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Review

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.

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1. Introduction

Drug addiction is a multifaceted disorder that places an enormous socioeconomic, legal, and medical burden on society, in addition to

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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 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, and review recent evidence showing 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 7300 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 (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