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Glutamate homeostasis and dopamine signaling: implications for psychostimulant addiction behavior

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Abstract

Cocaine, amphetamine, and methamphetamine abuse disorders are serious worldwide health problems. To date, there are no FDA-approved medications for the treatment of these disorders. Elucidation of the biochemical underpinnings contributing to psychostimulant addiction is critical for the development of effective therapies. Excitatory signaling and glutamate homeostasis are well known pathophysiological substrates underlying addiction-related behaviors spanning multiple types of psychostimulants. To alleviate relapse behavior to psychostimulants, considerable interest has focused on GLT-1, the major glutamate transporter in the brain. While many brain regions are implicated in addiction behavior, this review focuses on two regions well known for their role in mediating the effects of cocaine and amphetamines, namely the nucleus accumbens (NAc) and the ventral tegmental area (VTA). In addition, because many investigators have utilized Cre-driver lines to selectively control gene expression in defined cell populations relevant for psychostimulant addiction, we discuss potential off-target effects of Cre-recombinase that should be considered in the design and interpretation of such experiments.

Keywords

Addiction; psychostimulants; glutamate; dopamine; nucleus accumbens; ventral tegmental area

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1. Introduction

Psychostimulants including amphetamine (AMP), methamphetamine (METH), and cocaine are highly addictive drugs. Abuse of these drugs represents a serious health problem that leads to organ damage including the heart, lungs, kidneys, and liver (Lineberry & Bostwick, 2006; Perino, Warren, & Levine, 1987) as well as central nervous system dysregulation (Bramness et al., 2012; Neiman, Haapaniemi, & Hillbom, 2000). While these drugs have medical uses, they exhibit a substantial potential for abuse (George F. Koob, 2006). This potential for abuse occurs in part via their reinforcing effects. Amphetamines and cocaine are reinforcers, that is, they induce rewarding/euphoric effects mediated primarily through activation of the mesocorticolimbic dopamine (DA) system, which increase the probability that they will be taken again (Pierce & Kumaresan, 2006). The ventral tegmental area (VTA) is the origin of DA cell bodies that comprise the mesocortical and mesolimbic circuits (Adinoff, 2004; Ikemoto, 2010). It is well known that a defining characteristic of cocaine and AMP-like psychostimulants is their high affinity for DA transporters (DAT) (Ritz, Lamb, Goldberg, & Kuhar, 1987; Seiden, Sabol, & Ricaurte, 1993) resulting in an increase in the quantity and half-life of synaptic and extrasynaptic DA concentrations (Wayment, Schenk, & Sorg, 2001; J. E. Williams, Wieczorek, Willner, & Kruk, 1995). Traditionally, DAT ligands have been divided into two categories: cocaine-like inhibitors and AMP-like substrates (Schmitt, Rothman, & Reith, 2013). Cocaine-like inhibitors block monoamine uptake but are not translocated across the cell membrane whereas AMP-like substrates are translocated into the cell and induce DAT-mediated release of DA via reversal of DAT (Schmitt et al., 2013).

It has long been known that cocaine acts by elevating extracellular levels of DA via inhibition of the DAT throughout the striatum (Carboni, Imperato, Perezzani, & Di Chiara, 1989; Di Chiara & Imperato, 1988; Giros, Jaber, Jones, Wightman, & Caron, 1996; Rice, Patel, & Cragg, 2011; Sulzer, 2011; Sulzer, Cragg, & Rice, 2016). However, recent work suggests that cocaine also acts independently of DAT to increase DA transmission within the striatum via increasing DA neuronal firing within the VTA which is consistent with the continued reinforcing properties of cocaine in self-administration and cocaine place preference paradigms in mice whereby the DAT gene has been deleted (Buck, Torregrossa, Logan, & Freyberg, 2020; Carboni et al., 2001; Di Chiara et al., 2004). In contrast to cocaine, AMP and METH competitively inhibit DA uptake (Han & Gu, 2006; R. B. Rothman & Baumann, 2003) and increase DA release via reverse transport (Eshleman, Henningsen, Neve, & Janowsky, 1994; J. F. Fischer & Cho, 1976; S. R. Jones, Gainetdinov, Jaber, et al., 1998; S. R. Jones, Gainetdinov, Wightman, & Caron, 1998; Sitte et al., 1998; Wall, Gu, & Rudnick, 1995). DAT is thought to comprise 12 transmembrane segments containing numerous phosphorylation sites in the intracellular domains (Giros & Caron, 1993; Granas, Ferrer, Loland, Javitch, & Gether, 2003; Lin et al., 2003). Reversal of DAT induced by AMP requires phosphorylation of one or more of the first 5 serines in DAT (Khoshbouei et al., 2004). In addition to targeting DAT, amphetamines and cocaine accumulate at acidic, intracellular sites by a “weak base effect” (Sulzer, 2011; Sulzer & Rayport, 1990). More specifically, amphetamines and cocaine are lipophilic weak bases (Beckett & Moffat, 1969; Mack & Bonisch, 1979) that perturb proton gradients in

intracellular compartments of DA neurons (Sulzer & Rayport, 1990) resulting in alkalization of vesicles leading to a reduction in the vesicular transmembrane pH gradient (Sulzer, 2011; Sulzer & Rayport, 1990). This reduction in the vesicular transmembrane pH gradient results in the release of DA from vesicles into the cytosol via an unknown mechanism and the release of cytosolic DA into the extracellular space via AMP-induced reversal of DAT (Freyberg et al., 2016). As discussed above, cocaine acts by blocking DAT which differs from AMP in that it does not result in increased extracellular levels of DA via reversal of DAT (Sulzer, 2011; Sulzer & Rayport, 1990). In addition to the accumulation of extracellular DA by blocking DAT, cocaine also results in increased extracellular levels of DA via increasing the firing of midbrain DA neurons (Koulchitsky, De Backer, Quertemont, Charlier, & Seutin, 2012; Sulzer, 2011). Although unexplored, it is potentially the case that the increases in intraneuronal DA induced by cocaine resulting from its “weak base effect” could result in extra DA availability to be released when the DA neurons fire in response to cocaine.

Research focusing on the neurobiology of drug addiction has traditionally focused on the mesocorticolimbic DA system (Pierce & Kumaresan, 2006; Volkow, Fowler, Wang, Swanson, & Telang, 2007; Wise, 2004). However, a growing body of literature has emerged indicating an important role for glutamate (GLU) in mediating the adaptive processes underlying psychostimulant addictions (Ernst & Chang, 2008; Kalivas, 2004; Szumlinski et al., 2017). Accumulating evidence over the years has indicated that disruptions in GLU homeostasis play a critical role (Kalivas, 2009). Additionally, reports over the past decade have shed light on the importance of GLU signaling by DA neurons in mediating responses to psychostimulants (Birgner et al., 2010; Hnasko et al., 2010; Hnasko & Edwards, 2012; Mingote et al., 2017). In contrast to traditional views that each neuron uses a single transmitter, these reports have demonstrated the coexistence of GLU and DA in individual neurons (Bourque & Trudeau, 2000; Dal Bo et al., 2004; Mendez et al., 2008; Stuber, Hnasko, Britt, Edwards, & Bonci, 2010; Sulzer et al., 1998). The main purpose of this review is to highlight literature demonstrating how GLU homeostasis is altered within the mesocorticolimbic DA system during the acute and chronic stages of psychostimulant addiction behaviors.

2. Regulation of Glutamate Homeostasis

2.1. Glutamate Release

GLU homeostasis involves the regulation of extracellular GLU levels in the synaptic and extrasynaptic spaces (Bezzi, Vesce, Panzarasa, & Volterra, 1999; Engeli et al., 2020; Schousboe, 1981; Takahashi et al., 1997). The sinks and sources involved in the regulation of GLU homeostasis are neuronal and glial GLU release and uptake mechanisms. A major source of extracellular GLU is nonvesicular release, as GLU levels are mostly insensitive to blocking voltage-dependent Na^+ and Ca^{2+} channels (Bradford, Young, & Crowder, 1987; Jabaudon et al., 1999; Miele, Boutelle, & Fillenz, 1996; Timmerman & Westerink, 1997). A major source of nonvesicular, extrasynaptic GLU is from the cystine-GLU exchanger (xCT) (Bannai, 1986; Murphy, Schnaar, & Coyle, 1990; Warr, Takahashi, & Attwell, 1999). xCT is plasma membrane bound, Na^+-independent, and primarily located on astrocytes

(Cho & Bannai, 1990; Danbolt, 2001; Murphy et al., 1990; Ottestad-Hansen et al., 2018; Pow, 2001). This antiporter exchanges one extracellular cystine for one intracellular GLU molecule (Bannai, 1986). Within the NAc a major source of basal GLU levels arises from xCT (Baker, Xi, Shen, Swanson, & Kalivas, 2002). As will be discussed more later, basal levels of GLU are altered by cocaine (Baker, Shen, & Kalivas, 2002), METH (Lominac, Sacramento, Szumlinski, & Kippin, 2012; Parsegian & See, 2014), and other drugs of abuse (Griffin, Haun, Hazelbaker, Ramachandra, & Becker, 2014). Additionally, chronic reductions in extracellular levels of basal GLU contribute to the development of postsynaptic adaptations (Conrad et al., 2008; Massie, Boillee, Hewett, Knackstedt, & Lewerenz, 2015). One example of this is highlighted in Section 6.3, whereby chronic cocaine administration results in chronic reductions of basal GLU levels within the NAc leading to enduring synaptic potentiation within the NAc core (Conrad et al., 2008).

In addition to xCT, Baker and colleagues determined that mGluR2/3 and Na^+-dependent GLU transporters also contribute to regulating extracellular GLU levels in the NAc (Baker, Xi, et al., 2002). They found that blocking Na^+-dependent GLU transporters results in an increase in extracellular levels of GLU within the NAc that is prevented by blocking xCT. mGluR2/3 belongs to the group II metabotropic receptor family; they are negatively coupled to adenylyl cyclase and normally inhibit GLU neurotransmission (Conn & Pin, 1997). Within the NAc, these receptors are primarily located presynaptically and on glial processes (Robbe, Alonso, Chaumont, Bockaert, & Manzoni, 2002). Pharmacological activation of mGluR2/3 in the NAc inhibits GLU synaptic transmission and alters both the paired pulse ratio as well as the frequency of mEPSCs, thus indicating a presynaptic mechanism by which mGluR2/3s alter release (Robbe et al., 2002). Baker and colleagues demonstrated that the extracellular GLU that arises from xCT binds to mGluR2/3 thus resulting in a decrease in synaptic GLU release (Baker, Xi, et al., 2002). Interestingly, they also demonstrated that mGluR2/3 regulates the release of DA, as had been shown in earlier studies (Hu, Duffy, Swanson, Ghasemzadeh, & Kalivas, 1999). Baker and colleagues determined that xCT was the source for providing endogenous GLU tone on mGluR2/3 that is capable of modulating synaptic activity (Baker, Xi, et al., 2002).

In addition to modulating activity at mGluR2/3, extracellular GLU released via xCT has also been shown to regulate GLU synapse strength by suppressing the number of postsynaptic AMPA receptors in CA3-CA1 synapses (Massie et al., 2015; L. E. Williams & Featherstone, 2014). Using a mouse line in which xCT had been deleted, Williams and Featherstone demonstrated increased EPSC amplitudes at baseline, increased electrically evoked EPCS amplitudes, and increased AMPA receptor accumulation within hippocampus areas C13-CA1(L. E. Williams & Featherstone, 2014). The authors found that this phenotype (increases in baseline and evoked EPSCs and accumulation of AMPA receptors) was reproduced in control mice in which xCT had not been deleted and that the baseline and evoked EPSCs were blocked following application of the AMPA receptor antagonist, NBQX (L. E. Williams & Featherstone, 2014). The authors concluded that xCT in hippocampal astrocytes releases GLU that could potentially trigger loss of postsynaptic AMPA receptors to suppress synapse strength (L. E. Williams & Featherstone, 2014). Taken together, this work demonstrates how GLU homeostasis plays a role in regulating synaptic activity.

2.2 Glutamate Uptake

In addition to GLU release by both synaptic and extrasynaptic sources, another mechanism by which GLU homeostasis is maintained is via its uptake from the extracellular space. Excess levels of extracellular GLU can lead to excitotoxicity (D. W. Choi, 1988; Lipton & Rosenberg, 1994; Meldrum & Garthwaite, 1990). GLU transporters expressed in both glial cells and neurons serve to maintain low extracellular levels of GLU by binding (Wadiche, Amara, & Kavanaugh, 1995) and removing (Danbolt, Storm-Mathisen, & Kanner, 1992; Divac, Fonnum, & Storm-Mathisen, 1977; Levy, Lehre, Rolstad, & Danbolt, 1993; Schousboe, 1981; Storm-Mathisen & Iversen, 1979; Wilkin, Garthwaite, & Balazs, 1982) free GLU from the extracellular space. The removal of GLU from the extracellular space occurs via a family of five Na^+-dependent GLU transporters (EAAT1/GLAST, EAAT2/GLT-1, EAAC1, EAAT4, and EAAT5). GLAST is found predominantly in astrocytes, EAAT3 in neurons, EAAT4 in cerebellar Purkinje cells, and EAAT5 is expressed throughout the retina (Danbolt, 2001). GLT-1 is the major GLU transporter in the CNS representing 1% of total brain protein (Lehre & Danbolt, 1998) and is responsible for >90% of synaptosomal GLU uptake (Danbolt, 2001; Petr et al., 2015; Tanaka et al., 1997). GLT-1 is primarily expressed in astrocytes (Rothstein et al., 1994) but also in neurons (Chen et al., 2004; Petr et al., 2015). In the hippocampus, area CA1, neuronal GLT-1 protein expression represents 5–10% of total GLT-1 expression (Furness et al., 2008). GLT-1 is also expressed in neurons within the human cortex (Melone, Bellesi, Ducati, Iacoangeli, & Conti, 2011), rat somatic sensory cortex (Melone, Bellesi, & Conti, 2009), and rat striatum (Petr et al., 2013). Pan knockout of GLT-1, or conditional knockout of GLT-1 restricted to astrocytes results in intractable seizures and premature death (Petr et al., 2015; Tanaka et al., 1997).

As outlined in Table 1, there are two areas of study that have highlighted an important role for GLU homeostasis in addiction behaviors; one involves the acute setting after the initial administration of psychostimulants as exemplified by the work of Wolf and colleagues (Wolf, Xue, Li, & Wavak, 2000) and others (Del Arco, Martinez, & Mora, 1998) and the second is the late post withdrawal symptoms exemplified by the work of Kalivas and colleagues (Kalivas, Lalumiere, Knackstedt, & Shen, 2009; Knackstedt, Melendez, & Kalivas, 2010). As will be discussed more thoroughly in this review, GLT-1 has long been implicated in psychostimulant addiction [see (Reissner & Kalivas, 2010) for review]. Although it has been assumed that the role GLT-1 plays in drug-seeking is due to its location on astrocytes, studies investigating the role of GLT-1 in drug-seeking behaviors were done before the appreciation that GLT-1 is expressed in neurons, with few exceptions (K. D. Fischer et al., 2018; Xu et al., 2003). Thus, there has been no rigorous examination of the role of GLT-1 in neurons in addiction behavior.

3. Pitfalls of Cre/lox technology

Transgenic rodent models utilizing Cre-recombinase driver lines are frequently used to provide genetic access to particular cell populations in the brain (Lammel et al., 2015; Song & Palmiter, 2018). Many reports have used Cre-drivers to target genes expressed in midbrain DA neurons that coexpress other neurotransmitters including GLU (Hnasko et al., 2010; Hnasko & Edwards, 2012; Mingote et al., 2017; Papathanou et al., 2018; Stuber et al., 2010;

Wang et al., 2017) and GABA (J. I. Kim et al., 2015; Ntamati & Luscher, 2016; Tritsch, Oh, Gu, & Sabatini, 2014). These studies are generally focused on identifying roles for signaling by these “secondary” transmitters in addiction-related behaviors (Birgner et al., 2010; Hnasko et al., 2010; Hnasko & Edwards, 2012; J. I. Kim et al., 2015; Mingote et al., 2017; Papathanou et al., 2018). Two of the most commonly used Cre-lines drive expression under the tyrosine hydroxylase promoter (TH-Cre; (Lindeberg et al., 2004; Savitt, Jang, Mu, Dawson, & Dawson, 2005) or the DAT promotor (DAT-Cre; (Backman et al., 2006; Zhuang, Masson, Gingrich, Rayport, & Hen, 2005). The Cre-lox method has greatly impacted the field allowing for the understanding of gene functions whose global knockout might otherwise result in lethality (Song & Palmiter, 2018). However, while Cre-recombinase provides control over gene expression, there are limitations that need to be considered when both Cre-recombinase and loxP sites are expressed in animals that will be bred (Song & Palmiter, 2018).

One consideration is that there may be unexpected Cre-recombinase expression in the germline or in the animal during development, referred to as ‘ectopic’ expression (Luo et al., 2020; Rempe et al., 2006; Song & Palmiter, 2018). An example of ectopic Cre-recombinase expression was reported by Lammel and colleagues who showed that TH-Cre expressing mice exhibited profound transgene expression in non-DA neurons (e.g. TH-immunonegative neurons) (Lammel et al., 2015). An example of germline expression of Cre-recombinase was reported by Rempe and colleagues who found germline expression of synapsin-Cre in males related to physiological expression of synapsin 1 in the testes (Rempe et al., 2006). Expression of synapsin 1 in the testes necessitates use of females only for introduction of synapsin 1-Cre into conditional mouse lines. These reports exemplify the need for testing for ectopic or germline expression of Cre-recombinase (K. D. Fischer et al., 2018; Rempe et al., 2006).

The second consideration involves the oversimplification inherent in using single Cre-recombinase driver lines to study neurocircuitry and behavior (Stuber, Stamatakis, & Kantak, 2015). Many reports have demonstrated that midbrain DA neurons are associated with multiple modalities of neurotransmission (Aguilar et al., 2017; Papathanou et al., 2018; Stuber et al., 2010; Tecuapetla et al., 2010; Tritsch, Ding, & Sabatini, 2012). For example, 20% of VTA TH-expressing neurons coexpress a marker for GLU neurons, VGLUT2 (Hnasko et al., 2010; Hnasko & Edwards, 2012; Kawano et al., 2006; X. Li, Qi, Yamaguchi, Wang, & Morales, 2013; Mendez et al., 2008; Root et al., 2014; Yamaguchi, Wang, Li, Ng, & Morales, 2011). Optogenetic experiments have shown that stimulation of DA fibers results in the release of DA, GLU and GABA in striatal subregions (Stuber et al., 2010; Tecuapetla et al., 2010; Tritsch et al., 2012). Additionally, Root and colleagues found that the TH-expressing lateral habenula DA fibers that project to the VTA release both GLU and GABA (Root et al., 2014). These results indicate that single DA, GLU, and GABA related gene markers such as TH, DAT, VGLUT2, or GAD65/67 do not fully define the molecular phenotypes of midbrain DA cell subpopulations (Stuber et al., 2015).

The third consideration involves the potential for Cre-recombinase in itself to induce effects by off-target, “non-specific” actions that may or may not be defined, thus complicating interpretations of the role(s) that a particular gene may play in the phenomenon under

investigation (Giusti et al., 2014). One important off target effect is Cre-induced cell toxicity. Cre-recombinase insertion into the genome can result in growth arrest, chromosomal abnormalities, and cell death both in cultured cells and in whole animals (Janbandhu, Moik, & Fassler, 2014; Loonstra et al., 2001; Thanos et al., 2012). In addition. there is the potential for expression of Cre-recombinase in different cells and circuits to produce changes in cell physiology that results in non-lethal biochemical, cellular, electrophysiological, and behavioral alterations that have nothing to do with modulation of expression of the target gene. Giusti and colleagues demonstrated the importance of running relevant experimental groups to control for potential Cre-mediated behavioral effects (Giusti et al., 2014), and this caution applies to all experiments involving the use of Cre-recombinase. One of the most extensively used Cre mouse lines in psychiatric research, referred to as the Nestin^{Cre} mouse (Tronche et al., 1999) was found to have altered fear conditioning due to the expression of Cre-recombinase per se. Others utilizing this Cre-driver, reported behavioral abnormalities, including diminished fear learning, but these studies used “floxed” mice as their control groups (no Cre) and did not include a control for Cre itself (Gao et al., 2010; Suzuki, Ferris, Chee, Maratos-Flier, & Kahn, 2013). Thus, as pointed out by (Giusti et al., 2014), it was not clear whether the induced mutation in the Nestin^{Cre} mouse or Cre expression itself was responsible for the diminished fear learning response.

Given the problems inherent in using Cre/lox technology, an important question is how best to design an experiment relying on this approach to target genes for inactivation. Most important is the need to recognize that there are problems, and that appropriate controls need to be included in such experiments. One approach is for all groups to express the floxed allele(s) and for the test group to express Cre-recombinase under the appropriate promoter. Subsequently, if there is an effect of Cre expression, then a second experiment needs to be performed testing the effect of Cre-recombinase itself on a wild type background. The results of the first experiment are uninterpretable without the second experiment. An alternative approach is to design experiments in which all mice express the Cre-recombinase, and for the test mice to have the floxed allele(s). Any effect in this case would be related to modification of the floxed allele(s) and not the expression of Cre-recombinase per se. Obviously additional experiments would need to be done to be sure that the presence of the floxed allele(s) were not responsible for the effects observed. This approach of having all groups express Cre-recombinase would seem to eliminate the problem of confusing Cre-related effects for target specific effects. However, it is also important to note that the physiology of mice expressing Cre is not necessarily the same as the physiology of mice not expressing Cre (Gewin, 2019). Therefore, it is conceivable that effects that appear that are target specific but might occur only on a background of Cre-recombinase expression.

In summary, Cre/lox technology is a critically important approach for determining the role of specific proteins expressed in specific cells in neural circuits (Deisseroth, 2014; Yizhar, Fenno, Davidson, Mogri, & Deisseroth, 2011). However, the aforementioned considerations are crucial for the design and interpretation of any studies involving the expression of Cre-recombinase in mammalian cells.

4. Glutamate Signaling by Dopamine Neurons

Evidence demonstrating the release of GLU by midbrain DA neurons was obtained initially in microcultures of isolated VTA neurons (Bourque & Trudeau, 2000; Sulzer et al., 1998). Consistent with the use of GLU as a neurotransmitter in DA neurons was the discovery that VGLUT2 is coexpressed with TH and VMAT2 in DA neurons of adult rodents (Dal Bo et al., 2004; Hnasko et al., 2010; Mendez et al., 2008; Silm et al., 2019). In addition to mice and rats, the coexpression of VGLUT2/TH has been identified within the VTA of non-human primates and humans (Root et al., 2016). The primary question currently is what is the biochemical, cellular, and behavioral significance of GLU co-transmission in DA neurons? Using a VTA-NAc slice preparation, Chuhma and colleagues demonstrated that direct stimulation of VTA DA neurons elicits a monosynaptic EPSC in NAc shell medium spiny neurons (Chuhma, Choi, Mingote, & Rayport, 2009; Chuhma et al., 2004). Using this same preparation, Hnasko and colleagues demonstrated that conditional deletion of VGLUT2 from DA neurons by expression of Cre-recombinase under the influence of the DA transporter promoter (datVGLUT2 KO) results in reduced EPSC amplitude in NAc shell neurons in response to VTA stimulation suggesting that dual GLU-DA neurons in the VTA form excitatory synapses in the NAc (Hnasko et al., 2010). They also found reduced DA tissue content and electrically evoked DA release in the NAc shell of datVGLUT2 KO mice. These findings were explained by the phenomenon of vesicular synergy whereby the transport of GLU into presynaptic vesicles by VGLUT2 facilitates the loading of DA into the same vesicles (Hnasko & Edwards, 2012; Trudeau et al., 2014). It was recently shown in both a *Drosophila* and mouse model that DA vesicles hyperacidify in response to neuronal depolarization and that GLU transport across VGLUT2 into the synaptic vesicle is necessary to potentiate the depolarization-induced changes in pH (Aguilar et al., 2017). Furthermore, Stuber and colleagues utilized the datVGLUT2 KO combined with optogenetics to selectively stimulate DA terminals while recording postsynaptic currents in NAc medium spiny neurons (Stuber et al., 2010). They found that VGLUT2 in DA neurons is required for GLU release in NAc shell DA terminals of adult mice. While co-release has been detected from VTA DA terminals in the shell, it was not detected in dorsal striatal DA terminals (Stuber et al., 2010). It was recently shown that while DA neurons within the SNc that project to the medial dorsal striatum do not coexpress GLU, SNc DA neurons that project to the lateral dorsal striatum and to the tail of the striatum coexpress GLU (Cai & Ford, 2018; Chuhma et al., 2018; Poulin et al., 2018). Thus, within the striatum, GLU corelease from DA neurons appears to be highly regionally specific.

An important concern to address is the impact that DAT-Cre driven conditional knockout of VGLUT2 could have on the development of DA neurons. Fortin and colleagues found that the abrogation of GLU transmission in the DAT-Cre driven conditional knockout of VGLUT2 results in impairment of DA neuron survival and axonal arborization in vitro, and compromises DA neuron development resulting in a 20% decrease in DA neuron number (Fortin et al., 2012). These findings by Fortin and colleagues (Fortin et al., 2012) as well as by others discussed above (Fortin et al., 2012; Hnasko et al., 2010; Stuber et al., 2010) utilized the DAT-Cre mouse developed by Zhuang and colleagues (JAX Stock No: 020080) that express Cre-recombinase through the 5’UTR, immediately upstream

of the DAT translation start codon (Zhuang et al., 2005). The control groups by which comparisons were made to the datVGLUT2 KO mice in these reports were all DAT-Cre expressing. A problem with the 5' untranslated region (UTR) knockin approach is that it disrupts one copy of the DAT gene, and DAT heterozygous KO mice show decreases in DAT protein expression, D1/D2 receptor mRNA and protein expression and a decrease in DA and TH levels (Backman et al., 2006; Beeler et al., 2020; Giros et al., 1996; S.R. Jones, Gainetdinov, Jaber, et al., 1998). In addition to targeting the 5'UTR of the DAT gene, another DAT-Cre mouse model was developed by Backman (JAX Stock No: 006660) whereby the Cre gene insertion is preceded by an internal ribosomal entry site (IRES) in the 3'UTR of the DAT gene (Backman et al., 2006). Compared to targeting the 5'UTR of the DAT gene, DA transmission and mRNA levels of D1/D2 receptors are significantly less affected by targeting the 3'UTR (Backman et al., 2006). However, recently it was shown that DAT protein expression was downregulated and DA release dynamics were altered in the DAT-Ires-Cre mouse (Beeler et al., 2020). Evoked DA release assessed via fast-scan cyclic voltammetry showed decreased clearance and increased peak amplitude (Beeler et al., 2020). Although DA receptor loss or DA cell loss was not found in the DAT-IRES-Cre mouse (Backman et al., 2006; Steinkellner et al., 2018), it is important to note that the altered DA release dynamics associated with this mutation may complicate the interpretation of behavioral or molecular results derived from lines created by using this Cre-driver. As discussed, utilizing the proper Cre control groups whereby comparisons are made with groups that also express Cre-recombinase could alleviate this concern.

While evidence indicates that VGLUT2 is expressed more broadly in DA neurons during development, it is important to note that VGLUT2 expression is downregulated *in vivo* over the course of development (Berube-Carriere et al., 2009; Mendez et al., 2008). Though downregulated in the adult, coexpression of VGLUT2 and DA markers in the adult mouse is most pronounced in the medial VTA (Hnasko, Hjelmstad, Fields, & Edwards, 2012; Mendez et al., 2008; Steinkellner et al., 2018; Yamaguchi, Qi, Wang, Zhang, & Morales, 2015). Because it is these medial VTA DA neurons that are generally spared in Parkinson's Disease (PD) animal models (Berthet et al., 2014; Damier, Hirsch, Agid, & Graybiel, 1999; Hirsch, Graybiel, & Agid, 1988; Jackson-Lewis, Jakowec, Burke, & Przedborski, 1995; Schneider, Yuwiler, & Markham, 1987), Steinkellner wanted to determine the relationship between VGLUT2 expression and vulnerability to DA neuron degeneration (Steinkellner et al., 2018). They reported that VGLUT2 coexpression in adult SNc and VTA DA neurons is low but that the vast majority of these DA neurons expressed VGLUT2 during development (Steinkellner et al., 2018). Interestingly, compared to DAT-Cre expressing control mice, conditional VGLUT2 KO mice driven by the DAT-Ires-Cre promoter were found to have disrupted GLU transmission in DA neurons in the adult conditional VGLUT2 KO observed via a lack of optogenetic-evoked EPSCs in striatal MSNs (Steinkellner et al., 2018). Thus, in contrast to what was originally reported by Stuber and colleagues (Stuber et al., 2010), VGLUT2 expression in SNc DA neurons appears to be important for GLU corelease (Steinkellner et al., 2018). Furthermore, VGLUT2 coexpression specifically within SNc DA neurons reemerges in adult mice following DA neuron insult (6-OHDA or MPTP lesions) and deletion of VGLUT2 from DA neurons resulted in increased susceptibility of SNc DA neurons to Parkinsonian-related injuries such as 6-OHDA and MPTP lesions (Steinkellner et

al., 2018). Similarly, over-expression of VGLUT2 from DA neurons induced a Parkinsonian-related phenotype including death of SNc DA neurons and increased rotational behavior (Steinkellner et al., 2018). This group also investigated whether other neuronal populations were affected by over-expression of VGLUT2 and found that GABA neurons in the VTA, GLU neurons in the subthalamic nucleus, striatal cholinergic interneurons, and serotonin neurons in the dorsal raphe were spared (Steinkellner et al., 2018). These data suggest that the homeostatic balance of VGLUT2 levels in SNc DA neurons is a crucial determinant of SNc DA neuron survival and that either too high or too low VGLTU2 levels in SNc DA neurons may contribute to a Parkinsonian-phenotype (Steinkellner et al., 2018).

Mingote and colleagues took an alternate approach to investigating a role for GLU signaling in DA neurons by downregulating GLU signaling from DA neurons using GLU as a neurotransmitter (Mingote et al., 2017). They targeted phosphate-activated glutaminase (PAG; GLS1) in DA neurons with the idea that they would be reducing presynaptic GLU content modestly without having an effect on DA neuron vesicular dynamics or DA neuron development (Mingote et al., 2017). The majority of presynaptic GLU arises from the actions of PAG; once presynaptic GLU is release, it is taken up by neighboring astrocytes and converted to glutamine and then transferred back to the presynaptic terminal where it is converted back to GLU by PAG (Marx, Billups, & Billups, 2015; Mingote et al., 2017). Mingote and colleagues created a DAT-Ires-Cre-driven conditional HET GLS1 mouse (cHET) in order to determine whether GLU cotransmission in DA neurons was altered compared to DAT-Cre expressing control mice (Mingote et al., 2017). Since heterozygous reduction in GLS1 is sufficient to attenuate GLU transmission (Gaisler-Salomon et al., 2009), and in order to minimize compensatory mechanisms observed in the homozygous GLS1 KO mice (Bae, Wang, Li, Rayport, & Lubec, 2013), Mingote and colleagues used DAT GLS1 (cHET) mice and DAT-Ires-Cre mice as controls (Mingote et al., 2017). They measured DA neuron GLU cotransmission within the NAc shell utilizing single pulse photostimulation and burst photostimulation (thought to mimic in vivo phasic firing of DA neurons) (Paladini & Roeper, 2014) in DA nerve terminals (Mingote et al., 2017). Compared to DAT-Cre control mice, the frequency of single-evoked EPSCs in the NAc shell was decreased in cHET mice while the amplitude of EPSCs did not differ between genotypes (Mingote et al., 2017). Interestingly, DA neuron control of NAc shell cholinergic interneurons was attenuated in cHET mice which was quantified using the firing ratio defined as the firing frequency during train photostimulation divided by the preceding 2 s of baseline firing (Mingote et al., 2017). While they found no genotype differences in baseline firing frequencies, the firing ratio of NAc shell cholinergic interneurons was significantly reduced in cHET mice (Mingote et al., 2017). While they showed greater burst firing in DAT-Cre controls compared to cHETs, there was no difference in the post-burst period (Mingote et al., 2017). The authors concluded that PAG plays a role in mediating DA neuron GLU cotransmission at higher firing frequencies and controls their ability to drive NAc shell cholinergic interneurons to fire in bursts (Mingote et al., 2017). Finally, the authors wanted to determine whether DA transmission was altered in the cHET mice. They performed fast-scan cyclic voltammetry within the NAc shell of cHET and DAT-Cre control mice and found no differences in DA release (Mingote et al., 2017). The decay time constant of DA responses did not differ between genotypes following single or burst photostimulation

(Mingote et al., 2017). Thus, conditional GLS1 reduction does not appear to affect DA release within the NAc shell. Importantly, these authors also noted behavioral effects of this genetic manipulation that will be discussed in Section 5.5.

All of the gene targeting studies mentioned above that utilized promoters of both VGLUT2 and DAT genes have embryonic onset and thus suffer from the uncertainty that any of the phenotypes observed might be due to developmental circuitry adaptations to the knockout (Papathanou et al., 2018). Additionally, the apparent age-dependent decrease in VGLUT2 expression within VTA DA neurons make it challenging to dissociate a role for VGLUT2 in mature DA neurons from developmental compensatory adaptations (Papathanou et al., 2018). Papathanou and colleagues conducted a thorough series of experiments to address the role of VGLUT2 in fully matured DA neurons by utilizing a tamoxifen-inducible DAT-Cre transgene (DAT-CreERT2) (Engblom et al., 2008; Papathanou et al., 2018). This allowed them to fully control for the temporal aspects of DAT-Cre recombination (Papathanou et al., 2018). They compared the biochemical and behavioral phenotypes of two separate VGLUT2 mouse lines whereby VGLUT2 was deleted either during development that contained embryonal onset of the transgene or in mature DA neurons with a tamoxifen inducible DAT-Cre (Papathanou et al., 2018). The two DAT-Cre drivers that were used in this study were: 1 – DAT-Cre transgenic mouse line with embryonal onset of the transgene (Ekstrand et al., 2007) abbreviated ‘eDAT-Cre’ and 2 – Tamoxifen-inducible DAT-CreERT2 mice (Engblom et al., 2008) abbreviated ‘txDAT-Cre’. To achieve selective gene deletion in DA neurons, the Cre construct was based on a bacterial artificial chromosome harboring the DAT gene at the 5’UTR locus (Ekstrand et al., 2007). The advantage of this approach is that the endogenous DAT gene is not compromised (Papathanou et al., 2018; Parlato, Rieker, Turiault, Tronche, & Schutz, 2006) although it is still possible that the expression of DAT and other DA related genes might be affected. Similar to what they and others had shown with embryonic targeting of VGLUT2 (Wang et al., 2017), light-evoked EPCSs were significantly dampened in the txDAT-Cre VGLUT2 KO mouse thus confirming that GLU transmission is reduced when VGLUT2 is targeted in mature DA neurons (Papathanou et al., 2018). This group further analyzed the effects of cocaine on EPCS in these lines and these results will be discussed in more detail below in Section 5.5. Furthermore, in the following sections we will discuss how GLU signaling by DA neurons plays a role in the underlying adaptations associated with psychostimulant administration and addiction behaviors (Birgner et al., 2010; Fortin et al., 2012; Hnasko et al., 2010; Mingote et al., 2017; Paladini, Fiorillo, Morikawa, & Williams, 2001; Papathanou et al., 2018; Underhill et al., 2014; Ungless, Whistler, Malenka, & Bonci, 2001).

5. Psychostimulant-Induced Alterations in Excitatory Signaling and Glutamate Homeostasis

5.1. Acute AMP-induced Alterations of Excitatory Signaling

Acute administration of cocaine and AMP-related psychostimulants results in alterations in excitatory transmission and in GLU homeostasis (Adrover, Shin, & Alvarez, 2014; S. Jones & Kauer, 1999; M. H. Li et al., 2017; Padgett et al., 2012; Paladini et al., 2001; Schilstrom et al., 2006; Uchimura & North, 1991; Underhill et al., 2014; Ungless et al., 2001). Using

whole-cell patch-clamp recordings in VTA DA neurons, Jones and Kauer demonstrated that acute AMP administration results in an immediate depression of excitatory signaling in DA neurons by an unknown mechanism (S. Jones & Kauer, 1999). Paladini and colleagues conducted a thorough set of experiments to determine in what way acute AMP alters excitatory transmission. The authors proposed that AMP alters excitatory signaling in VTA DA neurons via two ways: 1 – inhibition of excitatory signaling via AMP-stimulated DA release and activating D2 autoreceptors on midbrain DA neurons (as had been previously reported) (Groves, Wilson, Young, & Rebec, 1975; Mercuri, Calabresi, & Bernardi, 1989), and 2 – excitation by desensitizing the mGluR-mediated hyperpolarization induced by AMP (Paladini et al., 2001). More specifically, they performed intracellular recordings of VTA DA neurons and found that with repetitive stimulation, the first 3–4 stimuli resulted in AMPA- and NMDA-mediated EPSPs (Paladini et al., 2001). After the first few stimuli, the membrane potential hyperpolarized (assessed via an increase in IPSPs) and this hyperpolarization resulted from mGluR1 activation (Paladini et al., 2001). Superinfusion of AMP in these DA cells attenuated the mGluR1-mediated hyperpolarization. Interestingly, the mechanism underlying the AMP-induced inhibition of IPSPs was found to involve activation α1 adrenergic receptors on VTA DA neurons, presumably via AMP-stimulated DA release (Paladini et al., 2001). Activation of these α1 receptors was found to suppress the release of Ca^{2+} by activation of mGluR1 or by intracellular application of inositol 1,4,5-triphosphate ($InsP_3$) (Paladini et al., 2001). Production of $InsP_3$ mediates the release of Ca^{2+} by mGluRs (Morikawa, Imani, Khodakhah, & Williams, 2000). To summarize, Paladini and colleagues propose that the AMP-induced inhibition of mGluR1 IPSPs involves the release of DA stimulated by AMP, DA-mediated activation of α1 receptors on VTA DA neurons, and inhibition of $InsP_3$-mediated Ca^{2+} release from internal stores (Paladini et al., 2001).

5.2 Acute AMP-induced Alterations of Glutamate Homeostasis

Since changes in excitatory transmission have been demonstrated following AMP then one might speculate that changes in GLU homeostasis, if they occur, might be important. Using in vivo microdialysis, Xue and colleagues demonstrated that acute AMP i.p. resulted in a delayed increase in GLU efflux in VTA and NAc (Xue, Ng, Li, & Wolf, 1996). However, this same group later reported that when AMP was administered directly into the VTA, there was an immediate decrease in VTA GLU efflux followed by a delayed increase in VTA GLU efflux (Wolf & Xue, 1998). The immediate decrease in VTA GLU accumulation reported by Wolf and colleagues is in agreement with Jones and Kauer's finding that acute AMP attenuates GLU synaptic transmission (S. Jones & Kauer, 1999). Furthermore, Xue and colleagues reported that the delayed increase in extracellular GLU becomes significant at ~3 hrs post-AMP injection and is not Ca^{2+}-dependent (Xue et al., 1996) suggesting that synaptic release is not responsible. Rather, they speculated that the delayed nature of AMP-stimulated GLU release involved inhibition of GLU transporters, allowing build up of GLU from other sources, or reversal of GLU transporters, recognizing that GLU transporters themselves might be the source (Wolf et al., 2000). In fact, they found that the sustained increase in AMP-induced GLU release was blocked by the GLT-1 specific inhibitor DHK (Wolf et al., 2000). This result argues for reversal of transport being the underlying mechanism of the AMP-induced increase in GLU release. In Figure 1, we have

depicted potential signaling pathways implicated in producing reversal of GLU transport following AMP administration.

The delayed nature of AMP-stimulated GLU release found by Wolf and Xue (Wolf & Xue, 1999) suggests that the rise in extracellular GLU is not responsible for the acute locomotor activating effects induced by AMP. In support of this conclusion, these authors reported that while ibotenic lesions of the PFC and administration of either a NMDA or D1 receptor antagonist blocked the delayed increase in AMP-induced GLU efflux, only the D1 receptor antagonist blocked AMP-stimulated locomotor activation (Wolf & Xue, 1999), suggesting a disconnect between the delayed increase in VTA GLU efflux and the increased locomotor activation induced by acute AMP, and also that the increase in locomotion was dependent upon D1R activation. Interestingly, all three of these treatments that were found to block the increase in the delayed AMP-stimulated GLU efflux prevented the development of sensitization suggesting an important role for repeated increases in AMP-stimulated GLU efflux within VTA in mediating longer term addiction behaviors. This is discussed in more detail in Section 6.2.

Because GLU is released by DA neurons, it is a reasonable assumption that DA neurons contain the machinery to remove GLU from the extracellular space. EAAT3 is one of five GLU transporter subtypes and is primarily expressed in neurons (Danbolt, 2001; Holmseth et al., 2012; Rothstein et al., 1994). Underhill and colleagues demonstrated that EAAT3 is coexpressed with DAT in VTA DA neurons that project to NAc (Underhill et al., 2014). They also found that uptake of AMP by DAT induces internalization of EAAT3; using acute brain slices they demonstrated that cocaine, which blocks the function of DAT, blocks the AMP-mediated endocytosis of EAAT3. More recently, they found that AMP is also transported by NET and DAT located in noradrenergic neurons and induces endocytosis of both NET and EAAT3 (Underhill, Colt, & Amara, 2020) thus suggesting that this phenomenon is not specific for DA neurons. Furthermore, Underhill et al. assessed the effects of AMP on evoked GLU synaptic currents (eEPSCs) in DA neurons within the VTA and substantia nigra (M. H. Li et al., 2017; Underhill et al., 2014). They found that acute AMP administration potentiates NMDA-mediated synaptic currents and decreases AMPA/NMDAR ratios (M. H. Li et al., 2017). Inhibition of the NMDA-GluN2B receptor subunit inhibits the potentiation induced by AMP (M. H. Li et al., 2017) thus indicating that NMDAR-GluN2B are activated by AMP. Additionally, inhibition of EAAT3 also blocks the NMDAR potentiation suggesting that the potentiation requires the transport of AMP into the cell by DAT (M. H. Li et al., 2017). A similar effect on GLU transmission in the midbrain has been observed with METH which is discussed in Section 5.6.

5.3. Acute Cocaine-induced Alterations of Excitatory Signaling

Umara and colleagues demonstrated that a single in vivo exposure to cocaine results in long-term potentiation of AMPA-receptor mediated currents at excitatory synapses onto VTA DA neurons (Ungless et al., 2001). Interestingly, when the GluA1 subunit of the AMPA receptor is deleted from VTA DA neurons, the cocaine-induced increase in EPSCs is abolished (Engblom et al., 2008). These results are in line with others showing that acute cocaine exposure results in the insertion of GluA2-lacking AMPA receptors onto VTA DA

neurons (Bellone & Luscher, 2006). In addition to enhancing signaling at GluA2-lacking AMPA receptors, acute cocaine exposure increases NMDA receptor function in the VTA that is mediated by DA D_5-like receptors leading to the insertion of NR2B-containing NMDARs in the membrane (Schilstrom et al., 2006).

Regarding cocaine-induced adaptations on excitatory signaling within the accumbens, following repeated exposure to cocaine, there is an increase in the amplitude of AMPAR-mediated EPSCs due to an increased insertion of GluA2 lacking (calcium permeable) AMPA receptors into NAc shell D1-expressing MSNs (Engblom et al., 2008; Mameli et al., 2009; Pascoli, Turiault, & Luscher, 2011). In summary, acute cocaine exposure induces a plasticity in both VTA DA neurons and NAc MSNs that is expressed by insertion of GluA2-lacking AMPA receptors and within the VTA induced through enhanced NMDA receptor signaling.

5.4. Acute Cocaine-induced Alterations of Glutamate Homeostasis

Acute cocaine administration was shown to increase extracellular levels of GLU within the VTA 20 mins after injection and this increase in GLU occurred in parallel with the increase in locomotor activity (Kalivas & Duffy, 1995). This effect of cocaine is in contrast with AMP-induced increases in extracellular levels of VTA GLU which does not occur over the same time course as the increase in locomotor activity (Wolf & Xue, 1999). However, similar to what has been observed with AMP, the D1 antagonist SCH-23390 blocked the increase in extracellular levels of VTA GLU induced by cocaine and delayed the increase in locomotor activation suggesting an important role for D1R-mediated GLU accumulation in the VTA. Whether the acute cocaine-induced increases in VTA GLU accumulation arise from synaptic or non-synaptic sources is unknown. It is conceivable that the GLU accumulation following acute cocaine exposure arises from reversal of GLU transport. It is known that D1 and D2 receptor activation inhibits activity of the sodium potassium ATP pump (Na/K-ATPase) (Bertorello, Hopfield, Aperia, & Greengard, 1990). The Na/K-ATPase resides on neurons and astrocytes and is responsible for maintaining ion gradients that underlie resting and action potentials in neurons (Bertorello et al., 1990; Larsen, Stoica, & MacAulay, 2016; Skou, 1965). One proposed mechanism by which exposure to both cocaine and AMP would result in increased accumulation of extracellular GLU is DA receptor-induced inhibition of the Na/K-ATPase leading to disruption of ion gradients necessary for the inward transport of GLU by GLU transporters (Bertorello et al., 1990; Pierce, Bell, Duffy, & Kalivas, 1996; Wolf et al., 2000).

Regarding the effects of acute cocaine on extracellular levels of GLU within the accumbens, in vivo microdialysis reports have shown that cocaine administration results in a dose dependent increase in extracellular levels of NAc GLU that is Ca^{2+}-dependent and coincides with the time course of behavioral activation (Smith, Mo, Guo, Kunko, & Robinson, 1995). The coinciding time course of cocaine-induced increases in locomotor activation and extracellular levels of VTA and NAc GLU are in contrast with the effects observed with AMP, whereby the increase in extracellular levels of GLU is observed 90 ins post-AMP injection, well after the increase in locomotor stimulation (Wolf & Xue, 1999). Furthermore, it is known that intra-NAc infusions of GLU agonists result in an increase in both locomotor activity and extracellular accumulation of DA within the NAc (Donzanti & Uretsky, 1983;

Wu, Brudzynski, & Mogenson, 1993; Youngren, Daly, & Moghaddam, 1993) and that the increase in locomotor activity induced by GLU agonists is abolished when the mesolimbic DA projections are abolished via 6-OHDA lesions of the VTA (Wu et al., 1993). Thus, the acute behavioral activation induced by cocaine likely arises from GLU-stimulated DA accumulation within the NAc.

5.5 Importance of Co-Transmission in Responses to AMP and Cocaine

In light of reports demonstrating the release of GLU from DA terminals, and that VGLUT2 is expressed in DA terminals and facilitates DA signaling by DA neurons, Birgner and colleagues predicted that the absence of VGLUT2 would disrupt behavioral responses mediated by AMP (Birgner et al., 2010). They found that datVGLUT2 KO mice, utilizing the DAT-Cre driver that targets the 5'UTR of the DAT gene (Zhuang et al., 2005), displayed a blunted acute locomotor response to AMP. In order to rule out an effect of DAT-Cre in itself, this group also compared AMP-evoked locomotor responses in DAT-Cre expressing and DAT-Cre lacking mice and found no differences (Birgner et al., 2010). Thus, it is unlikely that the blunted locomotor response to AMP was due to DAT-Cre expression in itself.

As discussed above, Mingote and colleagues targeted PAG in DA neurons, creating a DAT-driven conditional HET GLS1, utilizing the DAT-Cre driver that targets the 3'UTR of the DAT gene (Backman et al., 2006) and found that while the acute locomotor response to AMP was intact in the conditional PAG knockout mouse, locomotor sensitization to AMP was diminished (Mingote et al., 2017). Recently, DAT-Ires-Cre expressing mice were reported to show a blunted acute locomotor response to AMP (Chohan, Esses, Haft, Ahmari, & Veenstra-VanderWeele, 2020). This result potentially confounds interpretations of behavioral data reported using this specific Cre-driver. However, Mingote and colleagues took the approach of comparing groups of mice that all expressed DAT-Cre thus diminishing the problem of confusing Cre-related effects for target specific effects (discussed in Section 3). These reports could be interpreted as 1 - DA signaling by DA/GLU coexpressing neurons determine the acute locomotor responses to AMP (Birgner et al., 2010) and 2 - GLU signaling by DA/GLU coexpressing neurons via GLS1 determines the sensitization but not the acute locomotor response to AMP (Mingote et al., 2017). Collectively, these interpretations are consistent a previously mentioned report showing 1 - the temporal disconnect between the acute locomotor response to AMP and the increase in VTA GLU efflux, 2 - the acute locomotor response to AMP is blocked by a D1 receptor antagonist, and 3 - sensitization is blocked by interventions that prevent the elevation of extracellular glutamate in the VTA (Wolf & Xue, 1999).

A role for GLU signaling in VTA DA neurons in mediating the biochemical and locomotor effects induced by cocaine has been investigated. Although GLU transmission from VTA DA neurons onto medium spiny neurons represents a small percentage of all GLU inputs onto these cells (Adrover et al., 2014), some reports have indicated that these inputs are able to regulate the physiological response to cocaine. Hnasko and colleagues utilized a datVGLUT2 KO mouse, targeting the 5' UTR of the DAT gene (Zhuang et al., 2005), and demonstrated a reduced acute locomotor response to cocaine (20 mg/kg; ip) (Hnasko et al.,

2010) which as discussed above was similarly observed with AMP (Birgner et al., 2010). However, it is important to note that sensitization and the conditioned place preference response to cocaine were unaltered and self-administration was actually enhanced in the datVGLUT2 KO (Alsio et al., 2011; Hnasko et al., 2010). Note that the control mice used in these experiments for comparison to the datVGLUT2 KO mice were DAT-Cre expressing mice. Furthermore, if VGLUT2 expression in DA neurons is important for the loading of DA into vesicles (Hnasko et al., 2010; Hnasko & Edwards, 2012) then one possible explanation for the enhanced cocaine SA in the datVGLUT2 KO is reduced extracellular DA concentrations in response to cocaine due to impaired packaging of DA in synaptic vesicles (Ikemoto, Yang, & Tan, 2015; Wang et al., 2017). Thus, in the datVGLUT2 KO, animals may have to work harder (e.g. increased lever pressing) to achieve a similar reinforcing effect of the drug.

As discussed above in Section 4, these VGLUT2 conditional KO models suffer from potential developmental compensatory adaptations, as VGLUT2 is knocked out during development (Alsio et al., 2011; Birgner et al., 2010; Hnasko et al., 2010). Papathanou and colleagues utilized the eDAT-Cre (Ekstrand et al., 2007) and txDAT-Cre (Engblom et al., 2008) VGLUT2 KO mouse lines discussed above in Section 4 to pinpoint the role of the VGLUT2 gene in mature DA neurons (Papathanou et al., 2018). Note that the Cre control mice utilized for this study were DAT-Cre transgenic mice with embryonal onset of the transgene (eDAT-Cre) (Ekstrand et al., 2007) and txCtrl mice (tamoxifen treated control mice without VGLUT2 gene deletion) (Papathanou et al., 2018). The eDAT-Cre VGLU2 KO mice exhibited a blunted acute locomotor response to AMP (Papathanou et al., 2018), as was expected due similar findings discussed above by Birgner and colleagues that utilized a similar DAT-Cre VGLUT2 mouse with embryonic onset of DAT-Cre-recombinase through the 5’UTR, immediately upstream of the DAT translation start codon (Birgner et al., 2010; Zhuang et al., 2005). An additional finding by Papathanou and colleagues that was not assessed by Birgner and colleagues is that the eDAT-Cre VGLUT2 KO mice showed a blunted sensitized response to AMP (Papathanou et al., 2018). Furthermore, Papathanou and colleagues also assessed acute and sensitized locomotor responses to cocaine in the eDAT-Cre VGLUT2 KO and found there were no overall differences between the KO and eDAT-Cre control mice apart from the last day of cocaine administration whereby the eDAT-Cre VGLUT2 KO mice displayed higher locomotor activation than controls (Papathanou et al., 2018). The finding that eDAT-Cre KO mice and WT controls displayed similar acute responses to cocaine and that the KO mice showed enhanced sensitized locomotor responses to cocaine is in contrast with Hnasko and colleagues report that showed a blunted acute response and no differences in the sensitized locomotor responses to cocaine in the VGLUT2 KO mice (Hnasko et al., 2010). While the DAT-Cre drivers utilized in these reports are similar, it is important to note that the DAT-Cre driver utilized by Birgner and Hnasko is a 5’UTR knock-in (Birgner et al., 2010; Hnasko et al., 2010; Zhuang et al., 2005) whereas the DAT-Cre driver utilized by Papathanou and colleagues is a 5’UTR transgenic (Ekstrand et al., 2007; Papathanou et al., 2018). Thus, the discrepancy in the locomotor response to cocaine between these two reports by Hnasko and Papathanou could be due to different genetic backgrounds between the DAT-Cre mouse lines. Moreover, deletion of VGLUT2 in mature DA neurons did not affect the acute or sensitized response to AMP

or cocaine, as both txCtrl and txDAT-Cre mice displayed similar increases in acute and sensitized locomotor responses (Papathanou et al., 2018). These findings demonstrate that the temporal onset of VGLUT2 targeting in DA neurons determines the addiction-related phenotype. Finally, because repeated exposure to cocaine induces adaptations in synaptic transmission onto D1-receptor MSNs within the NAc shell (discussed in Section 5.3) (Engblom et al., 2008; Mameli et al., 2009; Pascoli et al., 2011), Papathanou and colleagues wanted to determine if GLU release from mature DA neurons affected synaptic plasticity specifically in NAc D1-receptor expressing MSNs (Papathanou et al., 2018). They found that compared to txCtrol mice, the AMPA/NMDA ratio was greatly increased in D1-receptor expressing MSNs in the txDAT-Cre VGLUT2 KO at baseline (Papathanou et al., 2018). Thus, with deletion of VGLUT2 in mature DA neurons, mice show normal sensitization responses to AMP and cocaine while also showing a decrease in NAc GLU transmission (decrease in EPSCs) and an elevated AMPA/NMDA ratio. The authors concluded that the elevated AMPA/NMDA ratio at baseline observed in the txDAT-Cre VGLUT2 KO was strong enough to block the enhanced synaptic plasticity effect induced by cocaine (Papathanou et al., 2018). These data suggest that even though VGLUT2 is down-regulated in DA neurons in adulthood, VGLUT2 in mature DA neurons nonetheless plays a critical role in regulating GLU transmission as well as synaptic plasticity in NAc MSNs.

As discussed earlier, the neuronal GLU transporter EAAT3 has been shown to colocalize with DAT in VTA DA neurons that project to NAc, and AMP administration results in internalization of this EAAT3 (Underhill et al., 2014). Although unexplored, a potential role for GLT-1 in DA neurons should be considered. The effects of AMP on extracellular GLU release are thought to be due to reversal of GLT-1 (Wolf et al., 2000; Xue et al., 1996). As is discussed in Section 7, GLT-1 has been identified as the major GLU transporter associated with excitatory terminals (Berger, DeSilva, Chen, & Rosenberg, 2005; Chen et al., 2004; Furness et al., 2008). It is conceivable that DA neurons that coexpress GLU also contain GLT-1 as a component of the excitatory transmission phenotype in these neurons, perhaps to assist in removing GLU from the extracellular space or for a metabolic role (McNair et al., 2019; McNair et al., 2020a). Careful investigation of the possibility that GLT-1 is localized in some or all DA neurons will aid in our understanding of its potential contributions to signaling by these neurons and role in mediating the effects of psychostimulants and other drugs of abuse (Xu et al., 2003).

5.6. Acute METH-induced Alterations on Excitatory Signaling

Similar to acute AMP administration, acute METH administration has been shown to decrease inhibitory signaling and enhance excitatory signaling (M. H. Li et al., 2017; Padgett et al., 2012). Padgett and colleagues found that acute METH results in a reduction in the inhibitory presynaptic $GABA_BR$ currents in VTA DA neurons (Padgett et al., 2012). Furthermore, Li and colleagues demonstrated that similar to acute AMP, acute administration of METH potentiates GLU neurotransmission in midbrain DA neurons via increasing NMDA-GluN2B-mediated synaptic currents and decreasing AMPA/NMDAR ratios (M. H. Li et al., 2017). Inhibition of EAAT3 also blocks the NMDAR potentiation suggesting that the potentiation requires the transport of METH into the cell by DAT (M. H. Li et al., 2017). Altogether, these reports indicate that both AMP and METH potentiate GLU

transmission in midbrain DA neurons through internalization of EAAT3 and subsequent activation of GluN2B-containing NMDARs (M. H. Li et al., 2017; Underhill et al., 2014). Li and colleagues postulated that internalization of EAAT3 in DA neurons by amphetamines could result in 1 - increased extracellular levels of GLU in the synapse and subsequent spillover to GLU receptors or alternatively, 2 - decreased GLU uptake by EAAT3 outside the synapse could potentiate GLU receptor activation (M. H. Li et al., 2017).

5.7. Acute METH-induced Alterations of Glutamate Homeostasis

While the effects of acute METH administration on extracellular levels of GLU within the VTA are unknown, as discussed above and postulated by Li and colleagues, it is conceivable that METH-induced internalization of EAAT3 in midbrain VTA DA neurons results in increased extracellular levels of GLU (M. H. Li et al., 2017). Furthermore, similar to AMP, acute METH administration results in a delayed (~2 h post METH injection) and sustained increase in extracellular NAc GLU accumulation (K. Ito, Abekawa, & Koyama, 2006). Similar to AMP, the delayed increase in extracellular GLU accumulation induced by METH is blocked by the NMDA antagonist MK-801 (K. Ito et al., 2006). Similar to both AMP and cocaine, the delayed increase in extracellular GLU accumulation induced by METH is blocked by the D1 antagonist SCH-23390 (K. Ito et al., 2006). Additionally, and consistent with the reports mentioned above on acute AMP and cocaine administration, only the D1 antagonist was found to block the acute locomotor response induced by METH (K. Ito et al., 2006).

Acute METH administration has also been shown to increase extracellular levels of GLU within the dorsal striatum (Mark, Soghomonian, & Yamamoto, 2004; Stephans & Yamamoto, 1994). However, acutely, this effect that METH has on dorsal striatal GLU levels has only been shown following a single day of binge METH treatment (10 mg/kg given 4 times i.p. at 2 h intervals) (Halpin, Northrop, & Yamamoto, 2014; Mark et al., 2004; Pu, Broening, & Vorhees, 1996; Simoes et al., 2008; Stephans & Yamamoto, 1994). The majority of reports that have assessed METH-induced alterations in dorsal striatal GLU levels have utilized binge METH treatment paradigms in order to assess effects on DA terminal depletion (which occurs at higher, more toxic doses of METH) as well as on striatal inflammatory responses (Halpin et al., 2014; Mark et al., 2004; Pereira et al., 2006; Pu et al., 1996; Stephans & Yamamoto, 1994). This is discussed more below in Section 6.4. As discussed above, a single, low dose of METH (2.5 mg/kg) and AMP (5.0 mg/kg) results in an increase in extracellular GLU levels within the ventral striatum (NAc) (K. Ito et al., 2006; Xue et al., 1996). This raises the question whether a single, lower dose of METH alters extracellular levels of dorsal striatal GLU levels.

6. Chronic Administration of Psychostimulants

6.1. Modeling Drug Addiction Behavior

The validity of an animal model in representing a human disorder is established by demonstrating face, predictive, and construct validity (Spanagel, 2017). Face validity is based on the presence of characteristic behavioral features that are seen both in laboratory animals and in humans. Construct validity is based on identity of underlying biological

mechanisms in the animal model and in humans (Sarter, 2002). Finally, predictive validity is assessed by success in discovering drugs that are useful in human patients based on performance in the animal model and is arguably the most relevant test of validity for developing potential therapeutics (Haney, 2009). An example of an animal model that has been proposed to be relevant for the understanding of relapse in human drug addicts is chronic exposure to psychostimulants and withdrawal. In this model, following a prolonged withdrawal period, exposure to drug associated stimuli usually results in reinstatement of self-administration, which appears to be due to a disruption in GLU homeostasis within the mesocorticolimbic circuit (Kalivas, 2009).

Models of drug addiction behavior can be broken down into contingent and non-contingent paradigms (Kuhn, Kalivas, & Bobadilla, 2019). A contingent model refers to the animal having to perform a task (i.e. lever press or nose poke) in order to receive the reward (i.e. cocaine) (Kuhn et al., 2019). The reinstatement model of drug self-administration behavior is arguably the most valid contingent animal model for studying addiction and manifests excellent face, predictive, and construct validity (for review see (Spanagel, 2017). The drug reinstatement model is widely used as a model of relapse in human addicts (Bossert, Marchant, Calu, & Shaham, 2013; Kalivas & McFarland, 2003). In this paradigm, animals are first trained to self-administer cocaine by pressing a lever or nose poking for an *iv* drug infusion in an operant conditioning chamber (David, Polis, McDonald, & Gold, 2001; Kalivas & McFarland, 2003). After this behavior is well learned, the animal is then placed in extinction training where the learned behavior becomes abolished (e.g. lever pressing does not result in delivery of the drug) or through a forced withdrawal period whereby the animal is left in the home cage without access to the drug (Spanagel, 2017). Following extinction training or withdrawal, the animals are re-exposed to a priming stimulus: the cue previously paired with the drug, a stressor, or the drug itself (reinstatement). Exposure to a drug-paired cue, exposure to a stressor, and re-exposure to the previously self-administered drug have all been demonstrated to result in reinstatement in rats (Ahmed & Koob, 1997; Childress et al., 1993; Kufahl & Olive, 2011; McFarland & Kalivas, 2001; Taslimi, Komaki, Haghparast, & Sarihi, 2018; Weiss et al., 2000). Two commonly used models based on non-contingent drug exposure are the conditioned place preference (CPP) and behavioral sensitization paradigms. CPP has been proposed as an alternative to drug self-administration for studying drug-seeking behavior (Spanagel, 2017). In this paradigm, animals are injected daily with the drug paired with a distinguishable compartment in a conditioning box while a second compartment is paired with a vehicle injection; animals will achieve drug-CPP, i.e. spending more time in the compartment paired with drug, after several days of conditioning (Spanagel, 2017). The CPP model can also be utilized to study drug-primed reinstatement after a period of extinction training whereby the drug-paired chamber is paired with a vehicle injection. While some investigators claim that CPP is a model of drug-seeking behavior, CPP is dependent entirely on Pavlovian associations. Therefore, CPP in itself cannot account for the instrumental nature of drug-seeking/drug-taking behavior that is perhaps bettered modeled by drug self-administration (Belin-Rauscent A, 2012). Furthermore, the repeated administration of psychostimulants leads to augmented behavioral effects, termed behavioral sensitization. This phenomenon is well characterized in both experimental animals and humans (Kalivas & Stewart, 1991; T. E. Robinson, 1984, 2010)

Sensitization of locomotor activity has been proposed as a model of addiction in humans (T. E. Robinson & Becker, 1986; T. E. Robinson & Berridge, 1993). That sensitization affects addiction behavior is illustrated by studies in which rats that develop locomotor sensitization in response to psychostimulants will subsequently work harder for the drug during self-administration than naïve animals (Lorrain, Arnold, & Vezina, 2000). Non-contingent models such as CPP and behavioral sensitization are easy to run and quick to set up and because of these advantages many investigators have used them to identify how drug exposure alters key reward-related neurobiological substrates (Kuhn et al., 2019). However, it is important to also understand the limitations of these non-contingent models (Kuhn et al., 2019).

6.2. AMP: Alterations in Glutamate Homeostasis Following Chronic Administration

A majority of the reports on the chronic effects of AMP on extracellular levels of GLU have used experimenter administered AMP sensitization paradigms. As mentioned above, acute systemic injection of AMP as well as intra-VTA administration of AMP or D1 agonists results in a delayed and sustained increase in VTA GLU levels (Wei et al., 2016). AMP sensitization can be produced by either repeated systemic or repeated intra-VTA infusions of AMP (Cador, Bjijou, & Stinus, 1995; Kalivas & Weber, 1988; Perugini & Vezina, 1994; Vezina & Stewart, 1990; Wolf, White, & Hu, 1994). The delayed increase in extracellular levels of GLU within the VTA also occurs in sensitized rats [e.g. rats treated with AMP (5 mg/kg) for 5 d and challenged 2 d following a withdrawal period with AMP] (Wolf et al., 2000; Xue et al., 1996). The magnitude of the increase in extracellular levels of GLU within the VTA is the same in acute and chronic AMP treated animals and occurs after each injection in a chronic AMP regimen (Wolf et al., 2000; Xue et al., 1996). Additionally, this increase in VTA GLU following chronic AMP treatment can be produced by intra-VTA infusion of AMPA (Giorgetti, Hotsenpiller, Ward, Teppen, & Wolf, 2001) and is attenuated following intra-VTA infusion with the D1 receptor antagonist SCH-23390 (Wolf & Xue, 1998) thus suggesting a causal role for AMPA and D1 receptor activation involvement in the delayed increase in AMP-induced GLU release in the VTA. Thus, both the acute and chronic effects of AMP on extracellular levels of VTA GLU are blocked by D1 receptor antagonists.

The critical question is whether or not the delayed increase in GLU is required for the induction of sensitization. Evidence for a role for elevated extracellular GLU is that intra-VTA infusions of AMP produce sensitization (Cador et al., 1995; Kalivas & Weber, 1988; Perugini & Vezina, 1994; Vezina & Stewart, 1990) and result in the delayed, long-lasting increase in VTA extracellular GLU (Wolf & Xue, 1998). Both sensitization (Bjijou, Stinus, Le Moal, & Cador, 1996; Stewart & Vezina, 1989; Vezina, 1996) and the increase in VTA GLU are blocked by intra-VTA infusion of D1 receptor antagonists (Wolf & Xue, 1998). However, a lower dose of AMP (2.5 mg/kg) is sufficient to induce sensitization but does not result in a delayed increase in extracellular VTA GLU (Xue et al., 1996). Xue and colleagues argue that 2.5 mg/kg AMP could induce small increases in GLU efflux that are not detectable by microdialysis due to efficiency of GLU clearance mechanisms (Xue et al., 1996). Additional evidence that VTA GLU efflux is required for the development of behavioral sensitization is that other treatments that prevent the AMP-induced increase in VTA GLU also prevent the induction to AMP sensitization. Alongside treatment with AMP,

treatment with PBN, an agent that blocks the formation of hydroxyl free radicals, blocks both the delayed increase in VTA GLU and the development of sensitization (Wolf et al., 2000). The exact mechanism underlying how PBN prevents the AMP-induced increases in extracellular GLU levels is not known however it is known that PBN also attenuates METH-induced toxicity of DA terminals (Cappon, Broening, Pu, Morford, & Vorhees, 1996). Thus, PBN is acting in some way to reduce increases in GLU levels and DA terminal damage associated with AMP/METH administration. Moreover, administration of the NMDA antagonist, MK-801, as well as ibotenic acid lesions of the PFC, prevent AMP from increasing VTA GLU efflux and also prevent sensitization (Wolf & Xue, 1999). One important question is, why does blocking NMDA receptors with MK-801 prevent AMP-stimulated GLU accumulation? One possible mechanism is that the increase in extracellular DA levels induced by AMP results in D1 receptor activation that evokes glutamate release by inhibition of the Na+/K+ -ATPase, or some other mechanism (see Section 5.4), which results in a disruption of ion gradients necessary for the inward transport of GLU by GLU transporters (Bertorello et al., 1990; Pierce et al., 1996; Wolf et al., 2000). In Fig. 1, we propose a mechanism underlying the GLU-mediated inhibition of the Na+/K+ -ATPase following AMP administration. In brief, AMP results in increased extracellular levels of VTA DA via reversal of DAT. DA released by DAT reversal stimulates DA receptors on VTA astrocytes (Liu et al., 2009; Zhang et al., 2009) resulting in increases in intracellular levels of Ca^{2+} that then causes the release of arachidonic acid (AA) from the phospholipid membrane (S. P. Lee et al., 2004). The release of AA results in increased levels of reactive oxygen species (ROS) (Chan, Chen, & Yu, 1988; Chan & Fishman, 1980; Sakuma et al., 2012). Both AA and ROS inhibit the Na+/K+ -ATPase (Chan, Kerlan, & Fishman, 1983; Hexum & Fried, 1979; Volterra, Trotti, Tromba, Floridi, & Racagni, 1994) that ultimately leads to a depolarization of the cell membrane and disruption of the Na+/K+ gradients that results in the reversal of EAATs in general and GLT-1 in particular (Anderson, Huguenard, & Prince, 2010; Nicholls & Attwell, 1990; Volterra et al., 1994). Increased levels of extracellular GLU in VTA can activate NMDARs located on the astrocyte resulting in further increases in intracellular Ca^{2+} and AA and sustained reversal of GLT-1 (Biber et al., 1999; Daniels & Brown, 2001; Lalo, Pankratov, Kirchhoff, North, & Verkhratsky, 2006; M. C. Lee et al., 2010). Thus, the increase in AMP-mediated GLU accumulation could activate NMDA receptors in a feed-forward manner to increase extracellular GLU accumulation further (Wolf & Xue, 1999). Collectively, these data strongly support a direct and necessary role for VTA GLU efflux in the induction of behavioral sensitization.

Repeated intra-VTA, but not intra-NAc, injections of AMP produce enhanced locomotor responses to subsequent systemic administration of AMP (Kalivas & Weber, 1988) suggesting an important role for the VTA but not the NAc in the induction of sensitization. The NAc is referred to as the brain region responsible for the expression of sensitization (Kalivas & Weber, 1988; Paulson & Robinson, 1991). Following induction of AMP sensitization, injection of AMP into the NAc enhances locomotor responses to AMP during expression (Paulson & Robinson, 1991) suggesting that the NAc is important in the expression of sensitization. In line with this, there is a delayed and sustained increase in extracellular levels of NAc GLU in rats pretreated with AMP (5 mg/kg) for 5 d and challenged 2 d following a withdrawal period with AMP (Xue et al., 1996). Moreover,

intra-VTA infusions of the non-NMDA receptor GLU agonist AMPA increased extracellular levels of NAc GLU in rats 3 d after the last day of AMP injections. Additionally, intra-VTA preadministration of the competitive GLU reuptake inhibitor, PDC (Bridges, Stanley, Anderson, Cotman, & Chamberlin, 1991), produces sensitization to a systemic AMP challenge (Aked, Coizet, Clark, & Overton, 2005). Collectively, these data suggest that alterations in GLU homeostasis, specifically increases in extracellular GLU within the VTA, are necessary and sufficient for the induction of sensitization. Alterations in GLU homeostasis within the NAc are associated with the expression of sensitization, but a causal relationship has not been demonstrated, unlike for VTA. Potentiation of AMPA receptor signaling in the VTA has been shown to occur following repeated AMP administration and appears to be important for the induction of AMP sensitization (Argilli, Sibley, Malenka, England, & Bonci, 2008; Giorgetti et al., 2001). A major question, then, is the mechanistic relationship between the alteration in GLU homeostasis and the potentiation of AMPA receptor signaling in the VTA that occurs following AMP administration.

Similar to cocaine and METH addictions (discussed below), treatment strategies for reducing the rewarding effects of AMP have focused on targeting GLU homeostasis. As outlined in Table 2, targeting GLT-1 has demonstrated promising results in preclinical animal models. If increases in NAc GLU efflux are responsible for the expression of AMP sensitization, one might expect that reducing the levels of extracellular GLU in this region would attenuate this process. One class of drugs known to increase GLT-1 expression in injured brain, or to prevent downregulation of expression with injury is β-lactam antibiotics (Jagadapillai, Mellen, Sachleben, & Gozal, 2014; Lipski et al., 2007; Miller et al., 2008; Rothstein et al., 2005). Of these, ceftriaxone is the most widely studied for its ability to attenuate relapse and sensitization behavior related to many classes of drugs of abuse (Roberts-Wolfe & Kalivas, 2015; Smaga, Fierro, Mesa, Filip, & Knackstedt, 2020). Repeated administration of ceftriaxone induces a reduction in extracellular levels of GLU within the NAc in healthy control rodents (Rasmussen, Unterwald, & Rawls, 2011). Treatment with ceftriaxone has been shown to attenuate AMP sensitization behavior in rats (Rasmussen et al., 2011). Riluzole, a neuroprotective drug currently marketed for the treatment of amyotropic lateral sclerosis, is another compound that increases GLT-1 protein expression measured via western blot (Carbone, Duty, & Rattray, 2012). Riluzole has demonstrated efficacy in attenuating AMP conditioned place preference in rats, a model of drug-seeking behavior (Tzschentke & Schmidt, 1998). However, this preclinical study with Riluzole was not supported in human studies whereby the subjective reporting of craving by human patients was not reduced following Riluzole treatment (Sofuoglu, Waters, Mooney, & Kosten, 2008). Importantly, there were several limitations discussed in the report by Sofuoglu and colleagues. These limitations included: 1 - a lack of examining the dose-effect relationship for Riluzole’s effects on d-AMP responses, 2 - a lack of examining d-AMP plasma levels in human patients, and 3 - their sample consisted of healthy volunteers and thus the generalizability of these findings to stimulant users would need to be determined in future studies (Sofuoglu et al., 2008).

6.3. Cocaine: Alterations in Glutamate Homeostasis Following Chronic Administration

A defining characteristic of cocaine addiction is repeated cycles of drug use followed by abstinence (Spencer & Kalivas, 2017). Prevention of craving and relapse has been a continuing focus in the study of cocaine abuse. Many reports have demonstrated that chronic cocaine administration, whether it is self-administered by the animal itself or experimenter administered, alters extracellular levels of GLU within the NAc (Baker, Shen, et al., 2002; Pierce et al., 1996; Schmidt, Anderson, Famous, Kumaresan, & Pierce, 2005). It is important to note that the NAc comprises two subregions, core and shell, which have differential functionality in cocaine-seeking behavior (Ambroggi, Ghazizadeh, Nicola, & Fields, 2011; Everitt & Robbins, 2005; R. Ito & Hayen, 2011; McFarland & Kalivas, 2001). Within the core, basal non-synaptic (TTX-independent) GLU levels are decreased following a history of cocaine self-administration (assessed before reinstatement testing that followed extinction training) (McFarland, Lapish, & Kalivas, 2003) and following experimenter administered cocaine for 7 days followed by a 3-week withdrawal period (Baker, Shen, et al., 2002; Pierce et al., 1996). When cocaine is self-administered or experimenter administered followed by extinction training or a forced withdrawal period (3 weeks in withdrawal length), there is a significant increase in extracellular synaptic (TTX-dependent) levels of GLU in NAc core (but not NAc shell) (McFarland et al., 2003; Pierce et al., 1996). The PFC-NAc core GLU projection has been found to play a role in both the relapse response and the increases in extracellular levels of NAc GLU (McFarland et al., 2003). However, it is important to note that PFC outputs to the NAc are not homogeneously distributed. The prelimbic region of the PFC sends GLU output selectively to the NAc core whereas the ventral PFC (infralimbic PFC) sends GLU output to the NAc shell (Vertes, 2004). Specifically, it has been shown that pharmacological inhibition of the prelimbic PFC projection to the core attenuates both relapse behavior and the rise in extracellular GLU (McFarland et al., 2003) whereas relapse behavior is unaffected by inactivation of the PFC (infralimbic) projection to shell (Capriles, Rodaros, Sorge, & Stewart, 2003). Furthermore, the decrease in non-synaptic levels of NAc core extracellular GLU that is observed 3 weeks following chronic cocaine exposure results from decreased expression and activity of xCT (Baker, McFarland, Lake, Shen, Toda, et al., 2003; Knackstedt et al., 2010) the GLU antiporter that is a major source of extrasynaptic GLU in the NAc (Baker, Xi, et al., 2002). Chronic cocaine administration also alters the regulation of GLU transmission by mGluR2/3 in the core. Following withdrawal from chronic cocaine, there is a decreased mGluR2/3-mediated inhibition of AMPA-mediated EPSCs (Moussawi et al., 2009) and decreased surface expression of mGlu2 in the core (Logan et al., 2020). The increase in extracellular synaptic NAc core GLU levels associated with relapse following withdrawal periods is thought to result from decreased capacity of mGluR2/3 to regulate the presynaptic release of GLU (Xi et al., 2002) as well as decreased expression and function of GLT-1 (Knackstedt et al., 2010). Collectively, these reports demonstrate that chronic cocaine administration reduces the basal extracellular level of non-synaptic NAc GLU and the capacity of mGluR2/3 and GLT-1 to regulate the synaptic release of NAc GLU in response to a cocaine challenge or relapse session.

The animal model of cocaine self-administration and reinstatement has been altered over the past 20 years to more accurately reflect human drug consumption patterns. The majority of cocaine self-administration reports have utilized extinction/reinstatement models in

animals exposed to limited-access conditions (~2 h/day in the self-administration chamber). However, increasing access during drug self-administration to 6 h/day and introducing long withdrawal periods (3 weeks or longer) induce behavioral and morphological alterations that more adequately capture key features of human addiction (Ahmed, 2012; Ahmed & Koob, 1998; Ferrario et al., 2005; K. D. Fischer, Houston, & Rebec, 2013). Extending access during self-administration to >6 h/d elicits behaviors that more closely mimic human compulsive drug seeking. Introducing long withdrawal periods following drug self-administration results in an increase in drug relapse behavior in animal models, referred to as the incubation of cocaine craving (Conrad et al., 2008; Grimm, Hope, Wise, & Shaham, 2001; Lu, Grimm, Hope, & Shaham, 2004; Zavala, Biswas, Harlan, & Neisewander, 2007). This effect is associated with increases in GluA2 lacking AMPA receptors in the NAc (Conrad et al., 2008) thus implicating GLU signaling within the NAc in relapse (but also see (See, Elliott, & Feltenstein, 2007)). Interestingly, it was determined that increasing access during cocaine self-administration from 2 to 6 h/d results in a greater NAc core and shell GLT-1 down-regulation and that introducing long withdrawal periods from 1 to 45 d results in greater GLT-1 down-regulation in the core (Fischer-Smith, Houston, & Rebec, 2012). However, these cocaine self-administration and withdrawal parameters that result in downregulation of GLT-1 expression are not accompanied by greater decreases in basal non-synaptic GLU or greater increases in synaptic GLU release during a reinstatement test (Lutgen et al., 2014). Nonetheless, interventions targeting up-regulation of GLT-1 have shown preclinical efficacy in the treatment of cocaine relapse behavior (K. D. Fischer et al., 2013; Knackstedt et al., 2010; Sari, Smith, Ali, & Rebec, 2009; Sondheimer & Knackstedt, 2011; Ward et al., 2011). It was also shown that up-regulation of GLT-1 expression following treatment with ceftriaxone was associated with attenuation of cue-induced cocaine-seeking behavior with a greater effect in rats exposed to both extended-access (6 h/d) and long-withdrawal (45 d) conditions (K. D. Fischer et al., 2013). Critically, in these studies GLT-1 blockade with DHK and DL-TBOA infusions in core, but not shell, reversed the ceftriaxone-induced attenuation of relapse behavior. Collectively these data indicate a critical role for GLT-1 within the NAc core in mediating cocaine relapse behavior. The effects that varying withdrawal periods from cocaine self-administration have on glutamate homeostasis are displayed in Figure 2.

N-acetylcysteine (NAC) is a cysteine prodrug and antioxidant precursor that has been used in humans for many years as a treatment for acetaminophen overdose (Prescott, Park, Ballantyne, Adriaenssens, & Proudfoot, 1977; Scalley & Conner, 1978). NAC is membrane-permeable and does not require active transport in order to deliver cysteine to the cell (Sen, 1997), although it has limited penetration across the blood brain barrier (Borgstrom & Kagedal, 1990; Sjodin, Nilsson, Hallberg, & Tunek, 1989; Tardiolo, Bramanti, & Mazzon, 2018). NAC is also a precursor of the antioxidant glutathione (GSH); the synthesis of GSH depends on the rate-limiting activity of xCT (Dringen & Hirrlinger, 2003). Treatment with NAC or ceftriaxone normalizes abnormal GLU levels in the NAc via increasing xCT protein expression and function (Baker, McFarland, Lake, Shen, Tang, et al., 2003) and, by mechanisms unknown, GLT-1 (K. D. Fischer et al., 2013; Knackstedt et al., 2010; Sari et al., 2009) expression and function in animals previously exposed to cocaine. While treatment with either ceftriaxone or NAC has been shown to up-regulate GLT-1 and xCT expression

and function in the NAc in animals that have been exposed to cocaine, the expression and function of both of these proteins in the NAc is unaltered in control animals (e.g. animals not exposed to cocaine but exposed to ceftriaxone or NAC) (K. D. Fischer et al., 2013; Knackstedt et al., 2010; LaCrosse et al., 2017), although see (Smaga et al., 2020). Furthermore, as outlined in Table 2, both of these treatments attenuate cocaine relapse behavior (Reissner et al., 2015; Sari et al., 2009) and the sensitized response to cocaine (Rasmussen et al., 2011; Sondheimer & Knackstedt, 2011). NAC-induced restoration of abnormal GLU levels was shown to be mGlu2/3 dependent (Kupchik et al., 2012), however, more recently it was shown that the restoration of GLT-1 is also critical for the more enduring protection from cocaine relapse (Reissner et al., 2015). Furthermore, NAC has demonstrated partial success in the translation from preclinical to clinical models of cocaine relapse. In a double-blind placebo-controlled study, NAC did not differ from placebo in ongoing cocaine use, however, this treatment did increase the number of days to relapse in a subset of abstinent patients (LaRowe et al., 2013). Recently, acute NAC was found to attenuate cocaine-primed cocaine-seeking in abstinent cocaine users (Woodcock, Lundahl, Khatib, Stanley, & Greenwald, 2020). These data are consistent with rodent reports indicating this treatment to be more effective at reducing reinstatement following extinction periods than at reducing ongoing cocaine self-administration (Baker, McFarland, Lake, Shen, Toda, et al., 2003; Madayag et al., 2007; Reissner et al., 2015).

In addition to ceftriaxone and NAC, other compounds targeting GLT-1 have shown promising preclinical results in the treatment of cocaine relapse in animal models (J. Kim et al., 2016; Reissner et al., 2014). Reissner and colleagues tested the effects of the glial modulator and neuroprotective agent propentofylline on cocaine relapse behavior and found that this treatment not only attenuates both cue- and cocaine-induced reinstatement but also restores GLT-1 expression to normal levels (similar to levels in a cocaine naïve rat) in the NAc core (Reissner et al., 2014). Additionally, this group found that restoring GLT-1 expression was necessary for propentofylline to inhibit reinstatement, as infusion of GLT-1 antisense into the NAc core reversed the effects of propentofylline on relapse behavior (Reissner et al., 2014). The hypothesized mechanism whereby propentofylline inhibits reinstatement is restoration of astrocytic-mediated clearance of synaptic NAc GLU (Reissner et al., 2014). Furthermore, clavulanic acid is a structural analog of ceftriaxone but has greater brain penetrability, increased oral availability, with negligible antibiotic activity (J. Kim et al., 2016). Clavulanic acid increases GLT-1 expression in the NAc and reduces cocaine self-administration responding on a progressive-ratio (PR) schedule of reinforcement learning (J. Kim et al., 2016). The PR schedule of reinforcement requires the animal to continuously work harder in order to achieve the drug (e.g. increasing the amount of lever presses it takes to receive a reward) and is useful for studying treatments that might affect the reinforcing strength of the drug (e.g. cocaine) (J. Kim et al., 2016; Negus, 2003; Roberts, Bennett, & Vickers, 1989; Roberts, Loh, & Vickers, 1989; Ward, Morgan, & Roberts, 2005). Interestingly, Kim and colleagues showed that Clavulanic acid reduced self-administration of cocaine under a PR schedule at lower doses than ceftriaxone (J. Kim et al., 2016). They also determined that the reinforcing efficacy of cocaine was reduced following treatment with clavulanic acid (J. Kim et al., 2016). However, clavulanic acid did not attenuate cue-primed reinstatement of cocaine-seeking in rats (Bechard, Hamor,

Wu, Schwendt, & Knackstedt, 2019). Whether or not this treatment is effective in human patients is currently unknown, however there is an on-going clinical study recruiting cocaine-dependent individuals to assess the tolerability and drug interactions between clavulanic acid and cocaine (NCT02563769).

6.4. METH: Alterations in Glutamate Homeostasis Following Chronic Administration

While METH and AMP share similar pharmacological and behavioral activating properties in animal models, it is commonly suggested that METH is more potent than AMP (Hall, Stanis, Marquez Avila, & Gulley, 2008). Of the AMP-type stimulants, METH is the most frequently abused (Courtney & Ray, 2014) and has the greatest clinical and societal relevance, particularly given that METH-associated deaths have been on the rise (Hedegaard, Bastian, Trinidad, Spencer, & Warner, 2018). The impact that METH has on mesocorticolimbic circuitry is perhaps more profound than other drugs of abuse due in part to its long half-life, fast uptake and accumulation, and its effects on GLU and DA transmission (Fowler et al., 2008; Parsegian & See, 2014; Stephans & Yamamoto, 1994). In vivo microdialysis reports have demonstrated that METH produces very rapid and large increases in extracellular levels of NAc DA concentrations, an effect believed to underlie the reinforcing effects of the drug (Camp, Browman, & Robinson, 1994; Di Chiara & Imperato, 1988). Additionally, using in vitro electrophysiology in DA neurons, Goodwin and colleagues demonstrated greater DAT-mediated whole-cell currents for METH stimulation than for AMP stimulation and also that METH produced five times greater extracellular levels of DA compared to AMP (Goodwin et al., 2009).

Chronic METH-seeking behaviors in rodents are associated with abnormalities in extracellular levels of GLU. More specifically, extracellular basal GLU levels are significantly reduced in the PFC and NAc core in rats following 10 days of METH self-administration and 10 extinction sessions (Parsegian & See, 2014). When extinguished rats are re-exposed to cues previously paired with the drug and to the drug itself, there is a rise in extracellular GLU within the PFC and NAc core (Parsegian & See, 2014). Notably, this rise in GLU efflux occurs immediately following re-exposure to the drug-paired cues or the drug itself and thus differs from acute exposure to METH which induces a delayed and sustained increase in NAc GLU efflux (K. Ito et al., 2006). Although (Parsegian & See, 2014) did not determine the mechanism underlying the rapid rise in extracellular levels of PFC and NAc core GLU during METH-induced reinstatement, the authors propose that the increase in GLU efflux in both of these regions could derive from multiple neuronal sources of GLU. For example, it is known that the PFC and NAc receive GLU inputs from multiple sources including the VTA, hippocampus, and amygdala (Sesack & Grace, 2010).

Although Parsegian and colleagues demonstrated reduced basal NAc GLU levels in rats following METH self-administration, Lominac and others showed that rats with a history of METH self-administration display increases in basal NAc GLU levels (Lominac et al., 2012). However, there are notable differences in the self-administration models used in these two reports. Parsegian and colleagues measured GLU levels following extinction training whereas Lominac's measurements occurred after a forced withdrawal paradigm. It is known that extinction vs. forced withdrawal can recruit different neural substrates

(Fuchs, Branham, & See, 2006) and can result in differential alterations in GLU receptors (Schwendt, Reichel, & See, 2012). An additional discrepancy between Parsegian's and Lominac's reports is the region studied wherein GLU efflux was increased during the METH relapse test. Parsegian and colleagues measured GLU efflux in the NAc core. Lominac and colleagues did not specify what subregion of the NAc they were targeting although according to the microdialysis probe verification figure provided, the NAc core was targeted in some animals and the shell in others (Lominac et al., 2012). The majority of those investigating psychostimulant-induced alterations in GLU efflux following extinction or withdrawal report measurements in the NAc core (Kalivas & Volkow, 2005; McFarland & Kalivas, 2001; McFarland et al., 2003; Parsegian & See, 2014). It is unknown whether NAc shell GLU efflux is altered following chronic METH administration. Furthermore, because increases in extracellular levels of GLU appear to play an important role in METH addiction behaviors, Fugio and colleagues wanted to determine if blocking GLU transport would affect locomotor responses induced by METH. This group found that intracerebroventricular administration of TBOA, a GLU transporter blocker, induced an enhanced locomotor response to a METH challenge injection in rats that were previously treated with METH (Fujio, Nakagawa, Suzuki, Satoh, & Kaneko, 2005). Collectively, these data suggest that preventing the rise in extracellular GLU that occurs during a challenge (or perhaps relapse) test may provide a new strategy to preventing METH addiction behaviors.

In addition to affecting GLU homeostasis within the PFC and NAc, administration of METH (either continuously or acutely in high doses) results in long lasting toxic effects on DA and serotonin neurons (i.e. decreased levels of transmitter, metabolites, and transporters) (Hotchkiss & Gibb, 1980; Morgan & Gibb, 1980; Ricaurte, Guillery, Seiden, Schuster, & Moore, 1982; Volkow, Chang, Wang, Fowler, Ding, et al., 2001; Volkow, Chang, Wang, Fowler, Leonido-Yee, et al., 2001; Wagner et al., 1980; Wilson et al., 1996). These toxic effects are likely due to increases in extracellular levels of GLU; inhibition of corticostriatal GLU release via inhibiting D1 or GABA-A receptors in the SNr which results in a decrease in corticostriatal activation affords protection against METH-induced toxicity to DA terminals (Mark et al., 2004). Additionally, treatment with GLU receptor antagonists (delivered locally within the striatum or systemically) prevents METH-induced damage to DA terminals within the striatum (Finnegan & Taraska, 1996; Halpin & Yamamoto, 2012). Interestingly, acute liver damage and subsequent increases in ammonia have been implicated to play a role in the METH-mediated excitotoxic events including DA and serotonin terminal damage (Halpin & Yamamoto, 2012). Ammonia is metabolized by the liver and has established neurological effects (Halpin & Yamamoto, 2012). Administration of METH acutely in high doses (10 mg/kg, i.p., every 2 h x 4) has been shown to increase plasma and brain ammonia concentrations (Halpin & Yamamoto, 2012). Interestingly, neurotoxicity (cell death) induced by systemic ammonia administration is dampened following systemic administration of GLU receptor antagonists (Kosenko et al., 2003; Saez, Llansola, & Felipo, 1999). Furthermore, intra-striatal infusions of ammonia in combination with METH, but not METH or ammonia alone, recapitulate the DA and serotonin terminal damage (Halpin & Yamamoto, 2012). In order to determine a causative role for ammonia in the release of extracellular levels of GLU and monoamine terminal damage, Halpin and colleagues performed studies whereby they enhanced peripheral ammonia excretion during and after

acute binge METH (10 mg/kg, i.p., every 2 h x 4) and examined the long-term effects on monoamine terminal damage in the striatum (Halpin et al., 2014). Following acute binge METH exposure, plasma and brain ammonia levels were increased (Halpin et al., 2014). It was also shown that METH administration in rats pre-treated with lactulose, a compound that lowers plasma and brain ammonia concentrations (Al Sibae & McGuire, 2009; Halpin et al., 2014; Jia & Zhang, 2005; Nicaise et al., 2008), prevents the METH-induced increases in extracellular levels of striatal GLU as well as the monoamine terminal damage (Halpin et al., 2014). In order to determine the mechanism by which ammonia increases extracellular levels of striatal GLU, the authors infused TBOA, a GLU transporter blocker, directly into the striatum of acute binge METH exposed rats (Halpin et al., 2014). This study revealed that intra-striatal infusions of TBOA blocked the ammonia-induced increases in extracellular levels of striatal GLU (Halpin et al., 2014), thus indicating that similar to the actions of AMP, ammonia-induced increases in extracellular levels of striatal GLU may involve the reversal of GLU transporters.

In addition to monoamine terminal damage, METH administration has also been shown to induce inflammatory responses within the CNS. Astrogliosis is a marker of inflammation and is demonstrated by increases in glial fibrillary acidic protein (GFAP) expression; this occurs in the somatosensory cortex 3 days following a single day of binge METH treatment (10 mg/kg given 4 times i.p. at 2 h intervals) (Pu et al., 1996). Microglial activation is elicited by METH in mouse and rat striatum (10–15 mg/kg given 4 times i.p. at 2 h intervals) (Guilarte, Nihei, McGlothan, & Howard, 2003; Thomas et al., 2004). It is conceivable that the increases in GLU in response to METH may activate inflammatory mediators. Indeed, GLU receptor stimulation increases proinflammatory cytokine production of interleukin IL-1β, tumor necrosis factor-α (TNF-α), and IL-6 (Chaparro-Huerta, Rivera-Cervantes, Flores-Soto, Gomez-Pinedo, & Beas-Zarate, 2005; de Bock, Dornand, & Rondouin, 1996; Marini et al., 2004; Vezzani et al., 1999). Conversely, GLU receptor antagonists decrease microglial activation (Taylor, Jones, Kubota, & Pocock, 2005; Thomas & Kuhn, 2005). This interaction between GLU and cytokine production may play a role in promoting dysregulation of glutamate homeostasis and consequent excitotoxicity.

Similar to cocaine, there is currently no FDA approved medication for the treatment of METH addiction. However, investigators have shown promising preclinical results in treating METH addiction behaviors by targeting GLU receptors and GLU transporters. More specifically, targeting mGluR5 has shown promising efficacy for the treatment of METH addiction in preclinical animal models. While mGluR5 receptors are expressed in numerous regions of the brain, they are expressed at relatively high levels within the NAc as well as on DA neurons within the VTA (Ferrada, Sotomayor-Zarate, Abarca, & Gysling, 2017; Mitrano & Smith, 2007; Romano et al., 1995; Shigemoto et al., 1993). MTEP is a selective mGluR5 antagonist that was shown to attenuate reinstatement of METH-seeking behavior induced by cues previously paired with METH or by METH itself (Gass, Osborne, Watson, Brown, & Olive, 2009; Osborne & Olive, 2008). This drug had no effect on food self-administration thus indicating specificity of effect on pathways reinforced by METH. Riluzole and ceftriaxone are other compounds that have been tested for their preclinical efficacy in the treatment of METH addiction; as mentioned above, both of these treatments increase the expression and function of the GLT-1. Riluzole treatment was shown to reduce

the expression of locomotor sensitization to METH (Itzhak & Martin, 2000) and ceftriaxone blocked the reinstatement of METH-seeking behavior in a CPP paradigm (Abulseoud, Miller, Wu, Choi, & Holschneider, 2012). Ceftriaxone was shown to increase the expression of GLT-1 in the PFC from METH treated animals compared to METH only treated controls (Abulseoud et al., 2012). One unanswered question from the studies by Abulseoud and colleagues and Itzhak and Martin is whether GLT-1 expression is altered following METH administration in itself (by comparing to expression in naïve animals). While this wasn't investigated directly, as discussed above in Section 6.3, ceftriaxone treatment seems to affect GLT-1 levels only in injured brain (Jagadapillai et al., 2014; Lipski et al., 2007; Miller et al., 2008; Rothstein et al., 2005). Therefore, it is likely that METH decreases GLT-1 expression, and that the effects of ceftriaxone are dependent on the injury produced by METH.

7. GLT-1 Contributions to Psychostimulant Addiction: Neuronal or Astrocytic?

As has been discussed, GLT-1 plays an important role in psychostimulant addiction behaviors and has served as a therapeutic target in many studies for the treatment of relapse behaviors (Abulseoud et al., 2012; Baker, McFarland, Lake, Shen, Toda, et al., 2003; K. D. Fischer et al., 2013; Itzhak & Martin, 2000; Knackstedt et al., 2010; Rasmussen et al., 2011; Smaga et al., 2020; Spencer & Kalivas, 2017; Tzschentke & Schmidt, 1998). GLT-1 is expressed primarily in astrocytes (Rothstein et al., 1994) and to a lesser extent in neurons (~5–10% of the total, determined in the hippocampus) (Furness et al., 2008). Thus, assay of protein expression by immunoblot would be expected to assess astrocytic GLT-1, because changes in neuronal expression would *a priori* be expected to be at or below the level of detection. To dissect the contributions of astrocytic and neuronal GLT-1 to GLU homeostasis, a conditional GLT-` knockout was generated and mouse lines produced using Cre/lox technology lacking GLT-1 in astrocytes or in neurons (Petr et al., 2015). The GLT-1 protein expression in the neuronal knockout was not distinguishable by immunoblot analysis from GLT-1 protein expression in wild-type littermates. The efficacy of the neuronal knockout was confirmed by EM immunocytochemistry. In contrast, GLT-1 expression assayed by immunoblot in the astrocytic knockout was reduced by 70–90%. These results establish that immunoblot analysis cannot reliably be used to detect changes in expression of neuronal GLT-1, and that when changes in GLT-1 expression are detected, these changes likely represent changes in astrocytic GLT-1.

A common approach to assessing GLT-1 function is by measuring uptake of radioactive substrates for GLU transporters, typically [^{3}H]L-GLU or [^{3}H]D-aspartate, in crude synaptosomal preparations. These typically are prepared simply by resuspension of the P2 pellet from brain, or brain region homogenates (M. B. Robinson, Sinor, Dowd, & Kerwin, 1993). Because of the predominance of astrocytic GLT-1 over neuronal GLT-1 in the brain, and the erroneous but persistent consensus that GLT-1 is not expressed in neurons, it had long been assumed that uptake of GLU or aspartate into synaptosomal preparations represented astrocytic GLT-1 function (Rimmele & Rosenberg, 2016). However, it was actually found using the conditional GLT-1 knockout that genetic deletion of astrocytic GLT-1 did not significantly decrease uptake of [^{3}H]L-GLU into crude synaptosomes

prepared from the forebrain (Petr et al., 2015). In contrast, knockout of neuronal GLT-1 using a synapsin 1-Cre driver reduced GLU uptake significantly by c. 40% in synaptosomes from the forebrain (Petr et al., 2015) and up to 80% in specific regions (Laprairie et al., 2019; McNair et al., 2019; McNair et al., 2020b; Zhou, Hassel, Eid, & Danbolt, 2019). When uptake was assayed into reconstituted liposomes using protein derived from either neuronal GLT-1 knockout or astrocytic GLT-1 knockout brain, then uptake was reduced to a degree expected from the relative amounts of GLT-1 in astrocytes and neurons—that is, a c. 85% decrease in liposomes reconstituted from the astrocytic GLT-1 KO brain, and no significant decrease in liposomes reconstituted from the neuronal GLT1–1 knockout brain (Petr et al., 2015). Synaptosomal uptake measured in crude synaptosomes, therefore, does not reflect the function of GLT-1 in astrocytic membranes, but rather represents the function of GLT-1 expressed in neuronal membranes, even though no effort was made to exclude astrocytic membranes from the preparation.

A powerful and elegant approach that distinguishes neuronal from astrocytic GLU transport sites is electron microscopic D-aspartate uptake autoradiography (Furness et al., 2008; Gundersen, Shupliakov, Brodin, Ottersen, & Storm-Mathisen, 1995). Using this approach in hippocampal slices, it was found that approximately 50% of the immunogold immunocytochemical labeling for D-aspartate was in axon terminals despite the fact that immunogold labeling of terminals for GLT-1 was only 6% of the total (Furness et al., 2008). D-aspartate uptake into terminals was shown to be mediated by GLT-1 because the build-up of D-aspartate immunoreactivity was blocked by an inhibitor of GLT-1 (e.g. DHK) and by GLT-1 knockout (Furness et al., 2008). These results, taken together, establish: 1) that changes in synaptosomal uptake likely reflect changes in function of neuronal GLT-1 (Zhou et al., 2019); and 2) that changes in uptake of GLU transporter substrates into slices cannot be assumed to represent uptake into astrocytes (Furness et al., 2008). Furthermore, these results demonstrate that assessing changes in neuronal GLT-1 function can only be achieved, at this time, by measuring changes in synaptosomal uptake, or using EM autoradiographic or immunocytochemical methods. Given the importance of ceftriaxone as a modulator of GLT-1 expression and function, it is important to note that in a careful study of its effects it was determined that this drug upregulates expression of GLT-1 in axon terminals as well as in astrocytic membranes of the cerebral cortex (Capuani et al., 2016). In addition, recent reports demonstrate that GLT-1 expressed in axon terminals has a significant metabolic function to promote the utilization of GLU by synaptic mitochondria (McNair et al., 2019; McNair et al., 2020b). Therefore, a potential role for neuronal GLT-1 in modulating glutamatergic synaptic transmission in the setting of exposure to drugs of abuse should not be overlooked (K. D. Fischer et al., 2018).

With these recent findings in mind, it is instructive to review work in which attempts have been made to assess changes in GLU transporter activity related to exposure to drugs of abuse by assaying radioactive substrates. The effects of chronic cocaine and heroin on [^{3}H]L-GLU uptake have been assessed in NAc core slices (Knackstedt et al., 2010; Shen, Scofield, Boger, Hensley, & Kalivas, 2014; Trantham-Davidson, LaLumiere, Reissner, Kalivas, & Knackstedt, 2012). Knackstedt et al. found that cocaine self-administration followed by 3 weeks of extinction training resulted in a reduction in NAc core [^{3}H]L-GLU uptake in rats (Knackstedt et al., 2010). This group subsequently demonstrated that

treatment with ceftriaxone reversed the cocaine-induced deficits in NAc core [^{3}H]L-GLU uptake (Trantham-Davidson et al., 2012). Shen et al. found that heroin self-administration attenuates NAc core slice [^{3}H]L-GLU uptake and that NAc core slices obtained from heroin-extinguished rats treated with ceftriaxone showed elevated uptake (Shen et al., 2014). Given what has been learned regarding cellular localization of the GLU uptake activity that is measured using radioactive substrates, these demonstrations of changes in GLU uptake activity should not be assumed to be showing changes exclusively localized to astrocytes, and may indicate a contribution of changes in neuronal GLT-1 activity to the alterations in GLU homeostasis produced by exposure to drugs of abuse.

8. Concluding Remarks

The concept of GLU homeostasis first appeared in the scientific literature nearly 40 years ago (Schousboe & Hertz, 1981). When first introduced, the focus was primarily on GLU metabolism and the compartmentalization of different aspects of GLU metabolism in neurons and astrocytes. Subsequently, with the discovery of the phenomenon of excitotoxicity (D.W. Choi, 1988; J.W. Olney, 1969; J.W. Olney & Ho, 1970; J. W. Olney & Sharpe, 1969; S. M. Rothman, 1983; S. M. Rothman & Olney, 1986) and the high sensitivity of CNS neurons to the toxic effects of GLU (M.B. Robinson, Djali, & Buchhalter, 1993; Rosenberg & Aizenman, 1989; Rosenberg, Amin, & Leitner, 1992), GLU homeostasis acquired additional importance because the regulation of extracellular GLU concentration was seen to be critical in determining whether neurons would survive the continual release of GLU from excitatory synapses (Lipton & Rosenberg, 1994; Schousboe, Sonnewald, Civenni, & Gegelashvili, 1997). In the last 20 years, our understanding of GLU homeostasis has been greatly expanded by a large body of evidence that suggests that the control of extracellular GLU concentration around synapses actually determines the changes in behavior that follow exposure to drugs of abuse. This is the subject of the present review. There is not a more compelling body of evidence suggesting that GLU homeostasis regulates behavior, although the evidence is mounting for a similarly important role for GLU homeostasis in other areas of investigation, including mental illness (Cui et al., 2014), pain (Inquimbert et al., 2012; Inquimbert et al., 2018), epilepsy, synaptic plasticity (Levenson, Weeber, Sweatt, & Eskin, 2002; Omrani et al., 2009; Pita-Almenar, Sol Collado, Colbert, & Eskin, 2006), and neurodegeneration (Scimemi et al., 2013; Zott et al., 2019). Collectively, the body of work reviewed here produced by many dedicated investigators support the need for further research focusing on the regulation of GLU homeostasis in the pathophysiology of addiction and as a target for clinical intervention.

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Abbreviations:

GLU	glutamate

DA	dopamine
NAc	nucleus accumbens
VTA	ventral tegmental area
PFC	prefrontal cortex
METH	methamphetamine
AMP	amphetamine
mGluR	metabotropic glutamate receptor
NAC	N-acetylcysteine
SA	Self-Administration
CPP	Conditioned Place Preference

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Highlights

- METH, AMP, and cocaine alter glutamate homeostasis within the mesolimbic circuit
- GLT-1 and xCT are the glutamate transporters primarily responsible for drug-induced changes in glutamate homeostasis
- GLT-1 and xCT are therapeutic targets for METH, AMP, and cocaine addiction behaviors
- Glutamate co-transmission by dopamine neurons is important for behavioral responses to psychostimulants

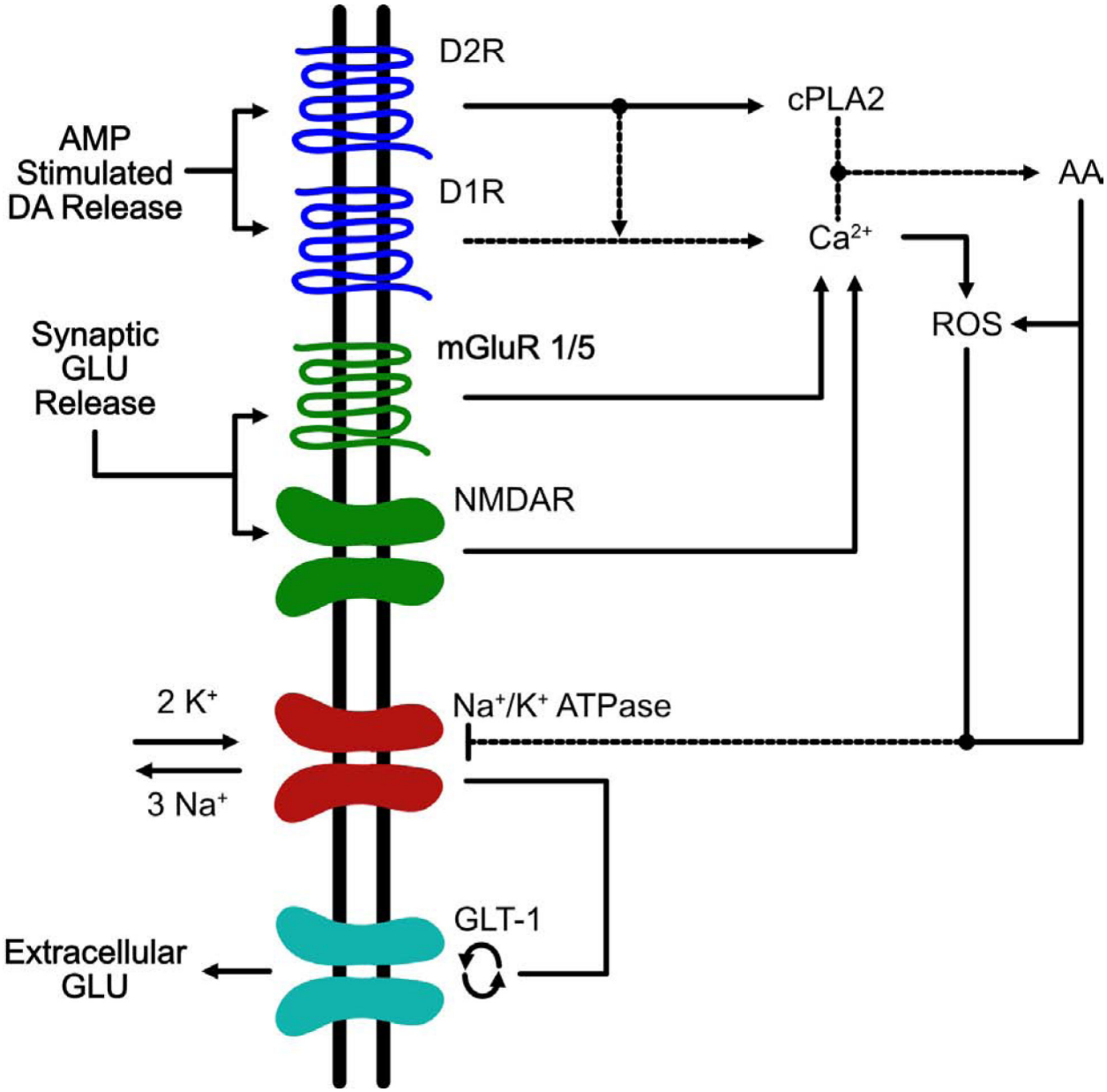

Figure 1. Signaling pathways implicated in the perturbation of glutamate homeostasis in the VTA induced by AMP.

This is an example of a VTA astrocyte in which AMP/METH activates a signaling cascade that ultimately results in the reversal of EAATs. Administration of amphetamines results in the reversal of the dopamine transporter DAT and a decrease in vesicular uptake via VMAT which ultimately results in an accumulation of extracellular levels of DA within multiple brain regions including the VTA (Sulzer and Rayport 1990, Giorgetti, Hotsenpiller et al. 2001). DA released by DAT reversal stimulates D1- and D2-like receptors on VTA astrocytes (Liu, Wang et al. 2009, Zhang, Zhou et al. 2009). Activation of D2 receptors results in activation of the effector enzyme, cytoplasmic phospholipase 2 (cPLA2) (Vial and Piomelli 1995, Bhattacharjee, Chang et al. 2006). The combined stimulation of D1/D2R increases the release of intracellular Ca^{2+} which along with cPLA2 helps to free arachidonic

acid (AA) from phospholipid membranes (Lee, So et al. 2004). AA release results in increased levels of reactive oxygen species (ROS) (Chan and Fishman 1980, Chan, Chen et al. 1988, Sakuma, Kitamura et al. 2012). Both AA and ROS inhibit the Na+/K+ pump (Na+/K+ -ATPase) leading to an increase in cytosolic potassium and a decrease in cytoplasmic sodium (Hexum and Fried 1979, Chan, Kerlan et al. 1983, Volterra, Trotti et al. 1994). The inhibition of Na+/K+ -ATPase results in two events: 1 – depolarization of the cell membrane and 2 – disruption of the Na+/K+ gradients; both of these events can result in the reversal of EAATs (Nicholls and Attwell 1990, Volterra, Trotti et al. 1994, Anderson, Huguenard et al. 2010). The increase in extracellular GLU following AMP administration is most likely due to reversal of GLT-1, as the increases in GLU are completely blocked by the GLT-1 blocker, DHK (Wolf, Xue et al. 2000). Another source of increased extracellular GLU within the VTA arises from GLU input from the PFC. DA projections from the VTA to the PFC play a critical role in modulating PFC GLU output back to the VTA (Sesack and Pickel 1992). By increasing the activity of VTA neurons, AMP/METH could activate this VTA-PFC-VTA circuit resulting in increased extracellular GLU levels within the VTA and in fact it has been shown that acute AMP results in increased activation of this circuit following AMP administration in rats (Colussi-Mas, Geisler et al. 2007). Furthermore, increased levels of extracellular GLU in VTA can activate mGluR1/5 and NMDARs located on the astrocyte resulting in a further increase in intracellular Ca^{2+} and AA (Biber, Laurie et al. 1999, Daniels and Brown 2001, Lalo, Pankratov et al. 2006, Lee, Ting et al. 2010) which continues the cycle of increases in ROS, decreases in Na+/K+ -ATPase function, and increases in extracellular levels of GLU via reversal of GLT-1.

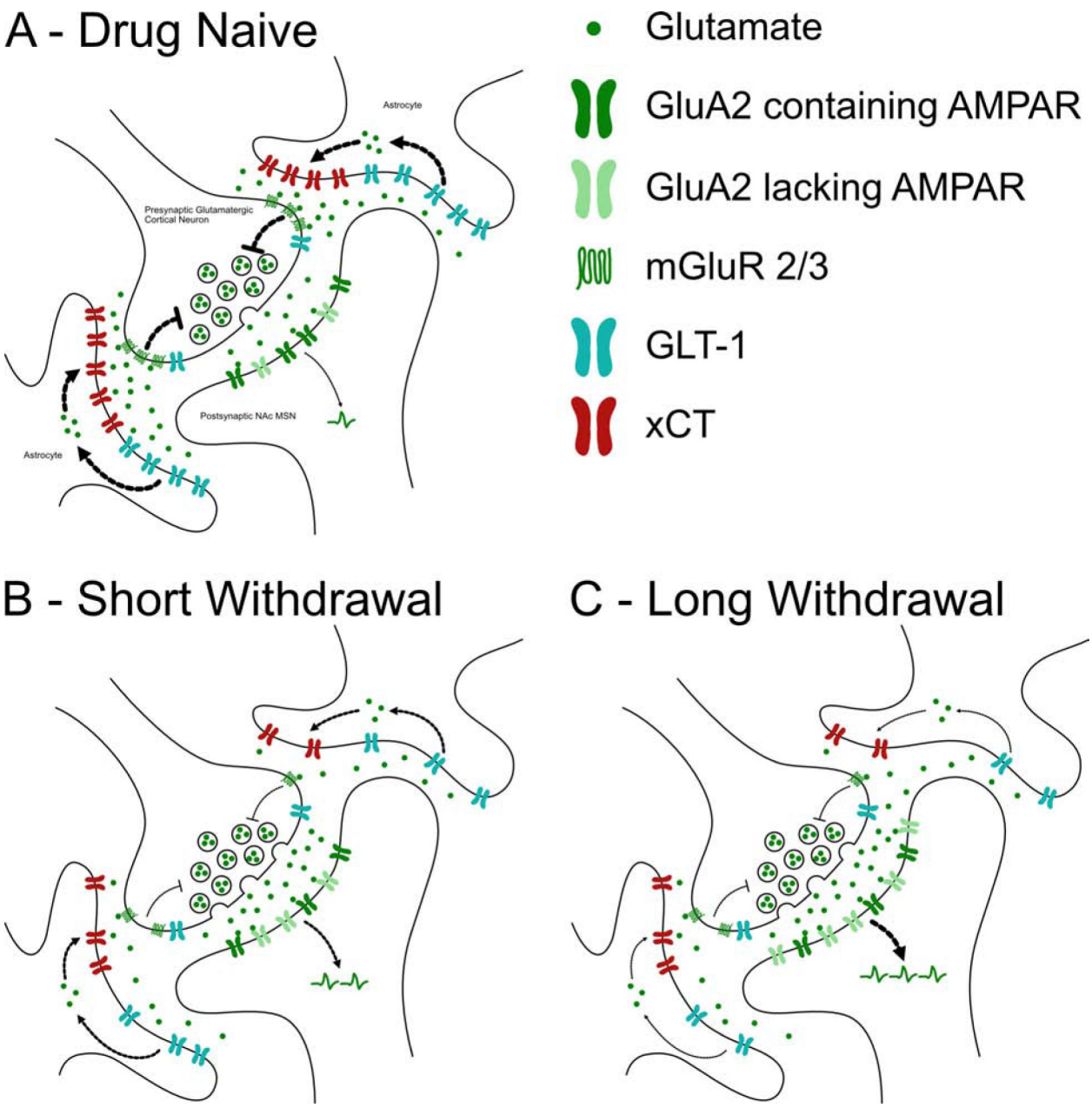

Figure 2. Alterations in GLU homeostasis following cocaine withdrawal within the NAc.

A simplified illustration of how GLU homeostasis is altered within the NAc core in an animal experiencing varying withdrawal lengths from cocaine administration. ***A. Drug naïve conditions:*** Under normal, drug naïve, conditions GLU is packaged into vesicles and released from the presynaptic terminal and is taken up by GLT-1 on the astrocyte. The cystine-GLU exchanger (xCT) located on the astrocyte exports GLU out into the extrasynaptic space (Baker, Shen et al. 2002); this GLU binds to mGluR2/3 located on the presynaptic terminal which decreases the synaptic GLU release probability (Moran, McFarland et al. 2005). By removing GLU from the extracellular space and maintaining tone at mGluR2/3, GLT-1 and xCT, respectively, both work to maintain GLU homeostasis (Baker, Xi et al. 2002). ***B. Short withdrawal following cocaine self-administration:*** The

alterations illustrated in panel B are compared to the drug-naïve synapse presented in panel A. As shown, cocaine self-administration followed by short withdrawal periods (1–3 days) or extinction training results in reduced basal levels of extracellular GLU, most likely due to the decreased expression of xCT (Knackstedt, Melendez et al. 2010, Trantham-Davidson, LaLumiere et al. 2012). Decreased expression of xCT reduces GLU tone at mGluR2/3 (Baker, Xi et al. 2002). Following short withdrawal periods from cocaine self-administration there is also a decrease in mGluR2/3 receptor expression in the NAc (Logan, Bechard et al. 2020). Additionally, GLT-1 protein expression is decreased following short withdrawal periods from cocaine self-administration (Fischer-Smith, Houston et al. 2012). Because mGluR2/3s serve to inhibit neurotransmission, the decreased tone at mGluR2/3s results in an increase in GLU release when the PFC-NAc projection is activated during drug-seeking behavior (Kalivas 2009, Reissner and Kalivas 2010). Decreased expression of GLT-1 results in reduced uptake of GLU from the extracellular space during drug-seeking behavior (Trantham-Davidson, LaLumiere et al. 2012). Furthermore, following short withdrawal from cocaine self-administration there is increased expression of the GluR2 lacking Ca^{2+} permeable AMPA receptors, more specifically the GluA3 subunit expressing AMPA receptors (Conrad, Tseng et al. 2008), suggesting that cocaine self-administration followed by short withdrawal increases signaling at the Ca^{2+} permeable GluR2 lacking AMPA receptors. ***C. Long withdrawal following cocaine self-administration:*** The alterations illustrated in panel C are compared to animals experiencing short withdrawal from cocaine self-administration in panel B. Long withdrawal periods (40–47 days) following cocaine self-administration yields an even greater reduction in GLT-1 expression compared to short withdrawal conditions (Fischer-Smith, Houston et al. 2012). Additionally, compared to short withdrawal conditions, there is an even greater increase in the expression of the GluR2 lacking Ca^{2+} permeable AMPA receptors (GluR1/3 subunit expressing) (Conrad, Tseng et al. 2008). There is also an increase in evoked excitatory postsynaptic currents (EPSCs) in NAc core slices that is blocked by Naspm, a selective blocker of GluR2-lacking AMPA receptors (Conrad, Tseng et al. 2008). Naspm has no effect on EPSCs in animals exposed to short withdrawal conditions from cocaine self-administration suggesting that these GluR2-lacking AMPA receptors contribute to enhanced NAc synaptic transmission only after long withdrawal periods (Conrad, Tseng et al. 2008, Wolf 2010).

Table 1

Changes in Extracellular Levels of GLU following Acute and Chronic Administration of Psychostimulants

Acute Administration of Drug				
	Brain Region	**Direction and Timepoint of Change in Extracellular Levels**	**Treatments that Block Drug Effects on Extracellular GLU Levels**	**Drug Administration Protocol**
AMP	NAc (core and shell)	Delayed (~3 hr) Increase (Xue, Ng et al. 1996)	Haloperidol	Single Injection 5 mg/kg i.p. (free base)
	VTA	Immediate Decrease following by Delayed (~3 hr) Increase (Wolf and Xue 1998; Xue, Ng et al. 1996)	DHK, SCH23390, lesions of PFC (Wolf and Xue 1999)	Single Injection 5 mg/kg i.p. (free base)
Cocaine	NAc (subregion unspecified)	Immediate Increase (Smith, Mo et al. 1995)	TTX (Smith, Mo et al., 1995)	Single Injection 15 and 30 mg/kg i.p.
	VTA	Immediate Increase (Kalivas and Duffy 1995)	SCH23390 (Kalivas and Duffy 1995)	Single Injection 15 mg/kg i.p.
METH	NAc (subregion unspecified)	Delayed (~2 hr) Increase (Ito et al. 2006)	SCH23390 (Ito et al., 2006)	Single Injection 2.5 mg/kg s.c. (salt form)
	Striatum	Immediate Increase following 3rd Injection (Stephans and Yamamoto 1994)	Bicuculline (Stephans and Yamamoto 1994)	10 mg/kg i.p. x 3, every 2 hr
Chronic Administration of Drug				
	Brain Region	**Direction of Change in Extracellular Levels**	**Treatments that Block Drug Effects on Extracellular GLU Levels**	**Drug Administration Protocol**
AMP	NAc (core and shell)	Delayed (~3 hr) Increase (Xue, Ng et al. 1996)	Data Not Shown	5 mg/kg i.p. x 5 d (challenge 2 d post-withdrawal) (free base)
	VTA	Delayed (~3 hr) Increase (Wolf and Xue 1998)	MK-801, SCH23390, lesions of PFC (Wolf and Xue 1998, 1999); PBN (Wolf, Xue et al. 2000)	5 mg/kg i.p. x 5 d (challenge 2 d post-withdrawal) (free base)
Cocaine	NAc core	Decrease after Self-Administration; Increase following Reinstatement or Challenge (McFarland, Lapish et al. 2003; Pierce, Bell et al. 1996)	TTX, muscimol infusions into the Prelimbic Cortex (McFarland, Lapish et al. 2003)	IV Self Administration (2 hr/day)/Extinction Training/ Drug-induced Reinstatement
METH	NAc core	Decrease after Self-Administration; Increase following Reinstatement (Parsegian and See 2014)	Data Not Shown	IV Self Administration (2 hr/day)/Extinction Training/ Drug and Cue-induced Reinstatement
	NAc (core and shell)	Increase after Self-Administration (Lominac, Sacramento et al. 2012)	Data Not Shown	IV Self Administration (2 hr/day)/Forced Withdrawal
	PFC	Decrease after Self-Administration; Increase following Reinstatement (Parsegian and See 2014)	Data Not Shown	IV Self Administration (2 hr/day)/Extinction Training/ Drug and Cue-induced Reinstatement

In the table. Amphetamine (AMP), Methamphetamine (METH), Haloperidol (D2 antagonist), SCH23390 (D1 antagonist), DHK (GLT-1 blocker), TTX (Sodium channel blocker), Bicuculline (GABA-A antagonist), MK-801 (NMDA antagonist), muscimol (GABA agonist), PBN (spin trapping agent for hydroxyl radicals). Rats were used in all experiments.

Table 2

Treatments Targeting GLT-1 or xCT for Chronic Psychostimulant Addiction Behaviors in Preclinical Animal Models

	Addiction Behavioral Protocol	Psychostimulant-induced effect on GLT-1 or xCT	Treatment Approach	Behavioral Outcome	Treatment Effect on GLU Homeostasis
AMP	AMP Sensitization	Data Not Shown	Ceftriaxone (200 mg/kg i.p.) for 8 days during induction (Rasmussen, Baron et al. 2011)	Reduction in Sensitization Expression	Reduced extracellular levels of NAc GLU (Rasmussen, Baron et al. 2011)
	AMP CPP	Data Not Shown	Riluzole (4 mg/kg i.p.) for 3 days during CPP training (Tzschentke and Schmidt 1998)	Blocked CPP	Data Not Shown
Cocaine	Cocaine Reinstatement following Extinction	Data Not Shown	Ceftriaxone (200 mg/kg i.p.) for 5 days during extinction (Sari, Smith et al. 2009)	Blocked Cue-Induced Reinstatment	Data Not Shown
	Cocaine Reinstatement following Long Withdrawal Periods (45 d)	Greater reduction in GLT-1 protein expression in NAc core following longer withdrawal periods (Fischer et al. 2012)	Ceftriaxone (200 mg/kg i.p.) for last 5 days of withdrawal (Fischer et al. 2012)	Blocked Cue-Induced Reinstatment	Increased GLT-1 protein expression in NAc (Fischer et al. 2012)
	Cocaine Reinstatement following Extinction	Reduced GLU uptake and expression of GLT-1 and xCT in the NAc core following extinction (Knackstedt et al. 2010)	Ceftriaxone (200 mg/kg i.p.) for 7 days during extinction (Knackstedt et al. 2010)	Blocked Cue- and Cocaine-Induced Reinstatment	Increased expression of GLT-1 and xCT in NAc core (Knackstedt et al., 2010)
	Cocaine Reinstatement following Extinction	Reduced GLU uptake and expression of GLT-1 and xCT in the NAc core following extinction (Knackstedt et al. 2010)	N-acetylcysteine (100 mg/kg i.p.) for 7 days during extinction (Knackstedt et al. 2010)	Blocked Cue- and Cocaine-Induced Reinstatment	Increased expression of GLT-1 and xCT in NAc core (Knackstedt et al., 2010)
	Cocaine Reinstatement following Extinction	Reduced NAc core basal GLU levels	Ceftriaxone (200 mg/kg i.p.) for last 5 days of extinction training) (Trantham-Davidson et al. 2012)	Blocked Cocaine-Induced Reinstatment	Restores basal GLU levels and increases GLU uptake in NAc core (Trantham-Davidson et al. 2012)
	Cocaine Self-Administration in Mice	Data Not Shown	Clavulanic acid (1 mg/kg i.p.) for 3 days prior to self-administration (Kim et al. 2015)	Reduced Self-Administration Behavior in Mice	Increased GLT-1 protein expression in NAc (Kim et al. 2015)
METH	METH Sensitization in Mice	Data Not Shown	Riluzole (20 mg/kg i.p.) for 5 days during induction (Itzhak and Martin 2000)	Reduction in Sensitization Expression in Mice	Data Not Shown
	METH CPP	Data Not Shown	Ceftriaxone (200 mg/kg i.p.) for 7 days during CPP extinction (Abulseoud, Miller et al. 2012)	Blocked METH-induced CPP Reinstatement	Increased GLT-1 protein and mRNA expression in PFC (Abulseoud, Miller et al. 2012)

In the table. Amphetamine (AMP), Methamphetamine (METH), Conditioned Place Preference (CPP), Unless specified otherwise, rats were used.