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Glutamate Transmission in Addiction

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Abstract

Cortico-striatal glutamate transmission has been implicated in both the initiation and expression of addiction related behaviors, such as locomotor sensitization and drug seeking. While glutamate transmission onto dopamine cells in the ventral tegmental area undergoes transient plasticity important for establishing addiction-related behaviors, glutamatergic plasticity in the nucleus accumbens is critical for the expression of these behaviors. This information points to the value of exploring pharmacotherapeutic manipulation of glutamate plasticity in treating drug addiction.

Keywords

glutamate; sensitization; drug-seeking; ventral tegmental area; nucleus accumbens

Glutamate is the primary excitatory neurotransmitter in the brain and a mediator of the synaptic plasticity required for organisms to adapt behavior to a changing environment (Abraham, 2008; Parsons et al., 2005). Drug addiction can be characterized as diminished ability to alter behavioral responding for drug reinforcement (Kalivas and O'Brien, 2008; Kelley, 2004). This is thought to arise from both enhanced motivation to obtain drug and a decreased capacity to appropriately adapt behavior in response to important non-drug environmental stimuli and circumstances. As a primary regulator of the synaptic plasticity underlying learning and memory, it is not surprising that research over the last 15 years has identified drug-induced pathological changes in glutamate transmission that contribute to drug addiction. Moreover, characterization of the glutamatergic neuroadaptations induced by drug abuse has revealed promising new avenues for treating addiction.

Glutamatergic Pathways

Although glutamate is a ubiquitous neurotransmitter in brain, certain glutamatergic projections are thought to be critically impacted by addictive drugs. Notably, research focus has been brought to bear on glutamatergic afferents to the basal ganglia, in particular to the nucleus accumbens (Kalivas and O'Brien, 2008; Wolf, 1998). This includes inputs from the amygdala, hippocampus, medial thalamus and prefrontal cortex (Groenewegen et al., 1996). With the exception of the medial thalamus, all of these projections have been found to be consequential in animal models of addiction (Pierce and Kalivas, 1997; Rogers and See, 2007; See et al., 2003), and activation of the prefrontal cortex and amygdala is commonly

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observed in brain imaging studies in human addicts that are exposed to drug associated stimuli that induce desire for drug use (Goldstein and Volkow, 2002).

In contrast to activation of the prefrontal and amygdala projections to the nucleus accumbens being important in the expression of addictive behaviors, such as drug-seeking or behavioral sensitization, when considering the development of addiction, focus has been brought to glutamatergic afferents to dopamine neurons in the ventral tegmental area (VTA) (Pierce and Kalivas, 1997; Vezina, 2004). However, it is less clear which glutamatergic afferents to the VTA are critical for the development of addictive behaviors. Candidates include glutamatergic projections from the prefrontal cortex, bed nucleus of the stria terminalis and pedunculopontine region (Carr and Sesack, 2000; Charara et al., 1996; Georges and Aston-Jones, 2002).

Glutamate in the VTA in the development of addictive behaviors

The first indication that glutamate was involved in drug addiction emerged from the studies into the neurobiology of locomotor sensitization. The motor stimulant effects elicited by most addictive drugs generally augments with repeated drug administration, and this sensitized behavioral response can endure for months after the last repeated drug administration (Berridge and Robinson, 1998). While many investigators in the 1980's linked behavioral sensitization metaphorically to glutamatergic forms of neuroplasticity such as electrical kindling of epileptiform EEG and synaptic long-term potentiation (LTP) (Kalivas and Barnes, 1988; Post et al., 1987), the first explicit demonstration of glutamatergic involvement was the blockade of the development of behavioral sensitization by systemic administration of antagonists of the NMDA subtype of the iontotropic glutamate receptors (Karler et al., 1989). Shortly thereafter, this was shown to arise, at least in part, from an action of glutamate on NMDA receptors in the VTA (Kalivas and Alesdatter, 1993). Importantly, a parallel set of experiments found that stimulation of D1 dopamine receptors in the VTA was also necessary for sensitization to systemic psychostimulant administration (Vezina, 1996), and that direct or indirect stimulation of D1 receptors in the VTA was sufficient to elicit locomotor sensitization (Pierce et al., 1996b; Vezina, 1993). By the mid-1990's it was proposed that stimulation of D1 receptors was linked to the release of glutamate in the VTA as a necessary sequence of synaptic events to induce sensitization (Kalivas and Duffy, 1995), and in a recent study, evidence was provided using measurements of NMDA currents that D1 mediated increases in NMDA currents on dopamine neurons results from a direct postsynaptic action to increase surface expression of NMDA receptors (Schilstrom et al., 2006). These authors speculated that the rise in presynaptic glutamate release may result from increased activation of dopamine cells via the increase in NMDA receptors elevating the activity of prefrontal glutamatergic input to the VTA. In addition to psychostimulants, nicotine-induced sensitization has also been linked to glutamate release into the VTA, presumably the result of presynaptic nicotinic receptors on glutamatergic afferents (Grillner and Svensson, 2000). Also, electrical stimulation of glutamatergic input from the PFC was shown to induce sensitization, linking this afferent in particular to the development of sensitization (Schenk and Snow, 1994).

In parallel with these behavioral experiments, a variety of neurochemical and electrophysiological studies were identifying drug-induced changes in the VTA consistent with a role for enhanced glutamate transmission mediating the development of behavioral sensitization. For example, microdialysis revealed that psychostimulants release glutamate in the VTA (Kalivas and Duffy, 1998; Xue et al., 1996; You et al., 2007) and that levels of the AMPA receptor subunit GluR1 are elevated in the VTA in a transient manner by repeated cocaine administration (Churchill et al., 1999; Fitzgerald et al., 1996). More recently, the enhanced glutamate release was found to depend upon CRF receptor

stimulation (Wang et al., 2005). Finally, the capacity of AMPA receptor stimulation to stimulate dopamine cells in the VTA was also shown to be transiently augmented by repeated cocaine (White et al., 1995).

A significant advance in our understanding of the role glutamate in the VTA plays in the development of enduring behavioral changes by addictive drugs was made in 2001 when it was shown that a single systemic injection of cocaine produced glutamate-dependent LTP in VTA dopamine cells (Ungless et al., 2001). This basic finding has been replicated and shown to be relevant not only for behavioral sensitization but also for the development of drug self-administration (Jones and Bonci, 2005). Moreover, other neurotransmitters in the VTA, including CRF and orexin have recently been shown to regulate drug self-administration by modulating glutamatergic transmission in the VTA (Borgland et al., 2006; Ungless et al., 2003; Wang et al., 2005). Importantly, these interactions between orexin and CRF with VTA glutamate may be important not only for the initiation of addiction-related behaviors, but also may play a role in the expression of these behaviors (Harris et al., 2005; Wang et al., 2007).

Glutamate in the nucleus accumbens and the expression of addiction-related behaviors

A role for glutamate release into the nucleus accumbens in the expression of behavioral sensitization was first shown by blocking AMPA receptors in the nucleus accumbens (Pierce et al., 1996a). These authors also first brought focus to a potential preferential role of the core subcompartment of the nucleus accumbens in the expression of addiction-related behaviors by showing cocaine-induced release of glutamate in the core, but not the shell of animals expressing behavioral sensitization (Pierce et al., 1996a). With the advancing popularity of the reinstatement model of drug-seeking to study the expression of addiction-related behavior (Shaham et al., 2003), research on the role of glutamate in the accumbens largely moved into this addiction model by 2000. In this model, animals are trained to self-administer an addictive drug, and after extinguishing the drug context and/or placing the animal in a period of abstinence, the animal is returned to the drug context and the reinstatement of drug-seeking induced by a drug associated cue, stress or the drug itself in extinguished animals, or by the context in abstinent animals. Following up on the role of AMPA receptors in the expression of locomotor sensitization, it was shown that AMPA receptor blockade in the core, but not the shell also prevented reinstatement to a drug or cue prime (Cornish and Kalivas, 2000; Di Ciano and Everitt, 2001). Also in parallel with the sensitization studies, the reinstatement of cocaine-seeking was found to be associated with increased glutamate release into the core of the accumbens (McFarland et al., 2003). This basic finding has been extended to cocaine, cue, stress and heroin induced reinstatement (LaLumiere and Kalivas, 2008; McFarland et al., 2004). Based upon studies employing reversible pharmacological inactivation of different glutamatergic afferent to the accumbens, it was found that inhibition of the PFC afferents attenuated drug-seeking induced by cocaine, heroin, stress and cue (Capriles et al., 2003; LaLumiere and Kalivas, 2008; McFarland and Kalivas, 2001; McLaughlin and See, 2003), while inhibition of amygdala afferents blocked cue and heroin reinstatement (Di Ciano and Everitt, 2004; Kantak et al., 2002; Rogers et al., 2007).

A number of recent studies indicate that in addition to a requirement for enhanced glutamate transmission in the accumbens to express drug seeking or sensitization, there are a number of glutamate-related cellular adaptations produced by chronic psychostimulant administration. While electrophysiological studies using dissociated neurons indicated a reduction in AMPA-induced excitation after withdrawal from chronic cocaine, studies in vivo pointed towards augmented AMPA sensitivity (Kalivas and Hu, 2006). Initially, it was

shown that after chronic cocaine the capacity of AMPA microinjection into the accumbens to induce motor activity or reinstate drug seeking was augmented (Pierce et al., 1996a; Suto et al., 2004). Also, the whole cell levels and surface expression of GluR1 were elevated in the accumbens of sensitized rats (Boudreau and Wolf, 2005; Churchill et al., 1999). More recently this increase in surface GluR1 was shown to augment in parallel with the augmentation of drug seeking produced by placing animals in extended withdrawal (e.g. incubation of drug seeking) (Conrad et al., 2008). Finally, after withdrawal from cocaine, accumbens cells appear to be in an LTP-like state since the ratio of AMPA to NMDA currents is elevated (Kourrich et al., 2007), and the increased AMPA/NMDA ratio was also shown to augment in parallel with the surface of expression of GluR1 after extended cocaine withdrawal (Conrad et al., 2008). Moreover, the fact that the number of dendritic spines is increased in the accumbens of cocaine withdrawn animals is consistent with an LTP-like condition (Robinson and Kolb, 2004). However, it should be noted that after withdrawal from chronic opioids there is a reduction in spine density (Diana et al., 2006; Robinson and Kolb, 1999), which may indicate that spine morphology per se is not a consistent cellular phenotype of drug addiction.

While a variety of data suggest that the response to AMPA receptor stimulation is upregulated in accumbens neurons of cocaine withdrawn animals, the actual behavioral expression of sensitization and drug seeking may involve internalization of AMPA receptors (Brebner et al., 2005), and 24 hrs after expressing behavioral sensitization there is a reduction in both the AMPA/NMDA ratio and surface expression of GluR1 (Boudreau et al., 2007; Kourrich et al., 2007; Thomas et al., 2001). It seems likely that this internalization of GluR1 and induction of an LTD-like state by the cocaine challenge may arise at least in part from the large release of glutamate associated with the expression of addictive behaviors. Thus the LTP-like resting state of accumbens neurons in cocaine-withdrawn animals may undergo rapid synaptic grading in parallel with the behavioral response (Thomas et al., 2008). In apparent contrast to this interpretation, accumbens neurons appear resistant to the induction of LTD by field stimulation in slices made from animals previously trained to self-administer cocaine (Martin et al., 2006). According to current thinking about synaptic grading (Kauer and Malenka, 2007), the loss of LTD could arise from the neurons already being in an LTD-like state. More directly problematic for LTD playing a critical role in the expression of drug seeking or sensitization is a recent report demonstrating an upregulation in the surface expression of GluR1 during cocaine-induced drug seeking (Anderson et al., 2008). Rapid trafficking of GluR1 following cocaine-induced relapse is consistent with data showing that cocaine induced rapid cycling of actin binding proteins (Toda et al., 2006) and enlargement of spine head in accumbens spiny cells (H Shen and PW Kalivas, unpublished observation) within the first hour after cocaine administration in rats withdrawn from repeated cocaine.

Glutamate as a pharmacotherapeutic target: focus on indirect regulation of synaptic glutamate release in the accumbens

The apparent role of glutamate in regulating both the development and expression of addictive behaviors in animal models identifies glutamate as a potential pharmacotherapeutic target. Primary in this consideration would seem the role of glutamate in the nucleus accumbens in mediating the expression of addictive behaviors as this may be related to the vulnerability to relapse to drug taking that characterizes human addiction (Kalivas and Volkow, 2005). While it is possible to simply block AMPA receptors and prevent drug seeking, the likelihood of severe side-effects makes this approach untenable (Parsons et al., 2005). While allosteric regulators of AMPA receptors, partial agonists or viral or fusion protein reagents to regulate subunit composition remain a possibility, recent

studies with drugs designed to presynaptically regulate the release of glutamate have shown promise in both animal models and preliminary clinical trials. Glutamate release can be presynaptically inhibited by stimulating group II metabotropic glutamate (mGluR2/3) release regulating autoreceptors (Dietrich et al., 2002). Accordingly, both systemic and intra-accumbens administration of mGluR2/3 agonists inhibit drug seeking (Baptista et al., 2004; Kim et al., 2005; Peters and Kalivas, 2006). Alternatively, regulating nonsynaptic glial release of glutamate by stimulating cystine-glutamate exchange with N-acetylcysteine has been shown to indirectly stimulate mGluR2/3, reduce accumbens glutamate release and inhibit cocaine and heroin seeking (Baker et al., 2003; Madayag et al., 2007; Moran et al., 2005). Importantly, since both cocaine and nicotine self-administration have been shown to down-regulate the cystine-glutamate exchanger (Baker et al., 2003)(Knackstedt, Markou and Kalivas, unpublished observation), restoring activity of the exchanger is directly normalizing a drug induced pathology. Because N-acetylcysteine is currently used for a variety of clinical applications (Duijvestijn and Brand, 1999), it has been relatively easy to conduct preliminary clinical trials. Thus, N-acetylcysteine has been shown in preliminary double-blind studies to inhibit cocaine cue reactivity in cocaine addicts and to suppress pathological gambling (Grant et al., 2007; LaRowe et al., 2007). While these early findings need to be fortified with larger, outpatient clinical trials these early findings have identified a promising avenue for drug development based upon the role glutamate transmission plays in the expression of addictive behaviors.

Summary of glutamate transmission in the induction and expression of addiction- related behaviors

Glutamate plays a crucial role in regulating both the development and expression of addictive behaviors, such as sensitization and drug seeking. The development of addiction-related behaviors requires glutamate receptor stimulation in the VTA and is associated with enhanced glutamate release and transient LTP in dopamine cells. In contrast, the expression of sensitization and drug-seeking requires glutamate release into the core of the nucleus accumbens. The glutamate arises from both the prefrontal cortex and amygdala. The enhanced releasibility of glutamate is associated with augmented postsynaptic responsiveness of accumbens cells to AMPA receptor stimulation. However, the release of glutamate in response to a stimulus inducing drug seeking elicits rapid postsynaptic changes in proteins regulating glutamate signaling and surface spine morphology that culminates in an LTD-like condition.

An important consideration for future research in the role of glutamate and addiction is to study the transient neuroplasticity that is occurring during the expression of addiction-related behaviors. Thus, while current research has nicely documented the enduring basal changes present in the drug withdrawn animal, how this neuroplasticity alters the glutamatergic transmission during relapse or sensitization is only now being studied. For example, we know that there is a large release of presynaptic glutamate that is critical for the expression of addiction-related behavior (McFarland et al., 2003), and this apparently produces an LTD-like reduction in postsynaptic AMPA receptors that is necessary for the expression of the behavior (Brebner et al., 2005). Perhaps a new generation of pharmacotherapeutic agents will target these rapid changes in glutamate transmission that accompany the expression of addiction-related behavior. Indeed, the efforts using N-acetylcysteine or mGluR2/3 agonists to blunt the release of glutamate that is produced during drug-seeking described are examples of targeting the cellular pathology manifested during the expression of an addiction-related behavior.

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