Chapter 14
Pharmacological Role of Glutamate Transporters in Substance Use Disorders

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Abstract Substance use disorders (SUD) represent a public health crisis worldwide. The development of effective pharmacotherapeutics to treat drug abuse and addiction requires the identification of targetable neurobiological mechanisms. As the primary excitatory neurotransmitter in the brain glutamate possesses a significant role in plasticity, learning, and memory, and represents a promising neurotransmitter of focus for intervention in the etiology of SUDs. Chronic drug exposure induces lasting neuroadaptations in the glutamatergic system specifically within the mesocorticolimbic (MCL) reward pathway which is posited to generate maladaptive deficits in behavioral-control, thus contributing to the addictive cycle. Maintaining the strict control of glutamate release and clearance is required for homeostasis as well as the prevention of neurotoxicity and oxidative stress. There are five excitatory amino acid transporters (EAATs) and three vesicular glutamate transporters. These function to preserve homeostatic levels of glutamate under normal physiological conditions. This review aims to highlight and summarize the preclinical evidence for dysregulation of glutamate transport following drug exposure. Additionally, alterations in glutamate transporters, with an emphasis on glutamate transporter 1 (EAAT2 encodes by *SLC1A2*) and its role in the development of detrimental

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drug-seeking behaviors, as well as current glutamate transporter-associated treatments being investigated are discussed.

Keywords Substance Use Disorder (SUD) · Glutamate · Excitatory amino acid transporters (EAAT) · Vesicular glutamate transporter (vGluT) · Ceftriaxone · n-acetylcysteine (NAC)

14.1 Introduction

Glutamic acid is a polar amino acid often found in an electrically charged state within the human body. The ionized form, glutamate, is the most abundant as well as the primary excitatory neurotransmitter in the mammalian central nervous system (CNS). Glutamate is directly involved in a number of biological functions including energy metabolism, cellular differentiation, protein synthesis, and synaptogenesis through activation of its distinct receptor subtypes or cellular uptake (Zhou and Danbolt 2014). Glutamate also serves as a precursor for GABA synthesis via glutamate decarboxylase (GAD) or is transferred into the TCA/Krebs Cycle as α-ketoglutarate following metabolism by glutamate dehydrogenase (Rowley et al. 2012; Bell et al. 2016b). Decades of research have demonstrated that glutamate neurotransmission is fundamental to the cellular and molecular mechanisms of synaptic plasticity and subsequent learning and memory (Kauer and Malenka 2007). Importantly, drug-induced pathological neuroadaptations to the glutamatergic system has been found to contribute significantly to the development of substance use disorders (SUDs) and other addictions (Kalivas 2009; Bell et al. 2016a; Kalivas and Volkow 2016; Scofield et al. 2016; Alasmari et al. 2018a, b). SUDs are characterized by reduced behavioral flexibility in response to drug reinforcement, which has been proposed to stem from enhanced drug-seeking behavior with simultaneous decreases in responses to non-drug stimuli (i.e., fixation; Volkow et al. 2019). Thus, integration of known changes that occur within the glutamatergic system, as well as opposing mechanisms that moderate glutamatergic signaling, following chronic drug exposure is necessary to construct accurate global models of the addiction process (Siggins et al. 2003; Basavarajappa et al. 2008; Leriche et al. 2008; Nam et al. 2012; Koob 2013; Tabakoff and Hoffman 2013). Therefore, the goal herein is to explore the mechanisms that regulate glutamate uptake and transport within the mesocorticolimbic reward neurocircuitry as it pertains to SUDs (Koob et al. 2014; Rao et al. 2015).

14.2 Glutamate & Reward Neurocircuitry

To process reward, the brain utilizes complex neurocircuitry that encompasses several nuclei, projections, and neuromodulators to integrate and evaluate responses to rewarding stimuli and direct motivational behavior accordingly. A well-established projection within this circuitry is the mesolimbic dopamine (DA) pathway (Fig. 14.1). This "reward" pathway originates in the ventral tegmental area (VTA) and projects to the nucleus accumbens (Acb) (Di Chiara and Imperato 1988; Volkow et al. 2019). A consistent observation throughout the literature is that addictive substances produce a significant elevation in DA levels within the mesolimbic pathway, thereby exerting a modulatory role on reward processing (Di Chiara and Imperato 1988; Volkow and Morales 2015). Currently, the more predominant view is that the net effect of an organism's exposure to rewarding/reinforcing stimuli is processed through both the direct and indirect actions of a drug on numerous nuclei within the CNS (Volkow et al. 2019). Neurocircuitry that functions to mediate behavioral and cognitive processes including decision making, learning, memory, emotion, and sensory processing is widespread and has been implicated to also have a role in reward processing (Bell et al. 2013; Floresco 2015; Rao et al. 2015; Koob and Volkow 2016). For instance, modulation of reward behavior by serotonin (5-HT) and norepinephrine (NE) can be traced to the dorsal (DR) as well as median (MR) raphe nuclei and the locus coeruleus (LC), respectively (Cools et al. 2011; Lisieski et al. 2019). Inhibitory influence by γ-amino butyric acid (GABA), the principal inhibitory neurotransmitter in the CNS, is released from medium spiny neurons (MSN) and interneurons throughout the reward neurocircuitry (Morales and Margolis 2017; Seo et al. 2016; Yang et al. 2018). Modulatory actions via glutamate is ubiquitous and occurs at several levels of reward processing (cf., Floresco et al. 2001, 2003; Bell et al. 2012, 2013, 2016b, 2017, 2019; Morales and Margolis 2017). Moreover, it has become increasingly clear that interactions between DAergic and glutamatergic systems within the "reward" neurocircuit play a major role in addiction (Schmidt and Reith 2005). Thus, glutamate plays an integral role in reward/reinforcement processing that mediates addiction.

The mesocorticolimbic (MCL) system encompasses several cortical and limbic brain structures with several projections which have been strongly implicated in addiction. Central to this system is the VTA which is primarily composed of DA neurons that project to the Acb (mesolimbic) and the prefrontal cortex (PFC; mesocortical) and, to a lesser extent, the amygdala (Amyg) and hippocampus (HPC; extended Amyg; McBride 2002; Morales and Margolis 2017). Activity in both pathways is heavily modulated by glutamatergic signaling which, under normal circumstances, maintains a state of glutamate homeostasis (Scofield et al. 2016). Structures including the PFC, basolateral amygdala (BLA), HPC, and paraventricular nucleus of the thalamus (PVN) provide glutamate innervation to the MCL and act to modulate neural activity associated with reward as well as reinforcement (Fig. 14.1; Wassum and Izquierdo 2015; Cooper et al. 2017; Bossong

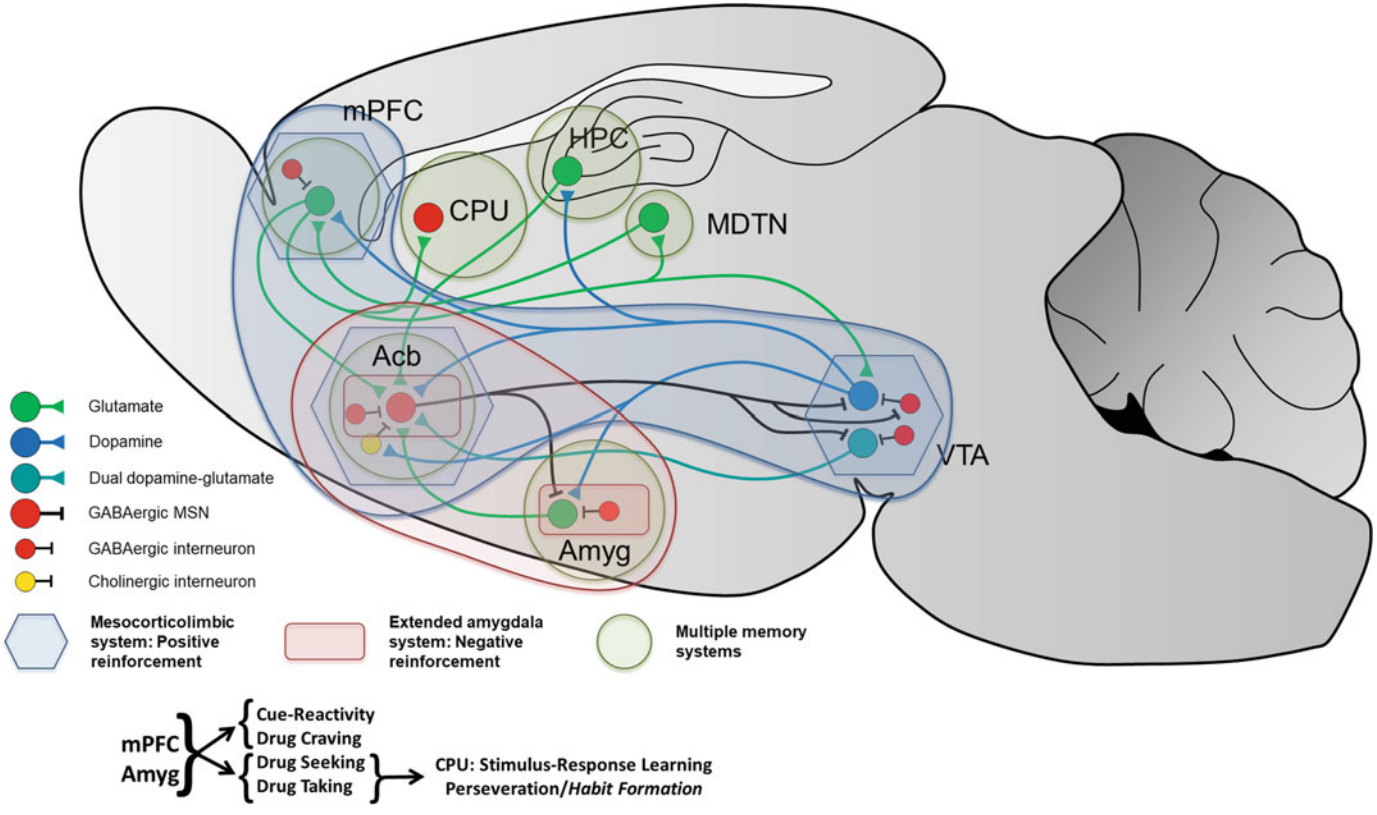

Fig. 14.1 Mesocorticolimbic reward circuitry. Simplified diagram of the ventral tegmental area (VTA) and nucleus accumbens (Acb) reward circuit. The illustration depicts key neuronal projections within the mesocorticolimbic system implicated in drug-related learning, reward, memory, and abuse. The primary reward circuit includes projections from the VTA to the Acb, which releases dopamine in response to reward stimuli. GABAergic projections from the Acb to the VTA occur through a direct pathway mediated by D1-type medium spiny neurons (MSNs) that innervate the VTA or the indirect pathway mediated by

D2-type MSNs which innervate the VTA via GABAergic neurons in the ventral pallidum (not shown). The Acb receives dense glutamatergic inputs from the hippocampus (HPC), basolateral amygdala (BLA), paraventricular nucleus of the thalamus (PVN), and medial prefrontal cortex (mPFC). These glutamatergic inputs control aspects of reward-related perception and memory. Additionally, modulation of reward circuitry occurs via serotonin and norepinephrine systems from the dorsal raphe nuclei (DR) and locus coeruleus (LC), respectively. CPU, caudate putamen; MDTN, medial dorsal thalamic nucleus. The multiple memory systems are depicted by the green circles and include: HPC-mediated spatial and autobiographical learning and memory; CPU-mediated automatic/stimulus-response learning and memory; amygdala-mediated fear-associated learning and memory as well as salience modulation of HPC- and CPU-mediated learning and memory; Acb-mediated conditioned place preference, which is also modulated by input from the amygdala; and PFC-mediated working memory

et al. 2018; Otis et al. 2019). The Acb is divided into the shell (AcbSh) and core (AcbCo) subregions which receive glutamatergic innervation from the infralimbic (IL) and prelimbic (PL) regions of the medial mPFC, respectively (Kelley 1999; McBride et al. 1999) and exhibit opposing influence on motivated behavior associated with reward (i.e., PL→AcbC = go; IL→AcbSh = stop; Peters et al. 2009; Gass and Chandler 2013; Gourley and Taylor 2016). Thus, the Acb represents an important point of convergence for reward signaling that is heavily influenced by MCL-associated glutamate projections (Fig. 14.1; Di Chiara and Imperato 1988; Floresco 2015; Scofield et al. 2016).

14.3 Glutamate Regulation & Trafficking

Glutamate synthesis and metabolism is cyclical in nature. The metabolic, diffusion, transport, and catabolic processes significantly contribute to the maintenance of glutamate homeostasis and the prevention of neuronal excitotoxicity that can result from excessive synaptic glutamate and subsequent overactivation of glutamate receptors. The concentration of glutamate is strictly controlled, with basal levels varying considerably across nuclei and neurocircuits. Intracellular glutamate concentration is the greatest within synaptic vesicles where it can reach 100 mM (Hayashi 2018). Other intracellular glutamate levels are estimated to be near 2 mM, while extracellular levels are in the low micromolar range. Glutamate in the synaptic cleft is maintained at an even lower level at less than 20 nM during resting conditions which can briefly exceed 1 mM following action potential mediated release (Moussawi et al. 2011; Hayashi 2018; Mahmoud et al. 2019). Glutamate returns to resting levels within milliseconds through both diffusion and transport. The subregional differences in concentration gradients within the CNS indicate the importance of maintaining normal physiological levels both temporally and spatially as well as its potential role in neuropsychiatric diseases (Kalivas 2009; Bell et al. 2016a; Spencer et al. 2016).

In contrast to many neurotransmitters that rely heavily on neuronal uptake, glutamate uptake regulation is highly dependent upon glial cells (i.e., astrocytes). Glial regulation occurs via active transport of glutamate from the synapse into surrounding astrocytes that is then converted into glutamine by glutamine synthetase (GS; Fig. 14.2; Danbolt 2001; Zhou and Danbolt 2014; Logica et al. 2016). Next, the newly synthesized glutamine is shuttled from astrocytes back to neurons via glutamine transporters (GlnT) found in the plasma membrane of both cell types (Fig. 14.2). Specifically, GlnTs are members of the sodium-coupled neutral amino acid transporter (SNAT) family and utilize the electrochemical gradient across membranes to transport against concentration gradient. These include SNAT3 (*SLC38A3*) and SNAT5 (*SLC38A5*), which move glutamine out of the glial cell and into the peri-synapse where concentrations range from 200 to 800 μM (Bröer and Brookes 2001; Pochini et al. 2014). Glutamine is then transported into the excitatory presynaptic compartment at concentrations up to 20 mM through

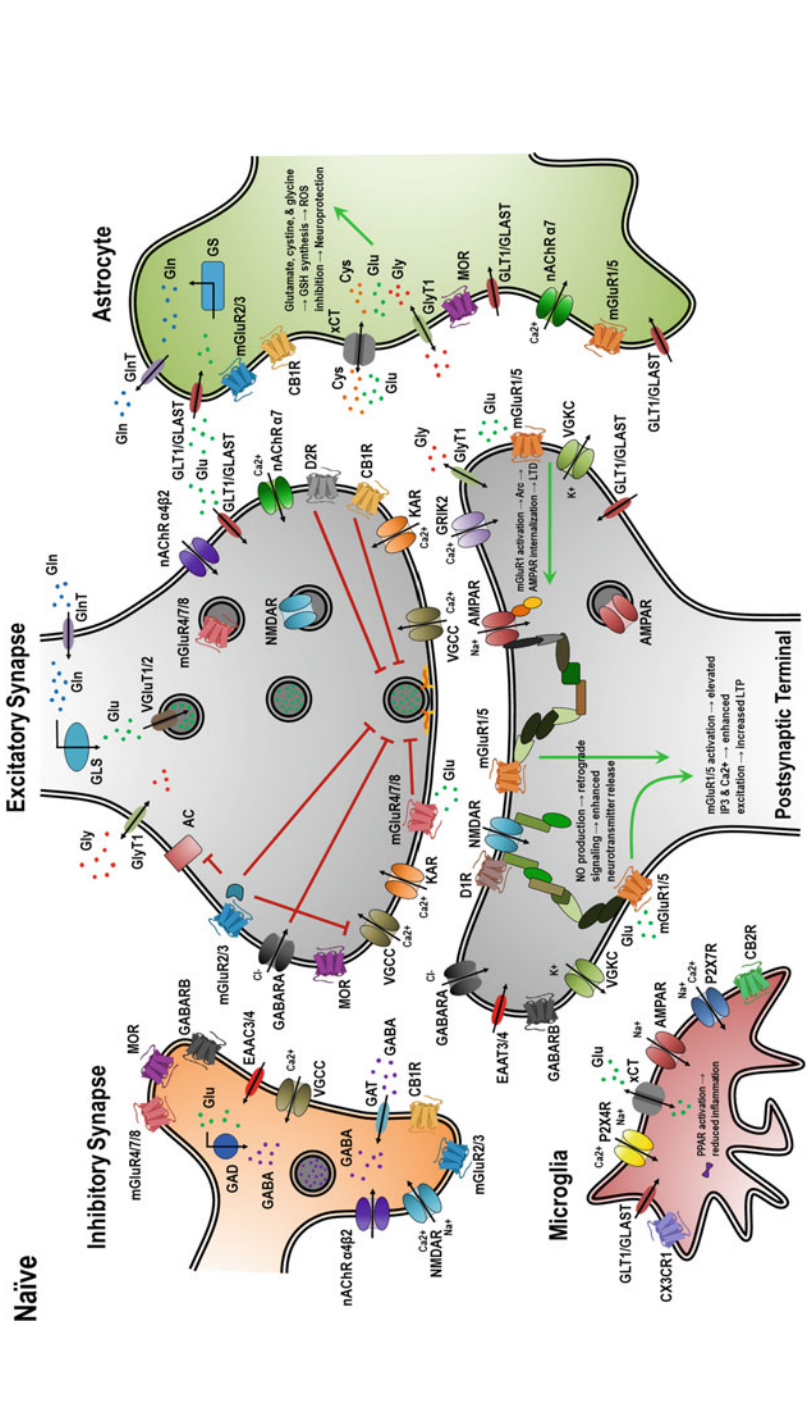

Fig. 14.2 Naïve excitatory synapse. Simplified illustration of a prototypic glutamatergic synapse in the brain. Functionally, Inhibitory control over excitatory neurotransmission is predominantly mediated through the release of GABA to maintain normal CNS function; and, microglia are the resident immune cells of the brain with activity levels and morphology that are highly dependent on physiological or pathological influences. Microglia in the surveillance state, previously referred to as resting state, are mobile cells that continuously monitor the surrounding microenvironment for immune signals. Once activated, microglia functioning can range from pro-inflammatory to neuroprotective based on the initiating neuroimmune factors. The presynaptic terminal governs glutamate release through a number of mechanisms. Under normal conditions, the reliability and magnitude of glutamate release can be reduced through stimulation of presynaptically located Gi/o coupled G-protein coupled receptors (GPCR) such as group II metabotropic glutamate receptors (mGluR2/3),

Fig. 14.2 (continued) dopamine receptor D2 (D2R), cannabinoid 1 receptors (CB1R), or mu-opioid receptors (MOR). Conversely, glutamate release can be enhanced by increased afferent stimulation through activation of presynaptic Gs coupled GPCRs, nicotinic acetylcholine receptors (nAChR), or retrograde messengers released from the postsynaptic cell. Postsynaptic terminals are highly dynamic and responsive to changes in *N*-methyl-*D*-aspartate receptor (NMDAR), voltage-gated calcium channels (VGCC), group I metabotropic glutamate receptors (mGluR1/5), and postsynaptic calcium transient activity. Additionally, the postsynaptic density (PSD) is a cytoskeletal specialization located in the postsynaptic terminal that contains integral receptors, scaffolding proteins, kinases, and other secondary messengers critical for downstream signal integration and synaptic plasticity. Finally, astrocytes play a central role in regulating glutamatergic transmission. Maintenance of homeostasis occurs through rapid buffering of potassium and glutamate, supplying neuronal glutamine (Gln) by its conversion from glutamate via the enzyme glutamine synthetase (GS), and generation of a primary CNS antioxidant glutathione (GSH)

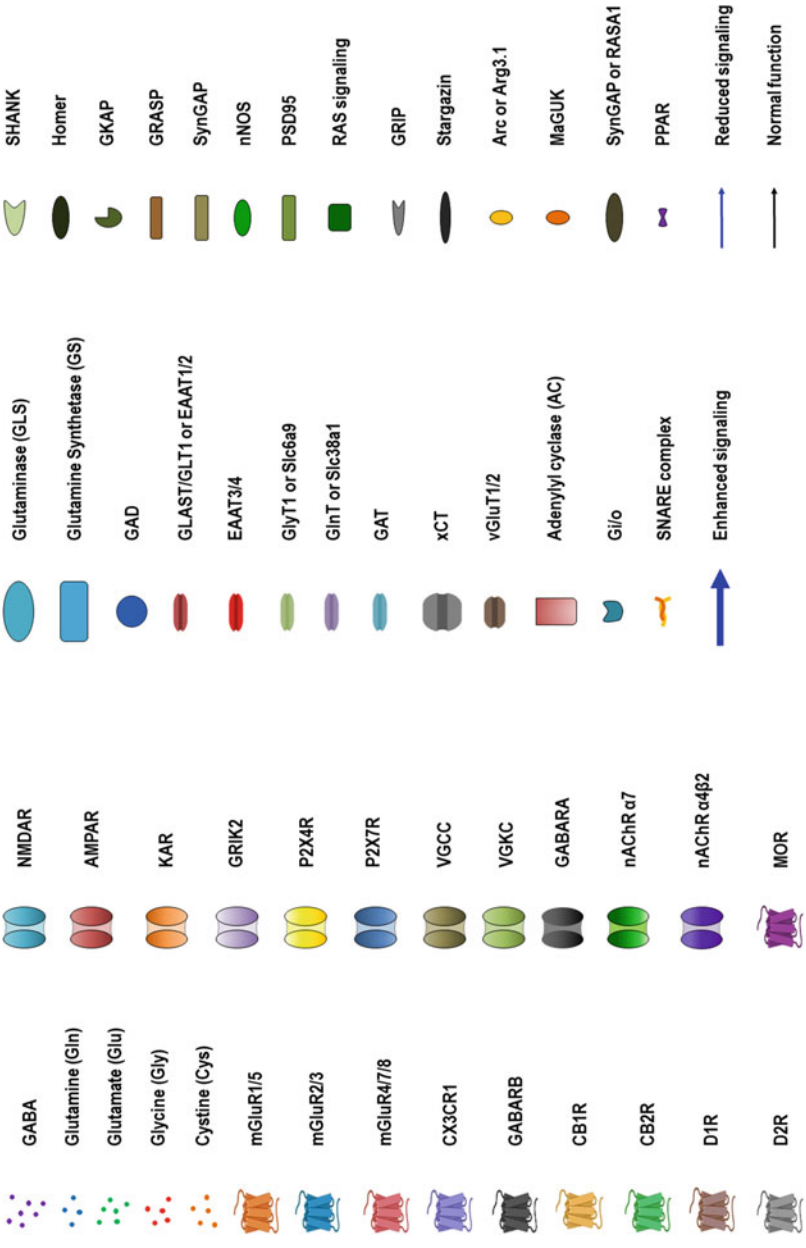

Fig. 14.2 (continued)

Table 14.1 Summary of glutamate transporters

Excitatory Amino Acid Transporters (EAAT)					
Human	Rodent	Gene	CNS distribution	Cell type	Subcellular localization
EAAT1	GLAST	SLC1A3	cerebral cortex, cerebellum, spinal cord	Astrocytes, oligodendrocytes	perisynaptic
EAAT2	GLT-1	SLC1A2	whole brain, cerebellum, spinal cord, retina	astrocytes, neurons	perisynaptic, presynaptic
EAAT3	EAAC1	SLC1A1	hippocampus, striatum, cerebellum	predominantly neurons, some glia	postsynaptic, cell soma, dendrites
EAAT4	EAAT4	SLC1A6	cerebellum	Purkinje cells	postsynaptic, dendrites
EAAT5	EAAT5	SLC1A7	retina	bipolar cells, photoreceptors	presynaptic
Vesicular Glutamate Transporters (vGluT)					
vGluT1	vGluT1	SLC17A7	cerebral cortex, cerebellum, spinal cord	glutamatergic neurons, astrocytes	synaptic vesicles, axon terminals
vGluT2	vGluT2	SLC17A6	ventral tegmental area, basolateral amygdala, nucleus accumbens, brain stem	glutamatergic neurons, dopaminergic neurons	synaptic vesicles, axon terminals
vGluT3	vGluT3	SLC17A8	hippocampus, nucleus accumbens, dorsal striatum, olfactory tubercle, medial raphe nuclei	serotonergic neurons, acetylcholinergic neurons, GABA interneurons, glutamatergic neurons, and astrocytes	synaptic vesicles, cell soma, dendrites, glial endfeet

SNAT1 (*SLC38A1*), SNAT2 (*SLC38A2*), and/or SNAT7 (*SLC38A7*; Chaudhry et al. 2002a, b). Importantly, glutamine can be moved in and out of the synaptic space without inducing neurotoxic cascades (Deitmer et al. 2003; Pochini et al. 2014; Zhou and Danbolt 2014; Rao et al. 2015). This metabolic/catabolic sequence is particularly advantageous in that it reduces excessive synaptic glutamate levels which can produce neuroadaptations associated with SUDs and neurotoxicity (Aschner et al. 2007; Lan et al. 2014). Glutaminase then converts intraneuronal glutamine into glutamate (Rowley et al. 2012), which is packaged into secretory vesicles by vesicular glutamate transporters (vGluT) in preparation for exocytosis. These include vGluT1 (*SLC17A7*), vGluT2 (*SLC17A6*), and vGluT3 (*SLC17A8*; Table 14.1; Bellocchio et al. 2000; Takamori et al. 2000a, b).

There is a significant potential for excessive glutamate in the synapse to induce overactivation of receptors leading to excitotoxicity and neuronal death. Thus, efficient glutamate uptake and transport from the synapse and surrounding area is essential to prevent cell death (Danbolt 2001; Rao et al. 2015; Bell et al. 2016a;

Mahmoud et al. 2019; Zhang et al. 2019). There are five transporters that regulate extracellular glutamate levels and these are part of the solute carrier 1 (*SLC1A*) family. These transporters are excitatory amino acid transporters (i.e., EAAT1, EAAT2, EAAT3, EAAT4, and EAAT5) and correspond to human genes *SLC1A3*, *SLC1A2*, *SLC1A1*, *SLC1A6*, and *SLC1A7*, respectively (Table 14.1). The rodent homologues are referred to as glutamate aspartate transporter (GLAST; *Slc1a3*), glutamate transporter 1 (GLT-1; *Slc1a2*), excitatory amino acid carrier 1 (EAAC1; *Slc1a1*), EAAT4 (*Slc1a6*), and EAAT5 (*Slc2a7*; Wadiche et al. 1995; Arriza et al. 1997; Tanaka 2000). Similar to GlnTs, EAAT makes use of electrochemical gradients to transport glutamate against its concentration gradient. This occurs through cotransport of one H^+ and three Na^+ ions along with the glutamate molecule while exporting a single K^+ ion (Grewer et al. 2008).

Glycine and glycine transport are also critical when exploring the prototypical excitatory synapse. The *N*-methyl-D-aspartate receptor (NMDAR) contains subunits with a co-agonist glycine binding site that potentiates glutamate signaling as well as priming the receptor for internalization (Nong et al. 2003). Glycine transporter 1 (GlyT1) encoded by *SLC6A9* is principally localized on glia, while GlyT2 (*SLC6A5*) is neuronally expressed at excitatory synapses. Additionally, there has been increased interest in the efficacy of N-acetylcysteine to treat neuropsychiatric disorders. It is therefore equally important to recognize the significance of the cystine–glutamate exchanger (xCT; *Slc7a11*) and its effects on reversing neuronal damage induced by excitotoxicity and/or oxidative stress (Lewerenz et al. 2013). The xCT is commonly localized on astroglial cells and functions to exchange extracellular cystine for intracellular glutamate at a one-to-one ratio (Watts et al. 2014). Glutamate is released in the exchange of cystine and binds at the presynaptic mGluR2/3, thereby blocking synaptic glutamate release (Javitt et al. 2011; Moran et al. 2005) and acting as a regulatory mechanism of glutamate homeostasis. Next, cystine can be converted into cysteine, which is used to synthesize glutathione as well as other proteins. Glutathione is a key antioxidant and functions to prevent or reverse neuronal injury induced by excessive levels of glutamate and free radicals (Patten et al. 2013).

14.4 Vesicular Glutamate Transporters

The vesicular glutamate transporters (vGluTs) are highly expressed in neurons throughout the CNS with vGluT1 and vGluT2 more commonly found in glutamatergic cells (Table 14.1). Specifically, vGluT1 localization is generally widespread and found in the HPC, Amyg, Acb, PFC, cerebellum, and spinal cord. Expression of vGluT2 is more limited and is localized to the BLA, Acb, and VTA. On the other hand, vGluT3 is found primarily in non-glutamatergic cells (e.g., serotonergic, glial, GABAergic, cholinergic) of the Acb, olfactory tubercle, HPC, and MRN (Wang et al. 2019; Zhang et al. 2019). Relative to EAATs, vGluTs display 100–1000-fold less affinity for glutamate (Shigeri et al. 2004). Importantly, vGluTs

have a micromolar affinity for glutamate but do not transport aspartate, glutamine, or GABA. The function of vGluTs is known to be dependent upon a vesicular proton electrochemical gradient that is produced by ATPase activity. The transporters also have a biphasic interaction with Cl^-, where low concentrations initiate uptake while higher concentrations have an inhibitory action on transporter function (Shigeri et al. 2004).

Alterations in vGluT1 have been associated with schizophrenia, addiction, Alzheimer's disease, and epilepsy (Alonso-Nanclares and De Felipe 2005; Eastwood and Harrison 2005; Mark et al. 2007; van der Hel et al. 2009). For example, vGluT1 mRNA was increased five-fold in the DRN of rats following peri-adolescent binge like alcohol drinking. This change was coupled with a significant reduction in both vGluT2 and vGluT3 mRNA expression levels (McClintick et al. 2015). Additionally, following exposure to methamphetamine there was a significant and long-lasting increase in vGluT1 mRNA and protein levels in the striatum (Mark et al. 2007). Knackstedt and colleagues (2009, 2010) reported a reduction in vGluT1 expression in the AcbCo following self-administration of cocaine or nicotine. Due to the distinct regional and cellular expression of vGluT isoforms, these proteins are often used as markers to delineate specific neuronal subpopulations. The deletion of vGluT2 induced prenatal or neonatal mortality and an almost complete loss of glutamate activity in the thalamus, but not in the HPC (Moechars et al. 2006). Activation of vGluT2 expressing DA neurons in the VTA enhanced learning of a conditioned place preference as well as reinforcing instrumental behavior (Wang et al. 2015). Repeated deprivations from alcohol reduced vGluT2 in the AcbSh (Zhou et al. 2006). The involvement of vGluT3 is involved in fear, stress, hearing, as well as stimulant-induced locomotor activity (Ryu et al. 2017; Balazsfi et al. 2018; Li et al. 2018; Mansouri-Guilani et al. 2019; Sakae et al. 2019). Collectively, these findings provide evidence that vGluTs may play an important role in addiction behaviors.

14.5 Plasma Membrane Glutamate Transporters

Glutamate transporters are located throughout the brain. EAAT1, or GLAST, is located both on the plasma membrane and the mitochondrial membrane of glial cells (i.e., astrocytes, microglia, and oligodendrocytes). EAAT2 (GLT-1) is located on astrocytes, microglia, oligodendrocytes and on axon terminals (e.g., CA3 of the HPC) and represents the primary transporter that removes more than 90% of glutamate from the synapse, which is necessary to prevent excitotoxicity and promote normal physiological function (Danbolt 2001). EAAT3, encoded by *SLC1A1*, is located on neurons, specifically dendrites and axon terminals. Like the predominantly glial transporters, EAAT3 removes excess glutamate from the synapse but also transports aspartate and cysteine. A *SLC1A1* polymorphism is present in a subpopulation of individuals with obsessive-compulsive disorder (Stewart et al. 2013). In addition, there is some evidence that amphetamine leads to internalization

of EAAT3 and this may coincide with internalization of the DA transporter as well (Underhill et al. 2014). EAAT4 is expressed predominantly in the cerebellum transporting both glutamate and aspartate concurrent with the transport of chloride ions (Fairman et al. 1995), as well as in spinal cord, forebrain, and astrocyte (Hu et al. 2003). In addition, the xCT (*SLC7A11*), a chloride-dependent, sodium-independent transporter is located primarily on astrocytes (Bridges et al. 2001; Lin et al. 2016). While the xCT is present throughout the brain, there is especially high expression in the BLA and PFC of the MCL (Bridges et al. 2012). Finally, the EAAT5 is found only in the retina (Table 14.1). For more information, there are additional reports that expand on the mechanisms of glutamate transport (Rothstein et al. 1994; Lehre et al. 1995; Wadiche et al. 1995; Arriza et al. 1997; Tanaka 2000; Danbolt 2001; Huggett et al. 2002; Beschorner et al. 2007; Bellesi and Conti 2010; Reissner and Kalivas 2010; Carbone et al. 2012; Karki et al. 2015; Bell et al. 2016a; Spencer et al. 2016; Mazaud et al. 2019).

14.6 Upregulating Glutamate Transporters and the Treatment of SUDs

Substantial evidence suggests that the development of substance dependence involves changes in many aspects of glutamate homeostasis. Glutamate transmission is heavily regulated by the glutamate transporters described in this review. Importantly, GLT-1 is considered the primary glutamate transporter in the brain that regulates up to 90% of extracellular glutamate. Concurrently, xCT regulates glutamate uptake through the exchange of extracellular cystine for intracellular glutamate (Bannai and Ishii 1982; Bannai 1984; Sari 2013). Modulation of glutamate transport through upregulation of GLT-1 is a promising avenue to treat dependence on drugs of abuse, including ethanol and cocaine (Rao et al. 2015; Spencer and Kalivas 2017; Alasmari et al. 2018a, b). Discussed here are the effects of medications, known to upregulate GLT-1, on the attenuation of drug-seeking behaviors. An emphasis on the use of β-lactam antibiotics, particularly ceftriaxone and N-acetylcysteine, as GLT-1 upregulators to attenuate drug-seeking behaviors is of particular interest.

14.7 Ceftriaxone and Ethanol

The expression of GLT-1 and its function can be upregulated by FDA-approved β-lactam antibiotics, which increase glutamate uptake (Rothstein et al. 2005; Spencer and Kalivas 2017). Ceftriaxone is a beta-lactam antibiotic that is known to increase glutamate reuptake through the upregulation of glial GLT-1 expression and/or function (Rothstein et al. 2005). Ceftriaxone decreases ethanol consumption and ethanol preference over water in alcohol-preferring (P) rats (Sari et al. 2011,

2013b; Rao and Sari 2014; Das et al. 2015) and outbred rats (Stennett et al. 2017). These decreases in ethanol intake are associated with normalization (i.e., reversal of ethanol-induced decreases) of GLT-1 and/or xCT protein levels in the Acb and/or PFC (Sari et al. 2011, 2013a, 2013b; Rao and Sari 2014; Das et al. 2015). Ceftriaxone attenuated ethanol-induced increases in extracellular glutamate in the Acb in male P rats (Das et al. 2015), an effect that is likely mediated through upregulation of GLT-1. In contrast, Stennett et al. (2017) found that ethanol intake in Sprague-Dawley rats did not alter GLT-1 and xCT protein levels, which suggests that there might be dysfunction of these transporters without alteration of their expression. However, Sprague-Dawley rats consume much less ethanol than Wistars, Long-Evans, and selectively bred alcohol-preferring rat lines (cf., Bell et al. 2014) possibly leading to a floor-effect in the Stennett et al.' (2017) study. It is important to note that the expression of GLT-1 was not affected in the PFC and Acb in P rats that were experiencing relapse-like ethanol behavior (Qrunfleh et al. 2013). However, ceftriaxone treatment upregulated GLT-1 in these brain regions and attenuated relapse-like ethanol-seeking behavior, which suggests that restoring dysfunctional GLT-1 is critical in the attenuation of ethanol seeking (Qrunfleh et al. 2013). Other studies confirmed the efficacy of ceftriaxone on reducing relapse-like ethanol-seeking behaviors (Abulseoud et al. 2014; Alhaddad et al. 2014b; Rao and Sari 2014) and alleviating ethanol withdrawal symptoms in male P rats (Abulseoud et al. 2014), and this effect was associated with an upregulation of GLT-1 and xCT in the Acb, PFC, and/or whole striatum (i.e., Acb, caudate, and putamen; Abulseoud et al. 2014; Alhaddad et al. 2014b) and specific upregulation of GLT-1 isoforms (GLT-1a and GLT-1b; Alhaddad et al. 2014a). Additionally, pretreatment with ceftriaxone during acquisition of ethanol drinking reduces the maintenance of ethanol intake in female adolescent and adult P rats, with a greater effect in adult rats (Sari et al. 2013a).

14.8 Ceftriaxone and Psychostimulants

Ceftriaxone appears to be more effective in reducing cocaine-seeking behaviors than cocaine self-administration itself (Sari et al. 2009; Sondheimer and Knackstedt 2011; Roberts-Wolfe and Kalivas 2015). Ceftriaxone attenuated cocaine-primed, context-induced, or other cue-induced reinstatement of cocaine-seeking behaviors (Sari et al. 2009; Knackstedt et al. 2010; Roberts-Wolfe and Kalivas 2015; LaCrosse et al. 2016; Bechard et al. 2018; Bechard and Knackstedt 2019). Ceftriaxone-induced attenuation of cocaine-seeking is associated with normalization (i.e., reversal of cocaine-induced reductions) of GLT-1 and/or xCT expression in the Acb (Kalivas 2009; Sari et al. 2009; Knackstedt et al. 2010; Sondheimer and Knackstedt 2011; LaCrosse et al. 2016; Spencer and Kalivas 2017; Bechard et al. 2018).

Importantly, ceftriaxone has also been found to attenuate reinstatement to methamphetamine seeking behavior in conditioned place preference paradigm (Abulseoud et al. 2012), possibly through overexpression of GLT-1. For instance, overexpression of GLT-1 in Acb using gene transfer technology blocked

methamphetamine reinstatement in conditioned place preference (Fujio et al. 2005). It is important to note that exposure to methamphetamine can lead to increase of glutamate release in the Acb and PFC (Ito et al. 2006; Labarca et al. 1995; Shoblock et al. 2003; Stephans and Yamamoto 1995; Xue et al. 1996). These studies would suggest that upregulation of GLT-1 with ceftriaxone is critical to the regulation of glutamate uptake and subsequent attenuation of the reinstatement of methamphetamine seeking behavior. Acute repeated exposure to high dose of methamphetamine of 10 mg/kg, i.p., every 2 h × 4/day downregulated the expression of GLT-1 in the dorsal striatum, medial PFC and Acb (Alshehri et al. 2017; Althobaiti et al. 2016b). Importantly, ceftriaxone attenuated the effects of methamphetamine-induced GLT-1 downregulation in these brain regions (Alshehri et al. 2017; Althobaiti et al. 2016b) as well as methamphetamine-induced alterations in tissue content of several neurotransmitters, including glutamate (Althobaiti et al. 2016a).

14.9 Ceftriaxone and Other SUDs

As with ethanol, cocaine, and methamphetamine, chronic nicotine exposure downregulated astrocytic GLT-1 and xCT within the Acb and/or VTA (Knackstedt et al. 2009; Gipson et al. 2013; Spencer and Kalivas 2017). However, ceftriaxone had no effect on the development of a nicotine conditioned place preference in mice (Alajaji et al. 2013), but did attenuate nicotine-induced reinstatement in conditioned placed preference paradigm (Alajaji et al. 2013; Philogene-Khalid et al. 2017) and reversed nicotine withdrawal signs (Alajaji et al. 2013). In rats, ceftriaxone reduced oral nicotine-sucrose and nicotine-ethanol intake by P rats, which was concurrent with normalization of GLT-1 expression levels in the Acb and PFC (Sari et al. 2016). Overexpression of GLT-1 in the Acb reduced morphine conditioned place preference but did not affect somatic signs of naloxone-precipitated morphine withdrawal (Fujio et al. 2005). Administration of ceftriaxone also attenuated the development of tolerance to the anti-nociceptive effect of morphine and reduced naloxone- or naltrexone-precipitated morphine withdrawal in mice and rats (Rawls et al. 2010; Habibi-Asl et al. 2014; Medrano et al. 2015). Moreover, morphine-induced conditioned place preference and morphine-associated locomotor sensitization were attenuated by ceftriaxone treatment (Schroeder et al. 2014). Shen et al. (2014) reported that heroin self-administration impaired functional glutamate uptake and decreased GLT-1 expression in the Acb. These authors also reported that ceftriaxone reduced cue-induced reinstatement of heroin seeking (Shen et al. 2014). In addition, ceftriaxone treatment attenuated morphine-induced hyperthermia (Rawls et al. 2007). A more recent study showed that ceftriaxone attenuated the reinstatement of hydrocodone-induced conditioned place preference and normalized a hydrocodone-induced reduction of xCT expression in the Acb (Alshehri et al. 2018).

14.10 Other Upregulators of GLT-1 and SUDs

Administration of the β-lactam antibiotics amoxicillin, Augmentin (amoxicillin/clavulanate; Goodwani et al. 2015; Hakami et al. 2016), and ampicillin (Alasmari et al. 2015; Rao et al. 2015) attenuates ethanol intake in male P rats. Similar to ceftriaxone, systemic administration of Augmentin and amoxicillin upregulated/normalized xCT and GLT-1 levels in the Acb and/or PFC (Alasmari et al. 2015; Goodwani et al. 2015; Hakami et al. 2016, 2017). A recent report by Hammad et al. (2017) examined the effects of the β-lactam antibiotic ampicillin/sulbactam on cocaine reinstatement by male P rats. These authors found that cocaine-primed reinstatement downregulated GLT-1 and xCT in the AcbSh and AcbCo, but not the dorsal medial PFC (dmPFC; Hammad et al. 2017). Ampicillin/sulbactam reduced cocaine-induced reinstatement in a conditioned place preference paradigm while normalizing the expression of GLT-1 and xCT in the AcbSh, AcbCo, and dorsal mPFC as well as mGluR1 levels in the AcbCo, although there was a decrease in locomotor activity following treatment (Hammad et al. 2017). Importantly, ampicillin/sulbactam attenuated cocaine-induced ethanol deprivation effects, and this effect was associated with upregulation of GLT-1 and xCT expression in the AcbSh and AcbCo as well as dmPFC (Hammad and Sari 2020).

Cefazolin and cefoperazone, both β-lactam antibiotics, decreased ethanol but not sucrose intake (Rao et al. 2015; Alasmari et al. 2016). Cefazolin and cefoperazone both upregulate GLT-1 and its isoforms (GLT-1a and GLT-1b) in the Acb and PFC (Rao et al. 2015; Alasmari et al. 2016). Regarding xCT, cefazolin increased expression in both the Acb and PFC, while cefoperazone only upregulated xCT expression in the Acb (Alasmari et al. 2016). Clavulanic acid, a β-lactamase inhibitor, upregulates GLT-1 in the Acb (Kim et al. 2016). Clavulanic acid decreased ethanol intake at a dose that was approximately 30-fold lower than ceftriaxone in P rats (Hakami and Sari 2017; Althobaiti et al. 2019). This effect was associated with restored expression of GLT-1 and xCT in Acb (Hakami and Sari 2017; Althobaiti et al. 2019) and increased the expression of mGlu2/3R in the AcbSh and mPFC (Althobaiti et al. 2019). In addition, clavulanic acid blocked the reinstatement of methamphetamine-induced condition place preference (Althobaiti et al. 2019) and this effect was associated with restoration of GLT-1 and xCT levels in the AcbSh, but not in the AcbCo. In Mice, clavulanic acid produced significantly lower breakpoints for cocaine maintained on a progressive ratio schedule of reinforcement (Kim et al. 2016). Clavulanic acid also attenuated reinstatement to morphine in rats tested using the conditioned place preference paradigm (Schroeder et al. 2014).

Other non-antibiotic drugs have been tested in male P rats and found to attenuate ethanol intake, an effect associated with upregulation/activation of GLT-1. Among these synthetic drugs, 3-(3-pyridyl)-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate (GPI-1046), an analog of FK506, and (R)-(−)-5-methyl-1-nicotinoyl-2-pyrazoline (MS-153). GPI-1046 treatment reduced ethanol intake in P male rats and upregulated the expression of GLT-1 levels in key central reward brain regions (i.e., Acb and PFC; Sari and Sreemantula 2012).

MS-153 treatment also reduced ethanol intake and attenuated an ethanol-induced reduction in the expression of GLT-1 in the Acb, Amyg, and HPC (Aal-Aaboda et al. 2015; Alhaddad et al. 2014b).

14.11 N-acetylcysteine

N-acetylcysteine (NAC) is an FDA-approved treatment for paracetamol (acetaminophen) overdose. NAC is oxidized into cystine leading to increase in availability of cystine for the astroglial xCT (Nocito Echevarria et al. 2017). Increased levels of cystine lead to an enhancement of glutamate exchange by astroglial cells resulting in elevated concentrations of glutamate within the extrasynaptic space, increased synthesis of glutathione (GSH) in astrocytes, and restoration of downregulated GLT-1 expression (Berk et al. 2013; Brown et al. 2013; Nocito Echevarria et al. 2017). We suggest that the restoration of GLT-1 is associated with decrease in extracellular glutamate concentrations in the brain and increases in the exchange of cystine and glutamate thereby leading to increases in the biosynthesis of GSH. This is an important process to reduce oxidative stress, which might be caused with chronic exposure to drugs of abuse. Substantial research has shown that NAC has antioxidant, anti-inflammatory, and neuroprotective properties (cf., Santus et al. 2014; Shahripour et al. 2014; Bhatti et al. 2017; Markoutsa and Xu 2017; Pei et al. 2018).

14.12 N-acetylcysteine and Ethanol

Oral administration of NAC reduced ethanol intake, relapse drinking, and relapse-associated blood ethanol concentrations in the Wistar derived University of Chile Bibulous (UChB) alcohol-preferring rats (Quintanilla et al. 2016, 2018; Israel et al. 2019). Additionally, NAC fully abolished increased levels of oxidative stress and the neuroinflammation induced by chronic ethanol intake by UChB rats (Quintanilla et al. 2018). NAC administration in an ethanol-dependent animal model reduced ethanol-intake, operant ethanol-self-administration, ethanol break-point (i.e., progressive ratio), ethanol-seeking behavior, and relapse-like ethanol-seeking behavior (Lebourgeois et al. 2019). Moreover, NAC prevented stress-potentiated ethanol intake and abolished conditioned stress-induced reinstatement of ethanol-seeking behavior in outbred rats (Garcia-Keller et al. 2019).

14.13 N-acetylcysteine and Cocaine

NAC appears to have limited effects on cocaine self-administration as it failed to alter cocaine self-administration in rats (Murray et al. 2012; Frankowska et al. 2014) or non-human primates (Kangas et al. 2019). Nevertheless, it appears to be intricately involved in drug learning as others have reported that NAC prevented cocaine-primed (Baker et al. 2003; Amen et al. 2011; Frankowska et al. 2014), and cue-induced (Reichel et al. 2011; Murray et al. 2012; Frankowska et al. 2014; Reissner et al. 2015) as well as stress-induced (Garcia-Keller et al. 2019), reinstatement of cocaine-seeking in rats but not in non-human primates (Kangas et al. 2019). NAC has also been found to facilitate extinction of drug-lever responding in rats (LaRowe and Kalivas 2010) and non-human primates (Kangas et al. 2019). In addition, Murray et al. (2012) reported that NAC was able to attenuate both early and late stages of acquisition and maintenance of cue-induced cocaine-seeking behavior. Intra-accumbal NAC attenuated cue-induced cocaine-seeking behavior and cue-cocaine primed reinstatement of cocaine-seeking behavior, which was enhanced by the mGluR5 antagonist MTEP (Kupchik et al. 2012). NAC restored the expression of GLT-1, but not xCT, in MCL subregions, which was critically important for the ability of NAC to suppress cue-induced reinstatement of cocaine-seeking behavior (Reissner et al. 2015; Ducret et al. 2016). Another study reported that NAC prevented the loss of control observed with chronic cocaine self-administration (Madayag et al. 2007). However, in other work acute, chronic, and progressive-ratio cocaine self-administration was not affected by NAC, although NAC did facilitate punishment-induced extinction (Ducret et al. 2016). The discrepancy between these studies may be due to differences in cocaine training history, the dose of cocaine used, or timing of NAC administration prior to drug availability or exposure among other experimental procedures.

14.14 N-acetylcysteine and Other SUDs

Acute administration of NAC can decrease nicotine self-administration without altering food self-administration, whereas chronic administration lasting 14 days had a non-specific attenuating effect on both nicotine and food self-administration (Ramirez-Niño et al. 2013). Furthermore, acute NAC attenuated cue-induced reinstatement of nicotine-seeking behaviors (Ramirez-Niño et al. 2013). Subchronic NAC administration for five days produced mixed results on cue-induced nicotine-seeking. One study found that this regimen of NAC exposure reduced cue-induced nicotine-seeking in male Sprague-Dawley rats but not female rats regardless of estrous cycle phase (Goenaga et al. 2020), while another study found that 5 days of NAC treatment did not alter cue-induced nicotine-seeking in male Sprague-Dawley rats (Powell et al. 2019). These results suggest that there may be sex specific effects of NAC with regard to nicotine craving/relapse behaviors (Goenaga et al.

2020) although the studies did possess differences in experimental procedures which may have affected the results.

Chronic administration of NAC for 14–15 days has consistently inhibited cue-induced nicotine-seeking behavior (Ramirez-Niño et al. 2013; Moro et al. 2019; Namba et al. 2019; Powell et al. 2019; Goenaga et al. 2020). In addition, Moro et al. (2019) indicated that chronic administration of NAC has long-lasting effects for up to 50 days post-treatment(Moro et al. 2019). Interestingly, Moro et al. (2019) observed that NAC administration during abstinence in the home cage failed to reduce cue-induced reinstatement, but administration during experimental cue-exposure therapy or during extinction sessions attenuated cue-induced seeking. This suggests pairing NAC treatment with experimental cue-exposure therapy or extinction sessions may increase the effectiveness of NAC to prevent relapse (Moro et al. 2019). These authors also reported that seven days post experimental cue-exposure therapy was associated with a lower expression of GLT-1 as well as higher expression of GluN2B in the AcbSh of nicotine self-administering rats, which was normalized by NAC treatment (Moro et al. 2019). Fifty days after NAC treatment there was a steep increase in mGluR2 levels in both the AcbSh and AcbCo, as well as normalization of xCT expression in the AcbCo, and normalization of GLT-1 expression in the AcbSh suggesting that NAC treatment can induce long-term increases in glutamate uptake (Moro et al. 2019).

Namba et al. (2019) found that NAC normalized GLT-1 expression in the AcbCo, reduced tumor necrosis factor-alpha (TNFα) expression in the AcbCo, and suppressed α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor to NMDA current ratios, which again suggests NAC acts to restore glutamate homeostasis and attenuate inflammatory response induced by cue-induced nicotine-seeking following nicotine self-administration. Bowers et al. (2016) indicated that NAC reduced the development of a nicotine conditioned place preference, nicotine somatic withdrawal signs, hyperalgesia, while inducing a conditioned place aversion in mice. However, it did not alter palatable food conditioned place preference, anxiety-like behavior, or motoric capacity. In alcohol-preferring UChB rats, oral administration of NAC reduced oral nicotine intake and fully suppressed the reinstatement of a nicotine conditioned place preference (Quintanilla et al. 2018). Moreover, NAC administration fully abolished increased oxidative stress and the neuroinflammatory markers induced by nicotine (Quintanilla et al. 2018). Clinical studies have shown that smokers treated with NAC reported a reduction in the number of cigarettes smoked (Knackstedt et al. 2009; McClure et al. 2015) and rated the first cigarette after an abstinence period as less rewarding (Schmaal et al. 2011). However, these effects were limited because NAC did not have any significant effects on craving (Knackstedt et al. 2009; Schmaal et al. 2011), withdrawal symptoms (Knackstedt et al. 2009; Schmaal et al. 2011), or breath carbon monoxide levels, which is a biomarker for smoking abstinence (Knackstedt et al. 2009). Furthermore, the majority of smokers did not maintain abstinence (Knackstedt et al. 2009; McClure et al. 2015). In contrast, a more recent study reported NAC treatment reduced craving, helped participants to maintain abstinence, and positively affected dysregulated corticostriatal connectivity (Froeliger et al. 2015). Thus, NAC

may act to alter reward processing thereby helping smokers to maintain abstinence immediately following cessation of smoking (Froeliger et al. 2015). Taken together, these findings suggest that NAC may have some efficacy in relapse prevention with regard to smoking.

There have been several clinical studies examining the efficacy of NAC in cocaine-using as well as -dependent subjects. In actively using cocaine-dependent individuals NAC did not alter cocaine use (LaRowe et al. 2013), however, there was evidence that it helped maintain abstinence in individuals who had already achieved abstinence (LaRowe et al. 2013). A more recent study found that cocaine use and problems (Drug Use Disorder Identification Test) were decreased with NAC treatment (Schulte et al. 2018). Lower cocaine-positive urine scores in the NAC group supported these findings (Schulte et al. 2018). Levi Bolin et al. (2017) indicated that NAC treatment significantly attenuated the reinforcing effects of cocaine. However, NAC has had mixed results on psychostimulant craving. It has been shown to reduce cocaine craving (Amen et al. 2011), although others did not find similar effects on craving or self-reported abstinence (Schulte et al. 2018). Also, NAC did not have an effect on cocaine cue-reactivity-associated neural correlates (Schulte et al. 2019). Nevertheless, others have found that NAC suppresses methamphetamine-craving (Mousavi et al. 2015). In early work, the administration of NAC, during extinction, inhibited cue-induced and heroin-primed reinstatement of heroin-seeking with long-lasting effects up to 40 days post-treatment (Zhou and Kalivas 2008). These findings suggest that repeated NAC administration may have therapeutic potential in enhancing abstinence and reducing drug-seeking behaviors and -craving.

14.15 Conclusions

SUDs are characterized by a long-lasting vulnerability to relapse across drug classes. Prolonged neuropathological changes to the glutamatergic system, within the MCL described above, appear to contribute to the addicted state through glutamate dysregulation. The significance of glutamate in learning and memory implicates the magnitude of its role in initiating and promoting addiction, Alzheimer's disease, posttraumatic stress disorder (PTSD), and other psychiatric conditions. The impact of glutamate transport and maintaining homeostasis to avoid neurotoxicity and damage from oxidative stress necessitates additional investigation of EAATs and vGluTs. Further research into the distinct neuroadaptations that result from glutamate dysregulation could provide information needed to develop more effective pharmacotherapeutics to treat addiction. Preclinical research has begun to explore the potential of glutamate transporters as therapeutic targets through NAC and cefazolin. Importantly, continued examination of the mechanisms behind the altered MCL and response to rewarding stimuli following chronic drug exposure may also support the development of pharmacotherapies for individuals with a dual-diagnosis of an SUD comorbid with another psychiatric disorder.

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