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Cognitive effects of Group I metabotropic glutamate receptor ligands in the context of drug addiction

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Abstract

Glutamate plays a pivotal role in regulating drug self-administration and drug-seeking behavior, and the past decade has witnessed a substantial surge of interest in the role of Group I metabotropic glutamate receptors ($mGlu_1$ and $mGlu_5$ receptors) in mediating these behaviors. As will be reviewed here, Group I mGlu receptors are involved in normal and drug-induced synaptic plasticity, drug reward, reinforcement and relapse-like behaviors, and addiction-related cognitive processes such as maladaptive learning and memory, behavioral inflexibility, and extinction learning. Animal models of addiction have revealed that antagonists of Group I mGlu receptors, particularly the $mGlu_5$ receptor, reduce self-administration of virtually all drugs of abuse. Since inhibitors of mGlu5 receptor function have now entered clinical trials for other medical conditions and appear to be well-tolerated, a key question that remains unanswered is - what changes in cognition are produced by these compounds that result in reduced drug intake and drug-seeking behavior? Finally, in contrast to $mGlu_5$ receptor antagonists, recent studies have indicated that positive allosteric modulation of $mGlu_5$ receptors actually enhances synaptic plasticity and improves various aspects of cognition, including spatial learning, behavioral flexibility, and extinction of drug-seeking behavior. Thus, while inhibition of Group I mGlu receptor function may reduce drug reward, reinforcement, and relapse-related behaviors, positive allosteric modulation of the mGlu5 receptor subtype may actually enhance cognition and potentially reverse some of the cognitive deficits associated with chronic drug use.

Keywords

drug addiction; rodent models; glutamate; metabotropic glutamate receptor; allosteric modulators; learning; memory; cognition; extinction

1. Introduction

Drug addiction is a multifaceted disorder that places an enormous socioeconomic, legal, and medical burden on society, in addition to the destructive influences it has on the addict and his or her family and peers. Current evidence suggests that drug addiction is a result of complex interactions between environmental, developmental, and genetic factors (Koob and

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Le Moal, 2007; Le Moal, 2009; Spanagel, 2009). At the behavioral level, drug addiction is typically characterized by a transition from casual, intermittent drug use to compulsive, uncontrolled drug intake coupled with repeated failed attempts at cessation of or curtailing drug use. At the cellular and molecular levels, repeated intake of drugs of abuse produce lasting neuroadaptations in gene expression, cytoarchitecture, and synaptic plasticity in various circuitries of the brain, including the limbic, prefrontal executive control, and reward systems (Christie, 2008; Crews and Boettiger, 2009; Feltenstein and See, 2008; Kalivas, 2008; Koob and Volkow, 2010; Robbins and Arnsten, 2009; Shaham and Hope, 2005; Thomas et al., 2008).

Although there is a substantial body of evidence supporting a role for the excitatory amino acid neurotransmitter glutamate and its ligand-gated ionotropic receptors (i.e., N-methyl-D-aspartate (NMDA), α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), and kainic acid (KA) subtypes) in mediating addictive behaviors that dates back more than two decades (Gass and Olive, 2008; Kalivas, 2004; Tzschentke and Schmidt, 2003; Wolf, 1998), it is only within the last decade or so that it has become apparent that metabotropic glutamate (mGlu) receptors are also involved in the neural mechanisms underlying drug addiction. Studies using pharmacological and genetic approaches have revealed clear evidence for a role of Group I ($mGlu_1$ and $mGlu_5$) receptors in regulating drug intake, reward, reinforcement, and reinstatement of drug-seeking behavior (Olive, 2009a). However, Group I mGlu receptors also mediate cognitive processes such as learning and memory, behavioral flexibility, and extinction (Darrah et al., 2008; Gass and Olive, 2009a; Moghaddam, 2004; Shipe et al., 2005; Simonyi et al., 2005), and deficits in these forms of cognition are frequently observed in drug addicts.

The purpose of the present review will be to summarize evidence that Group I mGlu receptors are involved in normal and drug-induced synaptic plasticity new evidence that Group I mGlu receptors are involved in various cognitive aspects of addiction, particularly learning and memory processes and associated synaptic plasticity. In addition, the effects of Group I mGlu receptor antagonists on drug self-administration, reward, and reinstatement are be reviewed along with possible neuroanatomical sites of action, underlying neural mechanisms, and effects of $mGlu_5$ receptor inhibition on cognition in recent clinical trials. Finally, recent findings on the ability of newly developed $mGlu_5$ receptor positive allosteric modulators (PAMs) to enhance cognition, synaptic plasticity, and extinction learning will also be reviewed, which provides a highly novel therapeutic avenue for potentially reversing some of the cognitive deficits that result from chronic heavy drug use.

1.1. Role of learning and memory processes in drug addiction

Drug addiction, referred to as “substance dependence” in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 2002) is characterized by compulsive drug use despite negative consequences, numerous failed attempts at abstinence, and a narrowing of the behavioral repertoire towards drug-seeking and consumption and away from normal social, occupational, or academic functioning. Evidence for deficits in numerous cognitive functions in drug addicts is manifested by behavioral perseverance and continued drug intake despite negative consequences, lack of impulse control, poor decision-making, working memory impairment, and attentional deficits (Goldstein and Volkow, 2002; London et al., 2005; Volkow and Fowler, 2000; Volkow et al., 1992).

It has become increasingly apparent that the brain circuits, neurotransmitter systems, and cellular and molecular substrates that mediate drug addiction have considerable overlap with those that underlie normal learning and memory processes (Berke and Hyman, 2000; Dalley and Everitt, 2009; Hyman et al., 2006; Kelley, 2004; Koob, 2009; Nestler, 2002; Robbins et

al., 2008; White, 1996). For example, acute and/or subchronic passive (i.e., experimenter-administered) delivery of various drugs of abuse such as cocaine, amphetamines, nicotine, opiates, or alcohol and can induce or modulate long-term potentiation (LTP) or long-term depression (LTD) of synaptic strength, two widely established cellular hallmarks of neural plasticity, in brain structures such as the hippocampus, mesoaccumbens dopamine pathway, and various regions of the limbic system (see Section 1.2. below). These same regions also mediate contextual, episodic, and emotional memory as well as spatial, habit, and incentive learning. The enduring neuroadaptations produced by chronic drug exposure can lead to the perseveration of drug-seeking behavior (Davis and Gould, 2008; Kalivas and O'Brien, 2008; Kauer, 2004; Kauer and Malenka, 2007), hypersalience of drug-associated stimuli, and a learned "imprint" of drug use in the brain (Boning, 2009).

One of the predominant forms of maladaptive learning that occurs as a result of chronic drug use is classical (Pavlovian) conditioning of the associations between the drug's effects, drug-specific withdrawal symptoms, and the environmental cues and contexts that are present at the time these drug-related effects are experienced (Robbins and Everitt, 2002). To give an example, suppose it takes 10 puffs to smoke a cigarette, and an active smoker smokes one pack of 20 cigarettes per day. In the course of one year, this would allow for approximately 7,300 pairings between the psychoactive ingredients of cigarette smoke (i.e., nicotine) and the cues and contexts that are present when cigarettes are smoked. As a result of these numerous drug-cue or context pairings, these external stimuli become overconditioned (a form of associative overlearning), and when experienced in the absence of the drug they can elicit expectation of drug availability and/or activate memories of previous euphoric experiences under the influence of a particular drug, which (Grant et al., 1996; Volkow et al., 2002a). Activation of these drug-related memories in turn can result in drug craving, drug-seeking behavior, and ultimately relapse (the so-called "addiction cycle"; see Carter and Tiffany, 1999; Dackis and O'Brien, 2005; Everitt et al., 2008; O'Brien et al., 1998; Weiss, 2005). Two key brain regions that mediate cue- and context-drug associations are the amygdala and hippocampus, respectively (Gould, 2006; Olive, 2009b), the activity of which is governed by the prefrontal cortex (PFC). Another form of maladaptive learning that occurs as a result of chronic drug use is drug-taking behaviors that become compulsive and automatic (i.e., instrumental overlearning), which is likely a result of perturbations in corticostriatal habit circuitry (Everitt et al., 2008; Kalivas, 2008; Kalivas et al., 2005; Koob and Volkow, 2010; Sesack and Grace, 2010).

As can be seen, a common neuroanatomical element involved in both of these maladaptive learning phenomena is the PFC, a multicomponent brain region that exerts executive control over numerous brain habit and motivational circuitries and is also involved in impulse control, working memory, attention, cue salience and extinction learning (Crews and Boettiger, 2009; Robbins and Arnsten, 2009). As will be discussed in Section 3.1., hypofunctioning of the PFC cortex is widely believed to mediate many of the cognitive deficits, including impaired decision making and impulse control, that are observed in chronic drug users.

1.2. Role of Group I mGlu receptors in addiction-related synaptic plasticity and learning and memory

Drugs of abuse including cocaine, amphetamines, nicotine, opiates, can induce and/or modulate forms of synaptic plasticity, such as LTP and LTD, in brain regions known to be involved in addiction, learning, and memory, including the hippocampus, ventral tegmental area (VTA), nucleus accumbens, and amygdala (Bao et al., 2007; Bellone and Luscher, 2006; Borgland et al., 2004; Delanoy et al., 1983; Goussakov et al., 2006; Grueter et al., 2008; Jones et al., 2000; Liu et al., 2005; Nugent et al., 2007; Saal et al., 2003; Thomas et al., 2001; Thompson et al., 2005; Ungless et al., 2001; Wanat et al., 2009; Yin et al., 2007).

While the aforementioned studies examined changes in synaptic transmission after passive exposure to drugs of abuse, both LTP and/or LTD of glutamatergic synapses in the nucleus accumbens from the ventral prefrontal afferents can be reduced or abolished or following active self-administration of the drug (Martin et al., 2006; Moussawi et al., 2009; Schramm-Sapyta et al., 2006), but remain unaffected in other regions such as the hippocampus (Del Olmo et al., 2006; Thompson et al., 2004). This “metaplasticity” of glutamatergic cortico-accumbens transmission may play a role in the development of maladaptive motivated behaviors in addiction such as the perseverance of drug-seeking, while the persistence of synaptic plasticity in the hippocampus may underlie the long-lasting nature of drug-associated memories.

$mGlu_1$ and $mGlu_5$ receptors have an almost complementary pattern of anatomical distribution in the brain (Shigemoto and Mizuno, 2000). High levels of $mGlu_5$ receptors found in forebrain regions such as the cerebral cortex, dorsal and ventral striatum, olfactory bulb and tubercle, lateral septum, and hippocampus (Romano et al., 1995; Shigemoto et al., 1993). In contrast, expression levels of $mGlu_1$ receptors in these regions are weak, except for the hippocampus, where it is highly expressed primarily in the CA3 region and dentate gyrus. Regions containing high levels of expression of $mGlu_1$ receptors include the cerebellum, thalamus, hypothalamus, and pallidal regions (Shigemoto et al., 1992), where $mGlu_5$ expression levels are often low or absent. Thus, the hippocampus is one of the few brain structures where high levels of both $mGlu_1$ and $mGlu_5$ receptors are found, and as such many investigations into the ability of these receptors to regulate synaptic plasticity have focused on this region.

It is well established that Group I mGlu receptors play a pivotal role in the induction and maintenance of synaptic plasticity (Anwyl, 2009; Bellone et al., 2008; Gladding et al., 2009). Electron microscopy studies have shown that Group I mGlu receptors are predominantly localized postsynaptically on perisynaptic annulus of dendritic spines (Romano et al., 1995; Shigemoto et al., 1997; Shigemoto et al., 1993), where they are structurally linked to NMDA receptors by various scaffolding proteins such as the Homer family of proteins (see Fig. 1) as well as other proteins including Shank and guanylate kinase-associated protein (GKAP) (Niswender and Conn, 2010). A small percentage of Group I mGlu receptors have been found on presynaptic terminals (Shigemoto et al., 1997), where they are thought to modulate neurotransmitter release (Anwyl, 1999).

Due to the predominant postsynaptic localization of Group I mGlu receptors, these receptors primarily regulate induction or maintenance of LTP or LTD by postsynaptic mechanisms such as potentiation of NMDA receptor function (discussed in further detail below), de novo synthesis of GluR2 subunits the AMPA receptor and other proteins, release of calcium ions from intracellular stores which activate a host of calcium-dependent effector proteins such as mitogen-activated and extracellular signal-regulated protein kinases (MAP and ERK kinases, respectively) which in turn modulate gene expression, as well as changes in phospholipid signaling (Anwyl, 2009; Bellone et al., 2008; Gladding et al., 2009). Group I mGlu receptors also regulate the synthesis of endocannabinoids, which act as retrograde signaling molecules to stimulate presynaptically localized cannabinoid CB_1 receptors to induce plasticity in axon terminals. One of the most widely studied mechanisms by which Group I mGlu receptors regulate LTP via postsynaptic mechanisms is through their aforementioned positive coupling to NMDA receptor function, whereby activation of these receptors increases NMDA receptor function (Alagarsamy et al., 1999; Attucci et al., 2001; Awad et al., 2000; Benquet et al., 2002; Doherty et al., 1997; Kotecha and MacDonald, 2003; Pisani et al., 2001; Ugolini et al., 1999). This positive coupling is primarily mediated by Group I mGlu receptor-induced activation of protein kinase C (PKC), which can

phosphorylate (among other substrates) specific subunits of the NMDA receptor, resulting in enhanced NMDA receptor function (Lu et al., 1999).

In accord with this well-established positive coupling between Group I mGlu and NMDA receptors, there is a wealth of evidence suggesting that Group I mGlu receptors play an important role in NMDA-dependent synaptic plasticity and learning and memory processes (Riedel et al., 2003; Simonyi et al., 2005). Genetic deletion or pharmacological blockade of Group I mGlu receptors inhibits the induction and/or expression of LTP in various brain regions including the CA1 and dentate gyrus regions of the hippocampus (Balschun et al., 1999; Balschun and Wetzel, 2002; Bikbaev et al., 2008; Jia et al., 1998; Lu et al., 1997; Manahan-Vaughan and Braunewell, 2005; Naie and Manahan-Vaughan, 2004; 2005; Neyman and Manahan-Vaughan, 2008), amygdala (Fendt and Schmid, 2002; Rodrigues et al., 2002), and dorsal and ventral striatum (Gubellini et al., 2003; Schotanus and Chergui, 2008), which are addiction-related brain regions that are involved in contextual/spatial learning, reward cue/emotional learning, and habit/incentive learning, respectively. Accordingly, microinjection studies have shown that local infusions of Group I mGlu receptor antagonists into the hippocampus produce decrements in contextual learning (Maciejak et al., 2003), disruption of emotional learning when infused into the amygdala (Bonini et al., 2003; Rodrigues et al., 2002), disruption of habit learning when infused into the dorsal striatum (Packard et al., 2001), and inhibition of reinforcer seeking when infused into the ventral striatum (Backstrom and Hyytia, 2007; Cozzoli et al., 2009; Gass and Olive, 2009b; Kumaresan et al., 2009). In contrast, local stimulation of Group I mGlu receptors in the amygdala has been shown to augment emotional learning (Rudy and Matus-Amat, 2009).

Emerging evidence suggests that Group I mGlu receptors also play a role in the neuronal plasticity and neuroadaptations produced by drugs of abuse (Bird and Lawrence, 2009a; Grueter et al., 2007). For example, acute cocaine-induced synaptic plasticity in the VTA (i.e., increased AMPA-mediated postsynaptic currents and associated insertion of high conductance GluR2-lacking AMPA receptors into the postsynaptic membrane) can be rapidly reversed by activation of $mGlu_1$ receptors (Bellone and Luscher, 2006), resulting in LTD characterized by endocytosis of GluR2-lacking AMPA receptors and their replacement by low-conductance GluR2-containing AMPA receptors replacement (Bellone et al., 2008; Grueter et al., 2007; Mameli et al., 2007). While acute cocaine-induced synaptic plasticity in the VTA is transient in nature (Ungless et al., 2001), functional disconnection of $mGlu_1$ receptors from Homer scaffolding proteins in the VTA allows for cocaine-induced synaptic plasticity in this region to become more persistent, and also leads to increased synaptic plasticity (LTD) in the nucleus accumbens, which may ultimately lead to the persistence of drug-seeking behavior (Mameli et al., 2009). In the bed nucleus of the stria terminalis (BNST), a region of the extended amygdala that mediates the negative emotional states produced by chronic drug use, LTD produced by repeated cocaine exposure is regulated by $mGlu_5$ receptors (Grueter et al., 2006; Grueter et al., 2008). Nicotine-induced enhancement of LTP in the hippocampus is also regulated by $mGlu_5$ receptors (Welsby et al., 2006). Thus, Group I mGlu receptors appear to regulate drug-induced synaptic plasticity in various addiction-related regions of the brain and may therefore serve as “gatekeepers” of the neuroadaptions produced by drugs of abuse, and ultimately the persistence of drug-seeking behavior that is characteristic of addiction (Bird and Lawrence, 2009a).

While the primary focus of this review is on Group I mGlu receptors, it should be noted that many neurotransmitter systems other than glutamate also modulate synaptic plasticity and learning and memory processes relevant to addiction, including acetylcholine, monoamines, endocannabinoids, GABA, and various neuropeptide systems (Koob and Volkow, 2010). Thus, the aforementioned contributions of Group I mGlu receptors to addiction related

learning and synaptic plasticity are likely a single component of numerous neurotransmitter systems acting in concert.

2. Reductions in drug intake, reward, and relapse produced by Group I mGlu receptor antagonists

Although the Group I mGlu receptors were first isolated in the early 1990's (reviewed in Ferraguti and Shigemoto, 2006), their role in drug addiction did not become evident until almost a decade later in a highly influential study published by Chiamulera and colleagues (Chiamulera et al., 2001). These investigators demonstrated that mice carrying a targeted deletion of the $mGlu_5$ receptor gene did not demonstrate hyperlocomotion in response to acute administration of various doses of cocaine (10, 20 or 40 mg/kg i.p.), and failed to acquire intravenous self-administration of cocaine. This latter phenomenon was not due to deficits in the ability to learn an operant task, as acquisition of lever pressing for food was unaltered in these mice. These investigators further confirmed a role for $mGlu_5$ receptors in regulating cocaine self-administration by demonstrating that intravenous administration of the mGlu5 receptor antagonist 2-methyl-6-(phenylethynyl)pyridine hydrochloride (MPEP) dose-dependently reduced cocaine self-administration without producing non-specific motor effects (as indicated by a lack of alteration in the rate of lever pressing). This pivotal study provided the first evidence that either genetic or pharmacological inhibition of $mGlu_5$ receptor function reduces the reinforcing effects of cocaine, and has provoked a wealth of speculation that suggested that $mGlu_5$ receptor antagonists may prove useful in treating drug addiction in humans (Bird and Lawrence, 2009b; Carroll, 2008; Cryan et al., 2003; Heilig and Egli, 2006; Jaeschke et al., 2008; Jupp and Lawrence, 2009; Kenny and Markou, 2004; Olive, 2005; 2009a; Spooren et al., 2001). Subsequent studies examining the effects of inhibition of Group I mGlu receptor function on the rewarding and reinforcing properties of cocaine and other drugs of abuse, and relapse-like behaviors, will now be reviewed.

2.1. Results from studies using the conditioned place preference paradigm

The conditioned place preference (CPP) paradigm is frequently used to assess the conditioned rewarding effects of a drug of abuse. In a typical CPP paradigm, an animal is passively administered a drug of abuse (such as cocaine) and then placed in a conditioning compartment with unique tactile, visual, and/or olfactory environmental cues. Drug conditioning sessions are alternated with saline conditioning session, where saline is administered and the animal is placed in an adjacent compartment with tactile, visual, and/or olfactory cues that are distinct from the drug conditioning compartment. During repetition of these conditioning procedures, contextual associative learning occurs between euphorigenic and physiological effects of the drug with the physical environment in which it is received. When given the opportunity to explore both compartments (i.e., the test phase), the animal will demonstrate an increased amount of time spent in the drug-paired compartment as compared to time spent in the saline-paired compartment or compared to the amount of time spent in the drug-paired compartment prior to drug conditioning (i.e., a conditioned place preference). Experimental manipulations (i.e., Group I mGlu receptor antagonist treatment) that are performed prior to drug conditions sessions are intended to determine effects on the acquisition of CPP, whereas such manipulations immediately prior to the test session are intended to determine effects on the expression of CPP. The CPP paradigm is also amenable to the study of extinction, which is accomplished either by repeatedly pairing the previously drug-paired compartment with saline, or by allowing the CPP to dissipate over a period of several weeks with repeated testing of place preference in the absence of further conditioning (see Section 3.3. for results of the effects of $mGlu_5$ receptor positive allosteric modulation on extinction of a cocaine CPP).

Following the landmark study by Chiamulera and colleagues, work from the author's laboratory demonstrated that pharmacological blockade of $mGlu_5$ receptors with MPEP (up to 20 mg/kg) dose-dependently attenuates the acquisition of a cocaine CPP in mice but did not alter the acquisition of a CPP for morphine, ethanol, nicotine, or amphetamine (Mcgeehan and Olive, 2003). Consistent with these findings, $mGlu_5$ receptor-deficient mice are capable of acquiring a CPP for ethanol (Bird et al., 2008). It is somewhat intriguing that the effects of MPEP on the acquisition of the CPP were selective for cocaine. However, other CPP studies have shown inhibitory effects of MPEP on CPP for other drugs of abuse. For example, in rats, MPEP at doses of 9 and 12 mg/kg has been shown to reduce (but not completely eliminate) the acquisition of a nicotine CPP in rats (Yararbas et al., in press), and higher doses of MPEP (30 mg/kg i.p.) have been shown to reduce the acquisition of a morphine CPP (Popik and Wrobel, 2002). Other studies have shown that MPEP actually potentiates the acquisition of a heroin- and ketamine-induced CPP in rats (van der Kam et al., 2009a). Some of these discrepancies may be attributable to procedural differences such as the use of rats vs. mice, the timing of MPEP administration prior to drug conditioning, the number and duration drug conditioning sessions, etc.

With regards to the *expression* of drug-induced CPP, MPEP has been shown to attenuate the expression of a CPP for morphine (Herzig and Schmidt, 2004), amphetamine (Herzig et al., 2005), and ethanol (Lominac et al., 2006) but not for cocaine, methylenedioxymethamphetamine (MDMA), or food (Herzig et al., 2005; Herzig and Schmidt, 2004). While the lack of consistency of effects of MTEP across different drugs of abuse may be attributable to procedural differences mentioned above, another possible explanation is a differential involvement of $mGlu_5$ receptors in the actual contextual learning process (CPP acquisition) versus the behavioral manifestation of that learning (CPP expression). Nonetheless, these studies show that $mGlu_5$ receptors are involved in the acquisition and expression of drug reward and drug-context associative learning for most drugs of abuse. Surprisingly, no studies on the effects of $mGlu_1$ receptor antagonists on drug CPP have been published. Since contextual learning that occurs during place conditioning is highly dependent on the hippocampus, where both $mGlu_1$ and $mGlu_5$ receptors are abundantly expressed and involved in synaptic plasticity, it is also surprising that inhibitory effects of $mGlu_5$ receptor antagonism on the acquisition of CPP were confined to only cocaine, nicotine and morphine. It is likely that specific combination of the neurochemical mechanisms of action of certain drugs of abuse and the resulting changes in neurotransmitter release that are induced by these drugs (i.e., increased dopamine and glutamate release), as well as procedural variables, are important determinants of any observed effects of Group I mGlu receptor antagonists on drug reward as measured by the CPP paradigm.

It is worth mentioning at this point that MPEP has been found to have numerous off-target effects at high (micromolar) concentrations, including direct inhibition of NMDA receptor function, inhibition of norepinephrine transporter activity, and activity at $mGlu_4$ receptors (see Lea and Faden, 2006 for review). As a result, the findings of some of the aforementioned studies that used high doses of MPEP (i.e., 30-50 mg/kg; Herzig and Schmidt, 2004; Popik and Wrobel, 2002) should be interpreted with caution, as these effects might not be mediated solely by $mGlu_5$ receptor antagonism. Along these lines, a dose of 20 mg/kg i.p. of MPEP has been shown to produce neither conditioned rewarding or aversive effects when used alone as the conditioning drug in mice (Mcgeehan and Olive, 2003). However, MPEP has been shown to induce a CPP in rats when administered at doses of 3 and 10 mg/kg intravenously but not intraperitoneally (van der Kam et al., 2009b), which is likely attributable to the resulting high concentrations of MPEP in the brain following intravenous administration, which could directly inhibit NMDA receptor function and therefore to produce a CPP (Layer et al., 1993).

2.2. Results from studies using oral or intravenous self-administration paradigms

Although some of the results of CPP studies have been mixed, more consistent effects of $mGlu_5$ receptor antagonism have been observed in paradigms where animals have been trained to either consume ethanol orally or self-administer other drugs of abuse intravenously. Systemic administration of $mGlu_5$ receptor antagonists such as MPEP or the more selective compound 3-((2-Methyl-4-thiazolyl)ethynyl)pyridine (MTEP) reduces operant self-administration of cocaine (Chiamulera et al., 2001; Iso et al., 2006; Kenny et al., 2005; Kenny et al., 2003; Lee et al., 2005; Martin-Fardon et al., 2009; Platt et al., 2008; Tessari et al., 2004), nicotine (Paterson et al., 2003; Tessari et al., 2004), heroin (van der Kam et al., 2007), ketamine (van der Kam et al., 2007), methamphetamine (Gass et al., 2009), and ethanol (Backstrom et al., 2004; Gupta et al., 2008; Hodge et al., 2006; Lominac et al., 2006; McMillen et al., 2005; Olive et al., 2005; Schroeder et al., 2005). The ability of MPEP and MTEP to suppress drug self-administration is due, at least in part, by a reduction in the reinforcing efficacy of the self-administered drug, as it has been shown that MPEP and MTEP can reduce breakpoints for drug self-administration on a progressive ratio schedule of reinforcement (Besheer et al., 2008b; Gass et al., 2009; Paterson and Markou, 2005). However, $mGlu_5$ receptor antagonism can also interfere with the interoceptive effects of some drugs of abuse such as ethanol (Besheer et al., 2006) and cocaine (Lee et al., 2005), which may underlie the ability of this compound to reduce self-administration of these drugs.

With regards to $mGlu_1$ receptor-mediated regulation of drug self-administration, most studies have focused on effects of $mGlu_1$ receptor antagonists on voluntary ethanol consumption. Several studies have found a consistent lack of effect of $mGlu_1$ receptor antagonism by 7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxylate ethyl ester (CPCCOEt) on operant ethanol self-administration in rodents (Hodge et al., 2006; Schroeder et al., 2005); however Lominac and colleagues found an inhibitory effect of CPCCOEt on ethanol self-administration (Lominac et al., 2006). The reasons for these discrepant findings remain unclear. A more recent study examining the effects of the highly potent $mGlu_1$ receptor antagonist JNJ16259685 also showed inhibitory effects on ethanol self-administration as well as reducing breakpoints in a progressive ratio paradigm, but nonspecific impairments in motor activity were also induced by this compound (Besheer et al., 2008a; b). Thus, to date the role of $mGlu_1$ receptors in regulating ethanol consumption are equivocal, and further studies are needed examining effects of $mGlu_1$ receptor antagonists on self-administration of other drugs of abuse are needed. Given the apparent locomotor inhibitory effects of such ligands noted by Besheer and colleagues, such studies should closely examine whether any observed reductions in drug self-administration are not the result of nonspecific motor inhibitory effects.

2.3. Results from studies using the reinstatement paradigm

Group I mGlu receptors also appear to regulate relapse-like behaviors, as measured by the reinstatement paradigm (increases in the number of operant responses that previously led to drug delivery prior to extinction procedures, a phenomenon that can be induced by presentation of drug-associated cues, contexts, drug priming, or stressors). In the case of alcohol, the alcohol deprivation effect (a transient increase in ethanol consumption following a short period of forced abstinence) is sometimes used. Reinstatement of drug-seeking behavior evoked by drug-associated cues has shown to be attenuated by $mGlu_5$ receptor antagonists in rats with a history of self-administration of cocaine (Kumaresan et al., 2009; Lee et al., 2005; Martin-Fardon et al., 2009; Moussawi et al., 2009), alcohol (Backstrom et al., 2004; Schroeder et al., 2008), nicotine (Bespalov et al., 2005) or methamphetamine (Gass et al., 2009). $mGlu_5$ receptor antagonism also attenuates the alcohol deprivation effect (Backstrom et al., 2004; Schroeder et al., 2005). Reinstatement of

drug-seeking behavior evoked by acute drug exposure (drug priming) is also attenuated by $mGlu_5$ receptor antagonists in rats with a history of self-administration of cocaine (Backstrom and Hyytia, 2006; Kumaresan et al., 2009) or nicotine (Tessari et al., 2004).

Although most reinstatement studies have focused on effects of $mGlu_5$ receptor antagonists, a recent study demonstrated that the selective $mGlu_1$ receptor antagonist (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone (EMQMCM) attenuated the reinstatement of nicotine-seeking behavior elicited by nicotine priming and nicotine-associated cues (Dravolina et al., 2007). These recent findings suggest that studies need to be conducted that examine the role of $mGlu_1$ receptors in mediating relapse-like behaviors in animals with a history of self-administration of other drugs of abuse such as cocaine, methamphetamine, heroin, and alcohol.

2.4. Possible underlying neural mechanisms of action

Most studies examining the effects of Group I mGlu receptor antagonists on drug reinforcement, reward and relapse-like behavior have used peripheral routes of administration. However, a handful of recent studies have employed intracranial microinjection procedures to determine potential neuroanatomical sites of action of these compounds. Thus far, $mGlu_5$ receptors in the nucleus accumbens have been shown to regulate ethanol consumption and reinstatement of cocaine-seeking behavior, and $mGlu_1$ receptors in the hippocampus have been demonstrated to regulate contextual reinstatement of cocaine-seeking behavior. More specifically, blockade of $mGlu_5$ receptors in the nucleus accumbens shell but not core subregion with MTEP attenuated intravenous alcohol reinforcement in rats (Gass and Olive, 2009b), an effect that was dependent on the activity of epsilon isoform of PKC (PKCε), a downstream signaling target of $mGlu_5$ receptors (Olive et al., 2005). Similar findings were reported by Cozzoli and colleagues, who demonstrated that intra-accumbens infusion of MPEP reduced binge-like alcohol consumption in mice (Cozzoli et al., 2009). Interestingly, Cozzoli and colleagues also demonstrated that disconnection of $mGlu_5$ receptors from Homer scaffolding proteins by incorporating a singe amino acid substitution in the Homer-binding domain of the $mGlu_5$ receptor eliminated the ability of intra-accumbens MPEP to reduce alcohol consumption. These data support the notion that the Homer family of scaffolding proteins that structurally link $mGlu_5$ to NMDA receptors are important mediators of drug self-administration as well as drug sensitivity (Szumlinski et al., 2004, 2005, 2006). Blockade of $mGlu_5$ receptors in the nucleus accumbens also attenuates cocaine- or cue-primed reinstatement of cocaine-seeking behavior (Backstrom and Hyytia, 2007; Kumaresan et al., 2009).

An important role for $mGlu_1$ receptors in the dorsal hippocampus in regulating cocaine-seeking behavior evoked by cocaine-associated contextual cues was recently demonstrated (Xie et al., 2010), consistent with the established role for the hippocampus in mediating drug-context associations and their ability to evoke drug-seeking behavior (Fuchs et al., 2005). Thus, it seems that Group I mGlu receptors in multiple brain regions mediate different aspects of drug addiction, such as drug reinforcement, self-administration, and cue- and drug-primed reinstatement (which are mediated, at least in part, by $mGlu_5$ receptors in the nucleus accumbens) and the ability of drug-associated contextual cues to elicit drug-seeking behavior (which are mediated, at least in part, by $mGlu_1$ receptors in the hippocampus). Studies examining the effects of pharmacological manipulation of Group I mGlu receptors in other brain regions known to be involved in addiction (i.e., the amygdala, VTA, PFC, etc.) on drug self-administration and relapse are needed to provide a more comprehensive understanding of the neural circuitry in which these receptors regulate various aspects of drug addiction.

On a cellular level, it is of interest to know precisely how inhibition of Group I mGlu receptor function attenuates drug reward, reinforcement, or relapse-like behaviors. A likely mechanism can be postulated as follows: inhibition of Group I mGlu receptors, primarily the $mGlu_5$ receptor subtype, dampens of the activity of medium spiny neurons in the nucleus accumbens, which comprise more than 90% of the neurons within this region and exhibit high levels of $mGlu_5$ expression (Romano et al., 1995; Shigemoto et al., 1993). Although this has not been demonstrated directly, it seems to be a plausible hypothesis as it has recently been shown that $mGlu_5$ receptor activation increases the spike firing and excitability of medium spiny neurons in the nucleus accumbens (D'Ascenzo et al., 2009). Therefore, $mGlu_5$ receptor antagonism in this region could possibly reduce the excitability of these neurons, and as a consequence, dampen the outflow of neural information from the nucleus accumbens to its target regions including the ventral pallidum and VTA. These regions are well known to be a part of the circuitry that mediates adaptive motivated behaviors (Kalivas and Nakamura, 1999; Kalivas et al., 2006; Koob and Volkow, 2010). However, given that effects of Group I mGlu receptor antagonists administered into regions other than nucleus accumbens or hippocampus on addiction-related behaviors have not yet been investigated, one cannot rule the potential role of other structures, circuitries, or physiological mechanisms at this point.

Another mechanism by which Group I mGlu receptor antagonists may reduce drug reward and reinforcement and relapse is by altering the functionality of the brain's reward circuitry. For example, Kenny and colleagues showed that a 9 mg/kg dose of MPEP elevated thresholds for intracranial self-stimulation of the medial forebrain bundle (Kenny et al., 2005), a well-established assay of brain reward function. Typically, elevations in thresholds for intracranial self-stimulation indicate a decrease in functioning of the brain's reward system are have been interpreted as representing an anhedonic or dysphoric state such as that produced by drug withdrawal (Markou and Koob, 1992). Thus, Kenny and colleagues have proposed that MPEP-induced deficits in brain reward function mediated the ability of this compound to reduce self-administration of cocaine (Kenny et al., 2005). While reductions in brain reward circuitry function could indeed contribute to the ability of $mGlu_5$ receptor antagonists to attenuate drug self-administration, findings that MPEP at a dose of 20 mg/kg does not produced conditioned aversive effects (Mcgeehan and Olive, 2003), and that MTEP does not alter self-administration of food (a non-drug reward) on fixed or progressive ratios schedule of reinforcement (Gass et al., 2009), suggest that additional mechanisms may be involved.

2.5. Cognitive effects of Group I mGlu antagonists in humans

Given the wealth of preclinical evidence suggesting that Group I mGlu receptor antagonists may be of use in the treatment of drug addiction, one critical unanswered question is - what cognitive effects will such ligands have in human beings with respect to drug craving and subjective drug effects? Several $mGlu_5$ (but not $mGlu_1$) receptor antagonists (or negative allosteric modulators, NAMs) have now entered Phase I and II clinical trials for the treatment of other medical conditions, such as Fragile X syndrome, gastroesophageal reflux disease (GERD), anxiety, depression, and L-dopa induced dyskinesias in Parkinson's disease (Jaeschke et al., 2008).. While the few reports detailed below on the clinical efficacy of these compounds as well as their cognitive (side) effects provide are relatively limited in detail, thus far they indicate that such ligands are fairly well tolerated and result in few serious adverse cognitive effects.

Several early clinical studies were conducted with [N-(3-chlorophenyl-N'-(4,5)-dihydro-1-methyl-4-oxo-1H-imidazol-2-yl)urea (fenobam) for the treatment of anxiety (Friedmann et al., 1980; Itil et al., 1978; Pecknold et al., 1980; Pecknold et al., 1982). While at the time of these studies fenobam had an unknown mechanism of action, it was later found to be an

$mGlu_5$ receptor antagonist with greater selectivity for the receptor than MPEP (Montana et al., 2009; Porter et al., 2005). The results of these early clinical studies demonstrated clear anxiolytic effects of fenobam, equivalent to those produced by diazepam, but adverse side effects such as nausea, dizziness, insomnia, blurred vision, depersonalization, and perceptual alterations were reported in approximately 25-40% of the patients taking fenobam, and many patients who experienced these side effects discontinued the study. Such adverse side effects occurred primarily in patients taking higher doses of fenobam (200-600 mg/day). Despite its apparent efficacy as an anxiolytic, the relatively high prevalence rates of adverse side effects associated with fenobam resulted in a discontinuation of clinical trials of this compound.

Recently, however, a re-examination of the therapeutic potential of fenobam for treating Fragile X syndrome, a common form of mental retardation, has been initiated by several pharmaceutical companies (Jaeschke et al., 2008). In a recent preliminary report on the safety and tolerability of fenobam in subjects with Fragile X syndrome, it was reported that doses of fenobam in the 50-150 mg/day range produced clinical improvements in cognitive function in 9 out of 12 patients, including increased eye contact and social interaction, and reduced anxiety and hyperactivity (Berry-Kravis et al., 2009). The only side effect observed in 3 of the 12 patients was mild sedation, and no subjects discontinued the trial.

The results of a clinical trial of the $mGlu_5$ receptor negative allosteric modulator (NAM) ADX10059 for the treatment of GERD have also recently been made public (Keywood et al., 2009). Although little has been revealed about the precise pharmacological properties of ADX10059, it is designated as an $mGlu_5$ receptor NAM rather than an antagonist, most likely because it dampens but does not completely antagonize the functioning of this receptor, as is the case with MPEP, MTEP, and fenobam. The mechanistic rationale for the treatment of GERD with compounds that reduce $mGlu_5$ receptor function has been based on the localization of $mGlu_5$ receptors on vagal afferent nerve endings that innervate and control the contractility of the lower esophageal sphincter, thereby regulating reflux of stomach acid into the esophagus (Young et al., 2007). In the study by Keywood and colleagues, 24 subjects with GERD received placebo prior to a high fat meal on the first day of reflux assessment, followed by ADX10059 at a dose of either 50 or 250 mg/day (n=12 per group) prior to a high fat meal on the second day of reflux assessment. ADX10059 was shown to be effective in reducing acid reflux, and no subjects taking either dose of ADX10059 discontinued the trial. In subjects receiving the 50 mg dose, 1 out of 12 subjects reported mild sedation, cough, and rhinorrhea. In subjects receiving the 250 mg dose, side effects such as dizziness and nausea occurred in 9 out of 12 participants. However, these side effects resolved following the first or second dose of ADX10059, and none were considered severe. Thus, like fenobam, ADX10059 appears to be fairly well tolerated with few adverse side effects that precipitate discontinuation of the medication. Another $mGlu_5$ receptor NAM, ADX48621, has recently entered clinical trials for the treatment of depression and anxiety (Jaeschke et al., 2008). Thus, mGlu5 receptor antagonists or NAMs such as fenobam and ADX10059 appear to be well-tolerated in humans with few side effects, and future clinical trials on their effects on the craving, use, and subjective effects of drugs of abuse in human addicts are eagerly awaited.

3. Plasticity- and cognition-enhancing of $mGlu_5$ positive allosteric modulators (PAMs)

In Section 1, the positive coupling of Group I mGlu receptors to NMDA receptor function was described along with the ability of antagonists of these receptors to negatively influence synaptic plasticity. In Section 2, studies providing a clear rationale for the use of ligands that reduce or inhibit Group I mGlu receptor function in reducing drug reward, reinforcement,

and relapse-like behaviors were summarized, along with recent exciting preliminary data on the favorable safety and tolerability of $mGlu_5$ receptor antagonist fenobam and the $mGlu_5$ receptor NAM ADX10059 in humans. Recently, however, efforts have also been made to develop compounds that indirectly enhance NMDA receptor function via positive allosteric modulation of Group I mGlu receptors (see Fig. 1) for the purposes of reversing the hypothesized NMDA receptor "hypofunction" that is believed to contribute to cognitive deficits in schizophrenia (Chen and Conn, 2008;Conn et al., 2009a;Conn et al., 2009b;Lindsley et al., 2006;Niswender and Conn, 2010;Rodriguez and Williams, 2007). Thus far, significant progress has been made in the development of $mGlu_5$ receptor positive allosteric modulators (PAMs). These compounds bind to an allosteric site that is distinct from the orthosteric glutamate binding site of the receptor, and while devoid of any agonistic activity on their own, they potentiate the receptor response to endogenously released glutamate. Due to the more widespread distribution of $mGlu_5$ vs. $mGlu_1$ receptors in the brain, particularly in forebrain regions, greater effort has been devoted to the development of $mGlu_5$ over $mGlu_1$ receptor PAMs.

The first $mGlu_5$ receptor PAM to be characterized was 3,3′-difluorobenzaldazine (DFB) (O'Brien et al., 2003), which is structurally related to MPEP and MTEP. However, DFB exhibits low potency, poor solubility in aqueous solutions, and does not cross the blood-brain barrier. These same investigators subsequently identified a more potent $mGlu_5$ receptor PAM, N-[4-chloro-2-[1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]phenyl]-2-hydroxybenzamide (CPPHA) (O'Brien et al., 2004). In the initial characterization of this compound, it was demonstrated that CPPHA was 7 to 8 times more potent than DFB in potentiating $mGlu_5$ receptor function in vitro. In addition, CPPHA potentiated NMDA receptor-mediated currents in rat hippocampal slices in the presence of threshold concentrations of the Group I mGlu receptor agonist dihydroxyphenylglycine (DHPG), and potentiated DHPG-induced depolarizations of rat subthalamic nucleus neurons. Unfortunately, like DFB, CPPHA exhibited poor solubility in aqueous solutions and did not show significant brain penetrance following systemic administration.

The first $mGlu_5$ receptor PAM that showed significant CNS activity following peripheral administration was 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB), which was shown to reverse amphetamine-induced disruption of prepulse inhibition, an animal model of sensorimotor gating deficits in schizophrenia (Kinney et al., 2005; Lindsley et al., 2004). Subsequently, the characterization and antipsychotic profile of another $mGlu_5$ receptor PAM, [S-(4-fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-[1,2,4]-oxadiazol-5-yl]-piperidin-1-yl}-methanone] (ADX47273) has also been described (Liu et al., 2008; Schlumberger et al., 2009). As will be discussed below, $mGlu_5$ receptor PAMs may be novel therapeutic approaches to enhancing synaptic plasticity and improving cognitive function in drug addicts.

3.1. Cognitive deficits produced by drug addiction

Chronic drug use leads to numerous deficits in cognitive function, including loss of executive control, impulsivity, poor decision making, behavioral inflexibility, memory impairments, amongst many others. One area of the brain that is particularly vulnerable to drug-induced neurological impairments which result in cognitive deficits is the PFC (Goldstein and Volkow, 2002; London et al., 2005; Volkow and Fowler, 2000; Volkow et al., 1992). The PFC is comprised of various subregions of the dorsal forebrain, including the medial prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex. As a whole, the PFC mediates a host of functions including working memory, impulsivity and response inhibition, selective attention, salience attribution, reward expectancy, decision-making, goal-directed behavior, drive and motivation, and emotional learning (Fuster, 1997; Shidara and Richmond, 2002; Tzschentke, 2000; Vertes, 2006). The PFC has reciprocal connections

with numerous other regions of the brain including the dorsal and ventral striatum, ventral midbrain, brainstem, thalamus, hippocampus, amygdala, and other cortical regions (Likhtik et al., 2005; Morgane et al., 2005; Sesack et al., 1989; Vertes, 2004). As a result of chronic drug use, a reduction in function and activity of PFC is often observed in drug addicts, a phenomenon commonly referred to as “hypofrontalism”. Loss of PFC functionality is believed to contribute to the loss of executive function and inhibitory control over compulsive behaviors, improper decision making, and the maladaptive motivational salience of drug-associated cues that are characteristic of addiction (Crews and Boettiger, 2009; Everitt et al., 2008; Isoda and Hikosaka, 2007; Jentsch and Taylor, 1999; Kalivas, 2008; Schoenbaum et al., 2006; Volkow et al., 2002b). Thus, “hypofrontal” drug addicts exhibit behavioral perseverance and inflexibility, and thus have difficulty changing their drug-taking behavior from compulsive and uncontrolled to self-regulated. Impaired functioning of the PFC may be due, in part, to drug-induced alterations of $mGlu_5$ receptor function or expression, as infusions of MPEP into the PFC has been shown to impair object recognition and spatial short-term memory (Christoffersen et al., 2008), while repeated drug exposure or drug self-administration alters expression levels of $mGlu_5$ receptors in this region (Ben-Shahar et al., 2009; Winstanley et al., 2007). As will be discussed below, $mGlu_5$ receptor PAMs appear to possess pro-cognitive properties and reverse experimentally-induced deficits in PFC function, and may therefore improve functionality of the PFC and reverse some of the cognitive deficits commonly observed in drug addiction.

3.2. Effects of $mGlu_5$ receptor PAMs on synaptic plasticity and cognition

Recently it was reported that the CDPPB analog VU-29 facilitated the induction of LTP in slice preparations of the CA1 region of the hippocampus, and these effects were blocked by AP-5, confirming a role for increased NMDA receptor function in this phenomenon (Ayala et al., 2009). VU-29 also potentiated DHPG-induced LTD in this region. In this same report, it was shown that systemic administration of CDPPB or ADX47273 improved performance in the Morris water maze, a hippocampus-dependent spatial memory task. Consistent with these findings, intracerebroventricular infusion of DFB has been shown to improve spatial memory in a Y-maze task (Balschun et al., 2006), whereas genetic deletion or pharmacological blockade of $mGlu_5$ receptors impairs performance in the Morris water maze and other spatial navigation tasks (Car et al., 2007; Christoffersen et al., 2008; Jacob et al., 2009; Manahan-Vaughan and Braunewell, 2005). CDPPB and ADX47273 have also been reported to improve cognition as measured by novel object recognition and five-choice serial reaction time tests, which involve proper functioning of the hippocampus and frontal cortex. In accordance with the observed ability of $mGlu_5$ receptor PAMs to facilitate the induction of synaptic plasticity, CDPPB and ADX47273 increase the expression of markers of synaptic plasticity in the PFC and hippocampus, such as increased phosphorylation of the NR1 and NR2B subunits of the NMDA receptor and the GluR1 subunit of the AMPA receptor, and activate α-calmodulin-dependent kinase II, cAMP-responsive element binding protein, and extracellular signal-regulated kinase (Liu et al., 2008; Uslaner et al., 2009). Further support for $mGlu_5$ receptor PAM-induced increases in PFC functioning have been recently demonstrated using in vivo electrophysiological techniques, where CDPPB was shown to reverse changes in frontal cortex neuronal firing patterns induced by the psychotomimetic NMDA receptor antagonist MK-801 (Homayoun and Moghaddam, 2006; 2008). Finally, and perhaps most importantly, CDPPB has been shown to reverse MK-801 induced impairments in performance in behavioral flexibility tasks (Darrah et al., 2008), which highly involve proper functioning of the orbitofrontal cortex. Thus, it is possible that enhanced functionality of the PFC produced by $mGlu_5$ receptor PAMs might reduce the behavioral inflexibility and perseverative nature of compulsive and uncontrolled drug-seeking and drug self-administration behavior that is a defining characteristic of drug addiction. Other cognition-enhancing agents such as inhibitors of acetylcholinesterase and

norepinephrine transporters, nicotinic acetylcholine receptor partial agonists, and α_2-adrenergic receptor agonists, have also been proposed to be of potential benefit in reversing some of the cognitive impairments associated with chronic drug use (Sofuoglu, 2010).

3.3. Effects of $mGlu_5$ receptor PAMs on extinction of drug-seeking behavior

Drug-associated memories evoked by exposure to contexts or distinct environmental stimuli that have been paired with drug intake can result in drug craving and ultimately relapse. It is therefore important that during the course of treatment of addiction, a weakening of drug-related memories and the motivational salience of drug-associated cues and contexts is needed, as is the formation of newer associations between environmental stimuli and drug effects or availability (Centonze et al., 2005; Diergaarde et al., 2008; Taylor et al., 2009). While weakening drug memories by interfering with the mechanisms of memory reconsolidation is one potential approach (Diergaarde et al., 2008; Lee, 2009; Taylor et al., 2009), these approaches would likely involve manipulation of long-term aspects of synaptic plasticity such as dendritic remodeling, de novo protein synthesis, and changes in gene expression related to synaptic plasticity, which may be difficult to achieve without affecting normal brain function.

An alternative approach to overcoming drug-associated memories is via facilitation of extinction learning. It is well accepted that extinction of conditioned associations between external stimuli and maladaptive behaviors or responses (such as drug craving and drug-seeking behavior) is a form of new and active learning. However, treatment approaches such as cue exposure therapy that are used to desensitize the addict to the psychological and physiological responses evoked by drug-associated stimuli have shown only modest success rates (Conklin and Tiffany, 2002; Havermans and Jansen, 2003). Therefore, pharmacological approaches to facilitating extinction learning could provide a novel avenue for treatment of drug addiction.

Indeed, there is recent data demonstrating that increasing glutamategic transmission via activation or positive allosteric modulation of Group I mGlu receptors can enhance extinction learning. For example, intra-hippocampal infusions of an $mGlu_1$ receptor antagonist attenuates the extinction of inhibitory avoidance learning (Simonyi et al., 2007), and infusions of $mGlu_1$ receptor antagonists into the amygdala attenuate the extinction of conditioned fear (Kim et al., 2007). It has also been shown that $mGlu_5$ receptor-deficient mice fail to extinguish cue- and contextually conditioned fear behavior (Xu et al., 2009). Relevant to drug addiction, studies from the author's laboratory have shown that CDPPB facilitates the extinction of a cocaine-induced conditioned place preference (Gass and Olive, 2009a) and reduces extinction responding following intravenous cocaine self-administration (see Fig. 2). Although excessive NMDA activation can produce excitotoxicity, repeated CDPPB administration does not produce evidence of neurotoxicity (Gass and Olive, 2009a). Thus, $mGlu_5$ receptor PAMs may be a novel class of compounds by which to facilitate the extinction of drug-stimuli or drug-context associations.

4. Conclusions and treatment implications

Group I mGlu receptors are intricately involved in regulating synaptic plasticity, including plasticity produced by drugs of abuse, as well as associated normal and pathogenic learning and memory processes. Group I mGlu receptor antagonists or NAMs may be of potential benefit in reducing drug reward, reinforcement and relapse-related behaviors, and a few recent clinical trials on such compounds acting on $mGlu_5$ receptors (i.e., fenobam and ADX10059) for other medical conditions have revealed that these compounds are safe and well tolerated. Thus, clinical trials examining the effects of these or similar compounds on drug intake and relapse are now clearly warranted, as are studies of their effects on

addiction-related cognitive phenomena such as drug craving and subjective drug effects. On the other hand, there now is evidence that $mGlu_5$ receptor PAMs, which indirectly increase NMDA receptor function and enhance synaptic plasticity, improve cognitive function in certain tasks, facilitate the extxinction of drug-associated contextual memories, and reverse experimentally-induced deficits in PFC function. Therefore, the clinical utility of pharmacologically inhibiting or enhancing Group I mGlu receptor function may ultimately depend on the specific aspect of the addict's condition that is most problematic (i.e., reducing the drug's reinforcing effects by $mGlu_5$ receptor antagonists or NAMs, or improving executive control, behavioral flexibility, and extinction learning by $mGlu_5$ receptor PAMs). Furthering the advancement of both types of ligands in clinical trials, as well as improving our understanding of the neural circuitry in which they exert their effects and the behavioral paradigms in which they most effective, should be top priorities for researchers in this field of study.

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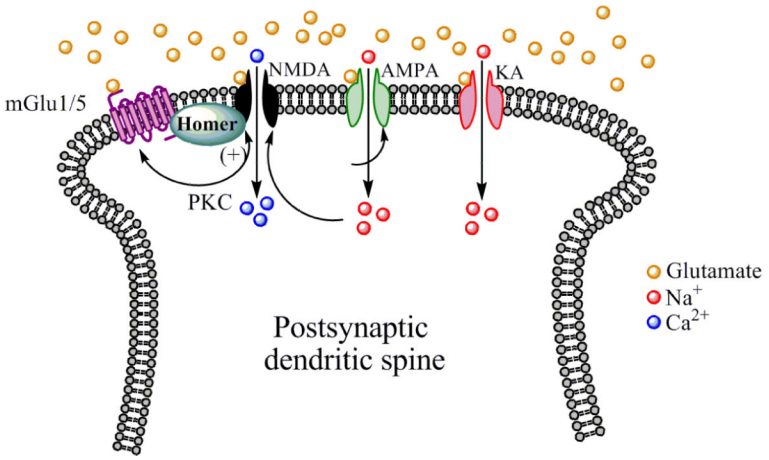

Fig. 1.

Diagram of a dendritic spine and postsynaptic localization of ionotropic and Group I mGlu receptors. Synaptically released glutamate binds to ionotropic glutamate receptors (NMDA, AMPA, and KA receptors), which allows the influx of Na^+ and/or Ca^{2+} ions to depolarize the postsynaptic membrane. Group I mGlu receptors are localized to the perisynaptic annulus of the dendritic spine where they are stimulated by high levels of synaptic glutamate release or glutamate released from glia. Group I mGlu are structurally coupled to NMDA receptor via Homer proteins (as well as other scaffolding proteins not shown), and are biochemically coupled to NMDA receptor function via PKC. Activation of Group I mGlu receptors increases the activity of NMDA receptors (denoted by a +), and NMDA receptor activation can positively influence Group I mGlu receptor function as well.

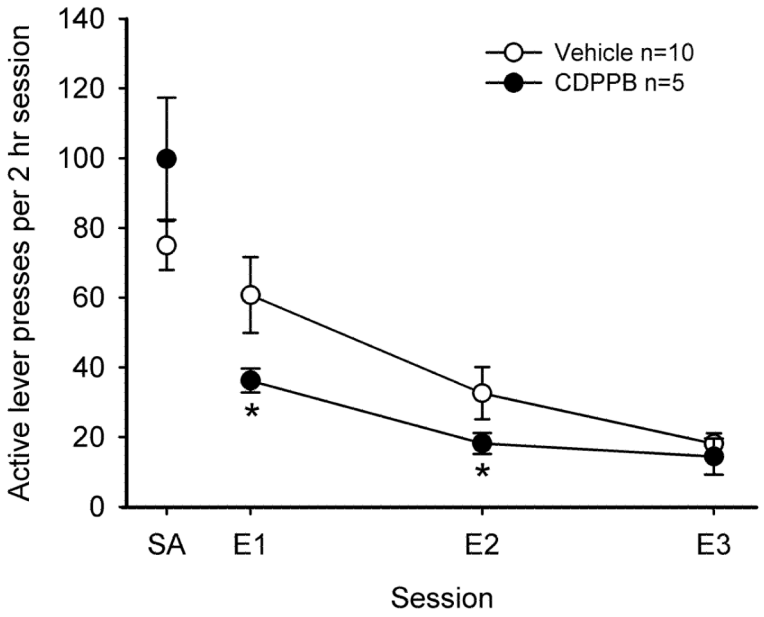

Fig. 2.

The $mGlu_5$ receptor positive allosteric modulator CDPPB reduces extinction responding following intravenous cocaine self-administration. Male Sprague-Dawley rats were trained to self-administer cocaine at a dose of 0.33 mg/kg/infusion under an FR1 schedule of reinforcement in 2 hr daily sessions. Following 12 days of active cocaine self-administration (the average of the last two days is depicted in the graph as SA), animals underwent extinction by eliminating infusions as a consequence of active lever presses, while stimuli that were previously presented during each cocaine infusion (i.e., light/tone stimulus and syringe pump activation) were still presented. Animals were administered vehicle (20% 2-hydroxypropyl-β-cyclodextrin) or CDPPB (30 mg/kg i.p.) 30 min prior to daily 2 hr extinction sessions (E1, E2, or E3). CDPPB significantly (*$P<0.05$) reduced extinction responding on extinction days E1 and E2, possibly reflecting increased extinction learning, as this dose of CDPPB has no effect on motor activity (Gass and Olive, 2009a).