victims has revealed significant upregulation of CREB and GluA2. While ΔFosB accumulation may reflect an important mechanism contributing to the transition from drug use to drug abuse (Nestler, 2001), the extent of postmortem ΔFosB accumulation in human cocaine addicts has not been determined. Additionally, given that the majority of studies observing increased AMPAR function after drug exposure have found a decrease rather than an increase in GluA2 function, the functional relevance of these CREB and Fos family-mediated GluA2 AMPA subunit changes remains to be fully elucidated. Finally, though intriguing parallels can be drawn between identified roles of CREB, ΔFosB, and AMPA receptor subunits in addiction-associated behaviors, it has not yet been determined if CREB, ΔFosB, and AMPARs lie within the same molecular network.

Psychostimulants can also interact with AMPAR plasticity in more complex ways. The capacity of ΔFosB to modulate AMPA subunit expression is limited by a negative feedback loop involving inhibition of PKA by Cdk5 and phospho-Thr75 DARPP-32 via ΔFosB. The DARPP-32 phospho-Tyr75 form is the predominant form of DARPP-32 following repeated cocaine exposure (Scheggi et al., 2007). AMPAR activation leads to dephosphorylation of phospho-Thr75 of DARPP-32 thereby disinhibiting PKA (Nishi et al., 2002). Thus, the capacity of ΔFosB to limit PKA signaling can be counteracted by increased AMPAR recruitment (Juo et al., 2007; Kelz et al., 1999; Olson et al., 2005) In accord with possible AMPAR-mediated PKA disinhibition, Cdk5 inhibitors augment behavioral sensitization (Bibb et al., 2001). Thus, ΔFosB upregulation appears in part homeostatic (Winstanley et al., 2009), perhaps through a Cdk5-mediated inhibition of PKA, since the ΔFosB downstream target Cdk5 can interface with AMPAR and DARPP-32 to modulate psychostimulant reinforcement, motivation, and sensitization.

Although CREB is predominantly thought of in relation to PKA-mediated signaling, extracellular signal-regulated kinase (ERK) preferentially activates CREB following repeated exposure to cocaine (Lu et al., 2005). ERK can act directly on AMPARs to increase AMPAR surface insertion, which is required for expression of NMDA-dependent LTP (Zhu et al., 2002). Furthermore, cocaine-induced striatal ERK activation is PKA- and DARPP-32-dependent, and ERK inhibition attenuated cocaine-induced conditioned place preference and behavioral sensitization (Valjent et al., 2005). Moreover, ERK in the central amygdala was shown to be both necessary and sufficient for the incubation of cocaine craving (Lu et al., 2005). While ERK acting directly on AMPA or through ΔFosB could facilitate the AMPAR role in psychostimulant reinforcement, further work is needed to define the relationship between ERK and AMPARs, and this remains an interesting area of investigation.

Synaptic strengthening can be accompanied by neurite outgrowth, spine splitting, and synaptogenesis. Repeated psychostimulant exposure leads to synaptogenesis in several mesocorticolimbic areas (Li et al., 2004; Pulipparacharuvil et al., 2008; Robinson and Kolb, 1999; Shen et al., 2009) and several molecules have been associated with this process, including the neuronal-activity-regulated pentraxin (Narp). Narp is secreted into the extracellular matrix, concentrates at excitatory complexes, and facilitates AMPAR clustering by forming extracellular, multimeric complexes (O'Brien et al., 1999). Following

a single methamphetamine injection, Narp mRNA is upregulated in the dorsal striatum, hippocampus, and some regions of the neocortex (Ujike et al., 2002), although a parallel increase in protein expression was not detectable after either acute or repeated psychostimulant exposure (Lu et al., 2002). However, Narp protein expression in the prefrontal cortex was correlated with the magnitude of spontaneous motoric response to a novel environment (Lu et al., 2002), and heightened reactivity to novel situations has been used as a measure of impulsivity and a putative drug abuse liability indicator (Lu et al., 2002; Stoffel and Cunningham, 2008). Narp knockout decreased cocaine-mediated reinforcement and time spent in the center of an open field (Pacchioni et al., 2009). Thus, psychostimulant-induced changes in Narp can augment AMPAR function and individuals with higher Narp may also exhibit higher drug abuse liability.

There are several molecular changes that emerge during abstinence from psychostimulant exposure that are not apparent in drug-naive animals or after recent drug exposure (Kalivas and O'Brien, 2008; Lu et al., 2004b). Some of these enduring molecular events, such as the increased AMPAR function, are hypothesized to drive the motivation to seek drug during relapse (Grimm et al., 2001; Kalivas, 2009; Nestler, 2001). In particular, mRNA for the brain-derived neurotrophic factor (BDNF) increases across abstinence in brain structures such as the NAcb and VTA (Filip et al., 2006; Grimm et al., 2003) and both BDNF and the related glial cell line-derived neurotrophic factor (GDNF) could support the increased motivation for drugs that develops across abstinence (Grimm et al., 2003; Lu et al., 2009). For example, GDNF (Li and Keifer, 2009) and BDNF (Berglind et al., 2007; Graham et al., 2007; Horger et al., 1999; Lu et al., 2004a) can reversibly modulate behavior and synaptic plasticity (Pu et al., 2006) associated with relapse to cocaine-seeking behavior. However, the effects of growth factors may differ among brain regions, since BDNF in the prefrontal cortex can decrease drug seeking (McGinty et al., 2009). Although the precise mechanisms through which BDNF and GDNF modulate drug seeking remain unclear, altered AMPAR signaling is an interesting possibility. For example, LTP induction is facilitated by an AMPAR-mediated increase in BDNF release and signaling at excitatory synapses (Jourdi et al., 2009; Lauterborn et al., 2009), and, conversely, BDNF can enhance LTP induction (Barco et al., 2005; Pu et al., 2006). BDNF signaling through the mammalian target of rapamycin (mTor) can increase dendritic mRNA translation, which, along with LTP, facilitates memory formation (Jourdi et al., 2009; Lauterborn et al., 2009; Slipczuk et al., 2009). Moreover, BDNF signals through ERK to increase AMPAR GluA1 subunit synaptic delivery (Li and Keifer, 2009). Thus, growth factors such as BDNF and GDNF have multiple pathways through which they can enhance AMPAR function, facilitate memory formation, and in this way stabilize memories that drive drug seeking even after prolonged abstinence from drugs.

AMPAR Pharmacotherapies: Past, Present, and Future

The translation of the current knowledge about the role of AMPARs in modulating synaptic plasticity to abate substance abuse would ideally produce a drug that limits AMPAR activation and reverses the long-term plasticity associated with continued cocaine seeking. This strategy is supported by the large body of rodent literature showing that AMPA antagonists inhibit the reinstatement of drug-, cue-, or stress-primed drug-seeking behavior (Bäckström and Hyytiä, 2007; Cornish et al., 1999; Cornish and Kalivas, 2000; Di Ciano and Everitt, 2001; McFarland and Kalivas, 2001; McFarland et al., 2003, 2004; Park et al., 2002; Ping et al., 2008; but see Bachtell et al., 2008). As a consequence, the motivation to self-administer drug as well as the propensity to relapse would be reduced. However, given the complexity of the mammalian nervous system, this may require reagents with broad-spectrum activity and indeed, several nonspecific glutamatergic agents have shown much promise (Table 1).

Selective AMPAR Antagonists

In general, AMPAR antagonists compete with glutamate to prevent AMPAR activation while noncompetitive allosteric ligands modulate AMPAR activity at a site distinct from the glutamate binding region. Several, structurally distinct classes of AMPA antagonists have been described including the quinoxalinediones, isatin oximes, decahydroisoquinolines and isoxazole derivatives (Chimirri et al., 1998; Nikam et al., 1999; Nikam and Kornberg, 2001; Sólyom and Tarnawa, 2002). Historically, these compounds were developed for indications other than substance abuse, but the clinical availability of these compounds provides an exciting opportunity for the treatment of drug addiction.

The first noncompetitive AMPA antagonist GYKI 52466 (Donevan and Rogawski, 1993) was found among a 2,3-benzodiazepine library, a group of compounds known for their anxiolytic and antiepileptic properties (Sólyom and Tarnawa, 2002). GYKI 52466 and structurally-related members that are AMPA/kainate receptor antagonists are currently undergoing clinical trials. For example, Talampanel (GYKI 53773, alternatively named LY300164), a synthetic derivative of dioxolobenzodiazepine, is currently being evaluated for efficacy at reducing symptoms of a variety of neurological conditions such as Parkinson's (clinical trial identifiers: NCT00108667, AMPA Receptor Antagonist Treatment of Parkinson's Disease; NCT00036296, Effects of Talampanel on Patients With Advanced Parkinson's Disease Who Have Been on Sinemet for More Than 5 Years and Have Dyskinesia; NCT00696332, A Multinational, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy, Tolerability and Safety of Talampanel in Subjects With Amyotrophic Lateral Sclerosis (ALS); NCT00034814, Efficacy and Safety of Talampanel as Adjunctive Therapy in Patients With Partial Seizures: A Phase II Clinical Trial). Additionally, perampanel (E2007), a 1,5-substituted bipyridinylone, is a first-in-class, orally administered, and highly selective noncompetitive AMPAR antagonist currently undergoing trials for several neurological indications (clinical trial Identifiers: NCT00505622, A Multi-Centre, Open Label Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of Perampanel (E2007) as an Adjunctive Therapy in Levodopa Treated Parkinson's Disease Subjects With Motor Fluctuations; NCT00592774, A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Tolerability Titration Study To Evaluate The Efficacy And Safety Of Perampanel (E2007) In Patients With Post-Herpetic Neuralgia

Table 1. Past and Ongoing Clinical Trials with Selective AMPAR Antagonists

Status	Study	Condition	Intervention
Talampanel			
Terminated	absorption, metabolism and excretion of talampanel	healthy	drug: talampanel (non-radiolabeled), [14C] talampanel
Not yet recruiting	effects of talampanel on the heart rhythm (phase 1)	healthy	drug: talampanel; drug: moxifloxacin; drug: placebo
Active, not recruiting	talampanel for amyotrophic lateral sclerosis (ALS)	ALS	drug: talampanel; drug: placebo
Completed	multicenter trial for adults with partial seizures	epilepsy	drug: talampanel; drug: placebo
Active, not recruiting	talampanel in treating patients with recurrent high-grade glioma	brain and central nervous system tumors	drug: talampanel
Active, not recruiting	safety and efficacy of talampanel in glioblastoma multiforme	glioblastoma multiforme	drug: Talampanel
Completed	effects of talampanel on patients with advanced parkinson's disease	dyskinesias; Parkinson's disease; movement disorders	drug: talampanel
Terminated	talampanel in patients with recurrent high grade gliomas (phase 2)	glioblastoma multiforme; anaplastic astrocytoma; anaplastic oligodendroglioma; anaplastic mixed oligoastrocytoma	drug: talampanel
Completed	talampanel to treat Parkinson's disease	Parkinson's disease	drug: IV levodopa; drug: talampanel
Completed	effect of talampanel (an AMPA receptor blocker) on brain activity	healthy	drug: talampanel
Tezampanel			
Completed	safety, tolerance and efficacy of tezampanel in patients with acute migraine	migraine	drug: tezampanel
Perampanel			
Recruiting	efficacy and safety of E2007 (perampanel) given as adjunctive therapy in subjects with refractory partial seizures	refractory partial seizures	drug: E2007 (perampanel); drug: placebo
Recruiting	efficacy and Safety of E2007 (Perampanel) given as adjunctive therapy in subjects with refractory partial seizures	refractory partial seizures	drug: E2007 (perampanel); drug: placebo
Completed	dose-tolerability titration study to evaluate the efficacy and safety of perampanel (E2007) in patients with post-herpetic neuralgia (PHN)	neuralgia	drug: E2007 (perampanel); drug: placebo
Recruiting	efficacy and safety of E2007 (perampanel) given as adjunctive therapy in subjects with refractory partial seizures	refractory partial seizures	drug: perampanel; drug: placebo
Recruiting	efficacy and safety of E2007 (perampanel) given as adjunctive therapy in subjects with refractory partial seizures	epilepsy	drug: perampanel; drug: placebo
Terminated	long-term safety, tolerability, and efficacy of perampanel (E2007) as an adjunctive therapy in levodopa treated parkinson's disease subjects with motor fluctuations	Parkinson's disease	drug: perampanel
Active, not recruiting	E2007 (perampanel) in patients with painful diabetic neuropathy (PDN) or post-herpetic neuralgia (PHN)	neuralgia	drug: E2007
Completed	efficacy and safety of E2007 in patients with painful diabetic neuropathy	diabetic neuropathy	drug: placebo; drug: E2007 (2 mg); drug: E2007 (4 mg); drug: E2007 (6 mg); drug: E2007 (8 mg)
Active, not recruiting	four-year open-label extension phase of the parallel-group study of E2007 in patients with refractory partial seizures	refractory partial seizures	drug: E2007 (perampanel)

Table 1. *Continued*

Talampanel			
Terminated	assessment of perampanel (E2007) on synaptic dopamine in mild-moderate PD patients: a pilot study with [^123I]-IBZM SPECT	Parkinson's disease	drug: E2007
Recruiting	a long-term extension study of E2007 in patients with refractory partial seizures uncontrolled with other anti-epileptic drugs (AEDs)	refractory partial seizures	drug: perampanel

(PHN); NCT00700310, A Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group Study to Evaluate the Efficacy and Safety of E2007 (Perampanel) Given as Adjunctive Therapy in Subjects With Refractory Partial Seizures; NCT00699582, A Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group Study to Evaluate the Efficacy and Safety of E2007 (Perampanel) Given as Adjunctive Therapy in Subjects With Refractory Partial Seizures; NCT00699972, A Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group Study to Evaluate the Efficacy and Safety of E2007 (Perampanel) Given as Adjunctive Therapy in Subjects With Refractory Partial Seizures; NCT00592904, A Multi-Center, Open-Label Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of E2007 (Perampanel) in Patients With Painful Diabetic Neuropathy (PDN) or Post-Herpetic Neuralgia (PHN)).

Perhaps the most promising compound from the decahydroisoquinoline family of AMPA/kainate receptor antagonists is tezampanel (NGX424), which has recently been used in a double-blind, placebo controlled, parallel group, multicenter phase 1 study (clinical trial identifier: NCT00567086, A Double-Blind, Placebo-Controlled, Parallel Group Multicenter Study to Assess the Safety, Tolerance and Efficacy of a Single Subcutaneous Dose of TEZAMPANEL in Patients With Acute Migraine). Importantly, the ester prodrug of tezampanel (NGX426) is bioavailable after oral administration and has also successfully completed phase 1 clinical trials (clinical trial identifier: NCT00832546, A Double-Blind, Randomized, Placebo Controlled, Cross-Over, Safety Tolerance and Experimental Hyperalgesia Study of Oral NGX426 in Healthy Male Volunteers). The AMPAR antagonists evaluated in clinical trials appear to be generally well tolerated, with only a few subjects reporting minor side effects such as dry mouth, dizziness and sedation (Gottwald and Aminoff, 2008; Pascuzzi et al., 2010). These early human trials are particularly interesting given that tezampanel reduced rat cocaine self-administration (Di Ciano and Everitt, 2001).

Clinical Trials with Nonspecific AMPAR Antagonists

Encouraging results have also been generated with agents that exhibit less specificity of action. Topiramate is commonly used as monotherapy in patients with partial onset or primary generalized tonic-clonic seizures and is FDA approved for migraine prevention. In addition to AMPAR antagonism, topiramate also enhances GABA levels in the CNS (Kuzniecky et al., 1998; Petroff et al., 1999; White et al., 2007). Interestingly, a double-blind, placebo-controlled pilot trial showed that topiramate-treated subjects were more likely to remain abstinent from cocaine use (Kampman et al., 2004) as craving intensity and duration were reduced in 25% of patients tested. Intriguingly, acute topiramate enhanced the pleasant subjective effects of methamphetamine (Johnson et al., 2007), suggesting a potential for replacement therapy. However, topiramate did not alter the rewarding properties of methamphetamine in mice (Tatsuta et al., 2007). A randomized, double-blind, placebo-controlled topiramate trial for alcohol and cocaine dependence is underway (clinical trial identifier: NCT00167245, A Phase II, Randomized, Double-blind, Placebo-Controlled, Pilot Trial of Topiramate for Alcohol and Comorbid Cocaine Dependence; NCT00223626, Lab Trials to Develop Medication for Cocaine Dependence). The anticonvulsant and mood stabilizer drug lamotrigine also exhibits antagonistic effects on AMPAR and reduces glutamate release (Lee et al., 2008). Importantly, two open-label studies have correlated lamotrigine with significant reductions in cocaine craving and use (Brown et al., 2003). Additional studies are recruiting patients at the time that this review was prepared (clinical trial identifier: NCT00280293, A Randomized, Double-Blind, Placebo-Controlled, Trial of Lamotrigine Add-on Therapy in Outpatients With Bipolar Disorder, Depressed or Mixed Phase and Cocaine Dependence).

Glutamatergic Modulators

A variety of agents that modulate glutamate receptor activity are also being studied as potential treatments against substance abuse. Reagents that increase basal extracellular levels of glutamate are also effective at preventing relapse and several forms of cocaine-induced plasticity (Baker et al., 2003; Knackstedt et al., 2010; Madayag et al., 2007; Martínez-Raga et al., 2008; Moran et al., 2005). Increased basal glutamate is thought to act on generally high-affinity autoreceptors to reduce the cue-, drug-, or stress-primed glutamate that acts through AMPAR to drive relapse (Baker et al., 2003). Accordingly, activation of receptors that can act as glutamate autoreceptors reduce cocaine seeking (Adewale et al., 2006; Peng et al., 2010; Peters and Kalivas, 2006; but see Bauzo et al., 2009). Thus, it is plausible to hypothesize a scenario where inhibiting excessive AMPA signaling while also promoting the diminished basal glutamatergic signaling that is often observed following repeated exposure to cocaine would represent a very effective way to prevent relapse. Indeed, other agents that weakly elevate activity of other glutamate receptors such as NMDARs, have shown some efficacy to reduce cocaine reinforcement in preclinical models (Bowers et al., 2007). Phase I clinical trials with campral (acamprosate), a nonspecific glutamate receptor modulator, have been completed (clinical trial identifier: NCT00385268, Pilot Trial of Acamprosate for the Treatment of Cocaine Dependence).

Among several other plausible mechanisms of action, acamprosate might also block the AMPA receptor pore, given the ability to modulate polyamine binding to the NMDA receptor (Kast and Altschuler, 2007). Similarly, agents such as provigil (modafinil), mucomyst/acetadote (*N*-acetyl cysteine), and rocephin (ceftriaxone) have shown efficacy to reduce cocaine seeking (Baker et al., 2003; Knackstedt et al., 2010; Madayag et al., 2007; Martínez-Raga et al., 2008; Moran et al., 2005). *N*-acetylcysteine elevates glutamate levels affecting both ionotropic and metabotropic glutamate receptors and is currently being studied as a therapeutic agent against substance abuse (clinical trial identifiers: NCT00136825, Effectiveness of N-Acetylcysteine in Treating Cocaine Dependent Individuals; NCT00218491, Effectiveness of N-Acetylcysteine (NAC) in Treating Cocaine Dependent Individuals). A thorough discussion of these compounds is beyond the scope of this review, but recent reviews have discussed the therapeutic potential of the most promising agents (Uys and LaLumiere, 2008; Kalivas, 2009).

Conclusions

While few, clinical studies performed with either selective or nonselective AMPAR antagonists suggest the therapeutic potential of this reagent class. Additional placebo-controlled, double-blind studies are needed to properly evaluate the clinical utility of these and similar compounds for substance abuse. Moreover, drugs acting nonspecifically at AMPARs should be further evaluated for efficacy to reduce cocaine seeking. At present, our armamentarium of clinically useful AMPAR antagonists is very limited; therefore, the development of novel AMPAR antagonists with fewer side effects is needed.

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