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Glutamatergic substrates of drug addiction and alcoholism☆

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ABSTRACT

The past two decades have witnessed a dramatic accumulation of evidence indicating that the excitatory amino acid glutamate plays an important role in drug addiction and alcoholism. The purpose of this review is to summarize findings on glutamatergic substrates of addiction, surveying data from both human and animal studies. The effects of various drugs of abuse on glutamatergic neurotransmission are discussed, as are the effects of pharmacological or genetic manipulation of various components of glutamate transmission on drug reinforcement, conditioned reward, extinction, and relapse-like behavior. In addition, glutamatergic agents that are currently in use or are undergoing testing in clinical trials for the treatment of addiction are discussed, including acamprosate, *N*-acetylcysteine, modafinil, topiramate, lamotrigine, gabapentin and memantine. All drugs of abuse appear to modulate glutamatergic transmission, albeit by different mechanisms, and this modulation of glutamate transmission is believed to result in long-lasting neuroplastic changes in the brain that may contribute to the perseveration of drug-seeking behavior and drug-associated memories. In general, attenuation of glutamatergic transmission reduces drug reward, reinforcement, and relapse-like behavior. On the other hand, potentiation of glutamatergic transmission appears to facilitate the extinction of drug-seeking behavior. However, attempts at identifying genetic polymorphisms in components of glutamate transmission in humans have yielded only a limited number of candidate genes that may serve as risk factors for the development of addiction. Nonetheless, manipulation of glutamatergic neurotransmission appears to be a promising avenue of research in developing improved therapeutic agents for the treatment of drug addiction and alcoholism.

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Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); AC, adenylyl cyclase; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; Amyg, amygdaloid complex; ATP, adenosine triphosphate; BLA, basolateral amygdala; cAMP, cyclic adenosine monophosphate; CB, cannabinoid; CPP, conditioned place preference; CPu, caudate-putamen; DARPP-32, dopamine and cAMP-regulated phosphoprotein-32 kDa; EAAT, excitatory amino acid transporter; EPSC, excitatory postsynaptic current; ERK, extracellular signal-related kinase; FC, frontal cortex; GABA, gamma-aminobutyric acid; GPCR, G-protein coupled receptor; Hipp, hippocampus; ICSS, intracranial self-stimulation; iGluR, ionotropic glutamate receptor; IP_3, inositol triphosphate; IVSA, intravenous self-administration; KA, kainic acid; MAPK, mitogen-activated protein kinase; LTD, long-term depression; LTP, long-term potentiation; MDMA, methylenedioxymethamphetamine; mGluR, metabotropic glutamate receptor; MSN, medium spiny neuron; NAcc, nucleus accumbens; nAChR, nicotinic acetylcholine receptor; NMDA, *N*-methyl-D-aspartate; PKA, protein kinase A; PKC, protein kinase C; PPT, pedunculopontine tegmentum; SNP, single nucleotide polymorphism; Thal, thalamus; THC, Δ9-tetrahydrocannabinol; VGCC, voltage-gated calcium channel; vGluT, vesicular glutamate transporter; VTA, ventral tegmental area; x_c, cystine-glutamate exchanger

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1. Introduction

Drug addiction is defined by several diagnostic criteria set forth by the American Psychiatric Association [1]. These criteria include a loss of control over drug intake, repeated unsuccessful attempts at quitting or reducing drug use, continued drug use despite negative consequences, a reduction in engagement in social, occupational and recreational activities in lieu of drug-seeking or self-administration behavior, and the emergence of symptoms of tolerance or withdrawal. Historically, research into the neurobiological substrates that underlie the rewarding and reinforcing effects of drugs of abuse has focused on the mesolimbic dopamine reward circuitry, comprised primarily of dopaminergic neurons in the ventral tegmental area (VTA) that project rostrally to forebrain and limbic regions such as the nucleus accumbens (NAcc), amygdala (Amyg) and frontal cortex (FC) [2]. However, as can be seen in Fig. 1, there has been a dramatic increase in attention that has been given to the role of the excitatory amino acid glutamate in drug addiction and alcoholism over the past two decades. The purpose of this review is to summarize the effects of drugs of abuse on glutamatergic neurotransmission as well as key findings on the role of glutamate transmission in drug reinforcement, the rewarding effects of drugs of abuse, extinction of drug-seeking behavior, and relapse. Various glutamatergic medications that are either approved for clinical use or are being examined in clinical trials for the treatment of addictive disorders will also be discussed. Finally, a brief summary of findings on potential genetic linkages between individual components of glutamate neurotransmission and addiction is presented.

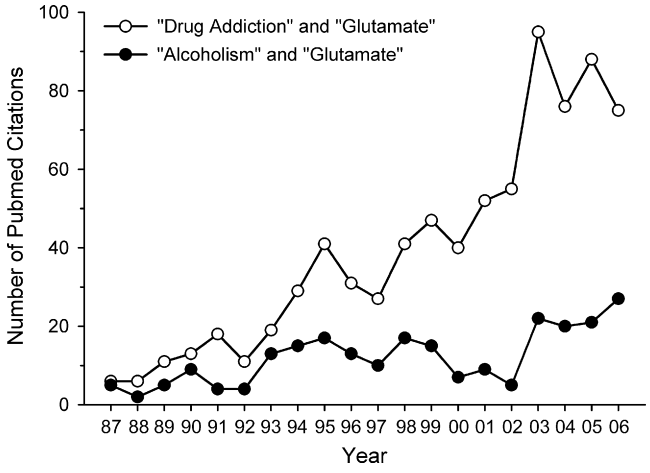

Fig. 1 – Graph showing the increasing number of publications on the topic of glutamate and addiction over the past 20 years. Two separate PubMed searches were performed in April 2007, one using "drug addiction" and "glutamate" as key words (open circles) and the other using "alcoholism" and "glutamate" as key words (filled circles). The resulting number of publications (including review articles and commentaries) are plotted by year for 1987–2006.

2. Animal models of drug addiction and alcoholism

One of the most widely used methods to study drug addiction in animals is the intravenous self-administration (IVSA) paradigm [3]. In this model, experimental animals are implanted with indwelling intravenous catheters (most often in the jugular vein in rodent studies) and are trained to perform an operant task (i.e., lever press or nose-poke) in order to receive an intravenous infusion of cocaine, amphetamine, nicotine, etc. In the case of alcohol (ethanol), execution of the operant task results in presentation of a small amount of an alcohol-containing solution in a receptacle where the animal can consume the solution orally (some studies measure alcohol consumption in the home cage by presentation of two or more bottles containing ethanol solutions). By definition, if the delivery or presentation of the drug solution increases this behavior (i.e., appropriate lever pressing or nose-poking), the drug or alcohol solution is considered to be a positive reinforcer. Environmental cues, such as presentation of stimulus lights or auditory tones, are often paired with drug delivery or alcohol presentation to promote stimulus-drug associations, which enhance drug-taking behavior and can be utilized in subsequent reinstatement tests (see below). The effects of experimental manipulations (i.e., administration of test compounds either systemically or intracerebrally) on drug or alcohol self-administration behavior can then be assessed. However, the effects of any such manipulation must be interpreted with caution. For example, while it is tempting to interpret an observed decrease in self-administration behavior as signifying a reduction in the desire to self-administer the drug (and thus having possible therapeutic applications), there are equally plausible alternative explanations for the observed reduction in drug self-administration. For example, the experimental manipulation might have caused an overall reduction motor output, or an increase in sensitivity to the drug, resulting in less drug required to produce the same subjective effects. Therefore, in this review, to avoid the pitfalls of these alternative explanations, we will refer to alterations in operant drug IVSA or ethanol consumption as changes in *reinforcement*.

The operant self-administration paradigm is also amenable to studying the phenomenon of relapse. The most widely used animal model of relapse is the reinstatement paradigm [3]. While this model by no means perfectly mirrors the phenomenon of relapse in humans, it is considered to be the best model developed thus far [4]. In the reinstatement paradigm, following the achievement of stable levels of drug self-administration, animals undergo extinction training procedures, where the behavior that previously resulted in the delivery of the drug solution (i.e., lever press or nose-poke) no longer produces any consequences. As a result of this imposed drug unavailability (i.e., "forced abstinence"), animals will gradually extinguish (i.e., reduce) the behavior that previously resulted in drug delivery. Once predesignated extinction criteria have been obtained (for example, presses on the "active" drug-delivering lever are reduced to less than 20% of those observed when the drug was available), it is possible to "reinstate" operant responding by presenting one of the three main types of stimuli that are known to evoke relapse in humans: exposure to

stressors, presentation of drug-associated environmental cues, or brief exposure to the drug itself. Upon presentation of one or more of these stimuli, animals will resume performing the operant task that previously led to drug delivery. This resumption, or ''reinstatement'', of performing of the operant task is commonly interpreted as ''drug-seeking behavior''. However, it should be noted that during reinstatement testing, the operant task does not result in actual drug delivery, so as to avoid the psychoactive effects produced by the drug which can confound interpretation of changes in drug-seeking behavior. This exemplifies one of the main divergences between the reinstatement model and relapse in humans, as the latter most often results in drug consumption.

Another animal model of drug addiction is the conditioned place preference (CPP) paradigm [3]. Although it is widely used, this paradigm does not measure actual drug reinforcement; rather, it utilizes Pavlovian conditioning procedures to provide an index of the ''rewarding'' (or subjective pleasurable) effects of drugs of abuse based on the animal's preference for a drug-paired environment over a non-drug paired environment. A typical CPP apparatus consists of two conditioning compartments with unique sensory characteristics (i.e., visually distinct wall patterns, flooring with unique tactile properties, or distinct olfactory cues). These two ''conditioning'' compartments are often connected by a neutral center ''start'' compartment. In a typical CPP experiment, an animal undergoes baseline preference testing and habituation, where it is placed in the center start compartment and allowed free access to both conditioning chambers for a specified amount of time. This allows for the animal to habituate to the testing environment as well as for the experimenter to determine if the animal exhibits any innate bias towards one of the two conditioning compartments (an ideal CPP apparatus would produce no innate preferences for either compartment). Then, the animal is subject to conditioning procedures where the conditioning drug (i.e., morphine, cocaine, amphetamine, etc.) is administered and the animal is confined to one of the two conditioning compartments for a specific amount of time. On alternate days, the animal is injected with saline or vehicle and then confined to the other conditioning compartment for the same amount of time. These conditioning sessions are repeated in an alternating fashion over a period of several days to allow the animal to form associations between the unique physical characteristics of the drug-paired compartment and the subjective effects of the conditioning drug. Finally, on the test day, the animal is placed back in the center compartment and allowed free access to both conditioning compartments. If the animal spends significantly *more* time in the drug-paired compartment as compared to the saline-paired compartment, a CPP has been acquired. A conditioned place aversion (CPA) is observed if the animal spends significantly *less* time in the drug-paired compartment as compared with the saline-paired compartment. Drugs with aversive subjective properties, such as lithium chloride, or withdrawal from chronic drug administration reliably produce CPA.

The CPP paradigm has provided substantial information on the neural substrates of the rewarding effects of drugs of abuse. One advantage of this paradigm is that the procedures are relatively simple, inexpensive, and less time-consuming to conduct than intravenous drug self-administration. In addition, CPP paradigms can also be used to model various aspects of relapse. This is accomplished by extinguishing an established CPP by repeatedly pairing the previous drug-paired compartment with saline, or by allowing the CPP to dissipate over time with repeated testing of place preference. Next, pharmacological or other experimental manipulations can be introduced that result in a reinstatement of the original CPP. A disadvantage of the CPP technique, however, is that it does not directly measure primary drug reinforcement, but rather the motivation for secondary reinforcers (i.e., drug-associated environments) [3]. In addition, attempts to manipulate drug CPP via pharmacological or genetic methods do not always predict effects of those manipulations on drug self-administration behavior [3,5,6].

3. Glutamatergic neurotransmission

Glutamate is the most abundant excitatory neurotransmitter in the brain, mediating as much as 70% of synaptic transmission within the central nervous system and reaching extracellular concentrations in the high micromolar to low millimolar range. A diagram of a typical glutamatergic synapse is shown in Fig. 2. Glutamate is packaged into synaptic vesicles in the presynaptic terminal by vesicular glutamate transporters (vGluTs) using a proton gradient generated by the hydrolysis of adenosine triphosphate (ATP). Thus far, three different vGluTs have been identified (vGluT1–3) [7]. Once released into the synaptic cleft, glutamate can bind to one of three different types of ionotropic glutamate receptors (iGluRs) located on the head of the postsynaptic spine: the *N*-methyl-D-aspartate (NMDA) receptor, the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor, and the kainic acid (kainate, KA) receptor. iGluRs are ligand-gated ion channels that mediate fast excitatory neurotransmission. Glutamate can also bind to metabotropic glutamate receptors (mGluRs) located in perisynaptic regions or on the presynaptic terminal (see Fig. 2).

NMDA receptors are heterotetrameric protein complexes that form ligand-gated ion channels composed of at least one NR1 subunit (for which there are at least eight splice variants) and a combination of NR2A-D and NR3A or 3B subunits [8–10] (In mice, the NR1 subunit was previously named ζ1 and the NR2A-D were previously named ε1–4). In addition to being stimulated by glutamate, amino acids such as D-serine and glycine act as co-agonists at the NMDA receptor. The NR2 subunits contain the glutamate binding domain, whereas the NR1 subunit contains the glycine binding domain. Under resting conditions, the NMDA receptor channel pore is blocked by Mg^{2+} ions, but once sufficient membrane depolarization has been established (i.e., by opening of AMPA receptor channels), the Mg^{2+} block is removed, allowing the influx of cations (primarily Ca^{2+} ions, but the NMDA receptor is also permeable to K^+ and Na^+ ions). Activity of the NMDA receptor is modulated by polyamines and inhibited by Zn^{2+}. The subunit composition of NMDA receptors are ontogenetically regulated and are neuroanatomically distinct. Once thought to be exclusively located on neurons, NMDA receptors have recently been shown to be expressed on glial cells including microglia,

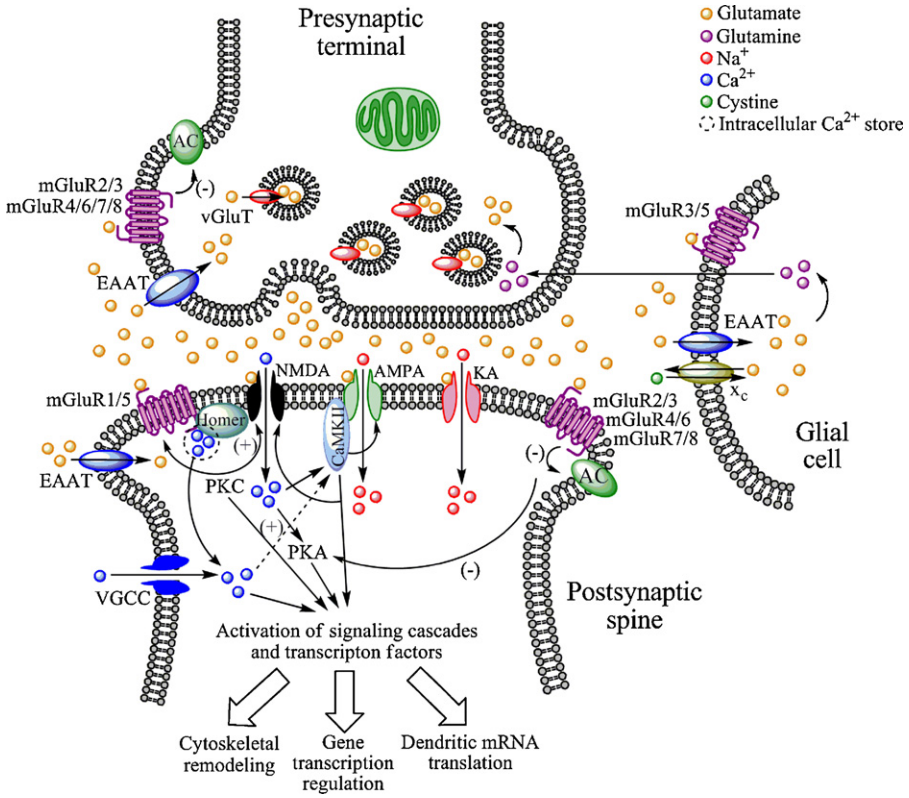

Fig. 2 – The glutamatergic synapse. Glutamate is packaged into synaptic vesicles in the presynaptic terminal by vGluT. When an action potential arrives at the terminal, glutamate is released by exocytosis into the synaptic cleft where it binds to and activates iGluRs (NMDA, AMPA and KA receptors) localized on the postsynaptic neuron, which results in cation influx and subsequent activation of voltage-gated calcium channels (VGCCs) that propagate the action potential. The resulting cation influx can activate numerous second messenger systems, including PKA and CaMKII, which in turn interact with other signaling molecules or transcription factors which can modulate gene expression, local mRNA translation, or cytoskeletal remodeling. iGluR subunits can be phosphorylated by numerous kinases such as PKC, CaMKII, Fyn and others, altering the activity and functionality of these receptors. NMDA receptor subunits have recently been discovered to be expressed by glial cells and on presynaptic terminals (not shown). Glutamate can also be released into the extracellular space via nonexocytotic mechanisms such as the cystine-glutamate exchanger (x_c) located on glial cells. Whether released from the presynaptic terminal or neighboring glial cells, extracellular glutamate binds and activates not only iGluRs but also postsynaptic mGluRs in the perisynaptic annulus, which are either positively coupled to PKC activity and mobilize intracellular Ca^{2+} from IP_3-gated intracellular stores (as is the case for mGluR1 and 5) or negatively regulate AC (as is the case for mGluRs 2, 3, 4, 6, 7, and 8). Group I mGluRs positively regulate NMDA receptor function via PKC. Like iGluRs, mGluR function can be altered via phosphorylation by various kinases. Glutamate release by the presynaptic terminal is negatively regulated by Group II or III mGluR autoreceptors, and is cleared from the extracellular space by EAATs located either on the presynaptic terminal, neighboring glial cells, or the postsynaptic neuron. In glia, glutamate is converted to glutamine, which is then transported back to the presynaptic terminal and converted back to glutamate. Although the numerous proteins that make up the postsynaptic density complex are not shown in this diagram, it should be noted that the Homer family of scaffolding proteins links NMDA receptors to Group I mGluRs and IP_3-gated intracellular Ca^{2+} stores, and several recent studies implicate Homer proteins in psychostimulant and alcohol addiction (see Sections 4 and 9).

astrocytes, and oligodendrocytes [10]. NMDA receptor subunits have also been found to exist on presynaptic terminals [11]. The NMDA receptor has been extensively implicated in mediating neural plasticity as well as learning and memory processes [12–14].

AMPA receptors are also heterotetrameric protein complexes that form ligand-gated ion channels composed of various subunits termed GluR1–4 (also termed GluRA-D) and GluRδ1 and 2 [8]. The mRNAs encoding AMPA subunits can be edited or alternatively spliced to form variants such as the *flip* and *flop* isoforms. Each GluR subunit contains a binding site for glutamate. Once activated, AMPA receptors are permeable to various cations including Ca^{2+}, Na^+ and K^+, although the majority of AMPA receptors in the brain contain GluR2 subunits, which render the channel impermeable to Ca^{2+}. Similar to NMDA receptors, AMPA receptor function can be modulated in the presence of polyamines. It is believed that both NMDA and AMPA receptors are necessary for the induction of many forms of synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD) [15–21].

Like NMDA and AMPA receptors, kainic acid (kainate, KA) receptors are also tetrameric protein complexes that form ligand-gated ion channels composed of various subunits. These subunits are termed GluR5-7 and KA1 and 2 [8]. KA receptors can form homomeric tetramers composed entirely of GluR5, 6 or 7 subunits or heteromeric complexes containg GluR5 or KA subunits. KA receptors are permeable to Na^+ and K^+ ions and, like NMDA and AMPA receptors, contribute to excitatory postsynaptic currents (EPSCs). The role of KA receptors in synaptic plasticity is less well defined, but KA receptors have been found to be localized presynaptically where they can modulate neurotransmitter release [22].

In addition to the iGluRs, glutamate can also bind to mGluRs, which are located either in the perisynaptic annulus or on presynaptic terminals. mGluRs are seven transmembrane domain-containing G-protein coupled receptors (GPCRs) that mediate slower, modulatory glutamatergic transmission. mGluRs can be divided into three distinct groups, based on their pharmacological and signal transduction properties. Group I mGluR receptors (mGluR1 and mGluR5) activate the $G\alpha_q$ class of G-proteins, which stimulate one of several phospholipases (including phospholipase C), resulting in phosphoinositol hydrolysis and the formation of lipid signaling intermediates such as inositol triphosphate (IP_3) and diacylglycerol (DAG), which in turn can activate various intracellular messengers including protein kinase C (PKC) [23–25]. Activation of Group I mGluR receptors also mobilizes calcium release from IP_3 receptor-mediated intracellular stores, which can in turn activate other intracellular messengers such as calmodulin-dependent kinase II (CaMKII). Group I mGluRs, particularly mGluR5, are positively coupled to NMDA receptor function via PKC, and are structurally linked to these receptors as well as IP_3-gated intracellular Ca^{2+} stores via the Homer family of proteins [26–30]. Group I mGluRs are rarely found presynaptically. Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7, and mGluR8) mGluRs, on the other hand, activate the $G\alpha_i$ class of G-proteins and are negatively coupled to adenylyl cyclase (AC) activity, and upon stimulation result in decreased intracellular levels of cyclic adenosine monophosphate (cAMP). Presynaptically localized Group II and Group III mGluRs, particularly mGluR2 and mGluR3, are thought to represent the classical inhibitory autoreceptor mechanism that suppresses excess glutamate release. mGluR3 and mGluR5 have been localized to glial cells such as astrocytes [31].

Activation of iGluRs alone is sufficient for the propagation of the action potential by the postsynaptic neuron, and can activate various intracellular signaling molecules including protein kinase A (PKA), mitogen-activated protein kinase (MAPK), and extracellular signal-related kinase (ERK) [32] (see Fig. 2). Activation of additional signaling molecules, such as PKC, is achieved by stimulation of mGluRs. Together, the simultanous activation of iGluRs and mGluRs stimulates a host of intracellular signaling pathways that result in protein phosphorylation of ion channels, other kinases, and transcription factors that eventually lead to the molecular events underlying neural plasticity. Such events include initiation and/or regulation of dendritic mRNA translation and de novo protein synthesis, changes in gene expression in the nucleus, and cytoskeletal remodeling (Fig. 2) [33]. Glutamate-mediated neural plasticity is also characterized by changes in iGluR subunit trafficking such as insertion of AMPA receptors into postsynaptic plasma membrane (see Section 11).

Glutamate is cleared from the extracellular environment by a family of sodium-dependent excitatory amino acid transporters (EAATs). To date, five separate EAATs have been idenfitied (EAAT1–5). EAAT1–3 are alternatively termed GLAST, GLT-1, and EAAC1, respectively. EAAT2 and EAAT5 are localized to the presynaptic terminal, EAAT3 and EAAT4 are localized to the postsynaptic neuron, and EAAT1 and EAAT2 are expressed in glial cells [7]. This family of EAATs provides numerous mechanisms to prevent an excessive accumulation of extracellular glutamate, which can result in excitotoxicity. Once inside glial cells, glutamate is converted to glutamine by glutamine synthetase, where it is secreted from the glia and taken up by the presynaptic terminal for conversion back to glutamate by glutaminase (Fig. 2). Conversely, glutamate can be transported from within glial cells to the extracellular environment by the cystine-glutamate exchanger (x_c) [34–37].

As mentioned earlier, glutamatergic transmission accounts for up to 70% of synaptic transmission in the central nervous system. Thus, there are glutamatergic projections and/or neurons expressing glutamate receptors in numerous circuitries of the brain, including the mesolimbic dopamine reward circuitry. This ''reward'' circuitry is composed primarily of dopamine-synthesizing neurons in the VTA of the ventral midbrain that project rostrally to target regions such as the nucleus accumbens (NAcc), amygdaloid complex (Amyg) and frontal cortex (FC). Each of these regions receives substantial glutamatergic input [38,39] (Fig. 3). For example, the VTA receives glutamatergic projections from the FC, Amyg, pendunculopontine tegmentum (PPT), and laterodorsal tegmentum (LDT) [40,41]. A recent report indicated that a subpopulation of VTA neurons express vGluT2 mRNA [42], suggesting the existence of neurons intrinsic to this region that utilize glutamate as a neurotransmitter. The NAcc receives a convergence of glutamatergic input from the FC, Amyg, hippocampal formation (Hipp), and various nuclei of the thalamus (Thal). The FC receives glutamatergic input from the Hipp, Amyg and Thal. Thus, there is a robust excitatory glutamatergic innervation of the mesolimbic dopamine reward circuitry which provides an anatomical basis for dopamine–glutamate interactions in regulating the addictive properties of drugs of abuse as well as synaptic plasticity [43–45] (see Section 11 for further discussion of this topic).

In light of all the receptor proteins and transporters associated with glutamatergic neurotransmission, a substantial array of pharmacological ligands has become available to researchers to examine the role of glutamatergic transmission in preclinical models of drug addiction. Table 1 details some of the more commonly used glutamatergic ligands that are employed in preclinical addiction research.

4. Glutamate and cocaine

Cocaine is a potent inhibitor of presynaptic monoamine transporter function, and as a result produces substantial increases in extracellular levels of dopamine, serotonin and norepinephrine in the synaptic cleft, particularly in forebrain

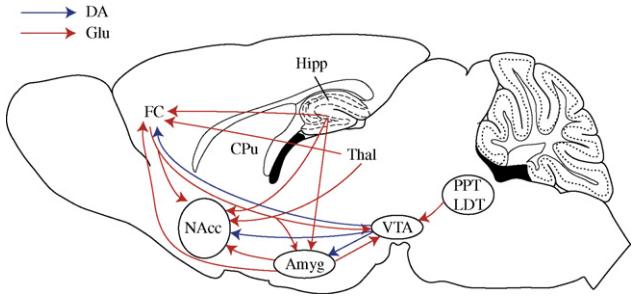

Fig. 3 – Sagittal section of the rodent brain showing neuroanatomical interactions between glutamate and mesolimbic dopamine systems. The "reward circuit" is hypothesized to consist of dopamine-synthesizing cell bodies in the VTA that project rostrally to innervate the NAcc, Amyg and FC, as well as other regions such as the portions of the CPu and ventral pallidum (not shown). This mesolimbic reward pathway is robustly innervated by glutamate-containing neurons. Dopamine-containing cell bodies in the VTA receive glutamatergic input from the PPT, LDT, Amyg and FC. The NAcc receives glutamatergic innervation from the FC, Hipp, Thal, and Amyg. The FC receives glutamatergic input from the Hipp, Thal and Amyg. Drawing adapted from the atlas of Franklin and Paxinos [906]. *Abbreviations*. Amyg, amygdala; CPu, caudate-putamen (dorsal striatum); FC, frontal cortex; Hipp, hippocampus; LDT, laterodorsal tegmentum; NAcc, nucleus accumbens; PPT, pedunculopontine tegmentum; Thal, thalamus; VTA, ventral tegmental area.

terminal fields that receive monoamineric projections. Cocaine also acts as a local anesthetic by blocking sodium channels and thereby inhibiting the propagation of action potentials. Some of the first observations that cocaine interacts with glutamatergic systems in the brain were reported in the late 1980s and early 1990s, when several groups of investigators showed that sensitization to the locomotor stimulant effects of cocaine was blocked by pretreatment with the NMDA antagonist MK-801 [46], and that infusion of iGluR antagonists into the NAcc reduced the motor stimulant and reinforcing effects of cocaine [47–51]. Since these observations, a tremendous amount of evidence has accumulated indicating an important role for glutamate in the motor stimulant properties of cocaine and its role in locomotor sensitization, and the reader is directed to various reviews elsewhere for in depth details on this topic [52–60]. Here we will focus on the effects of cocaine on glutamatergic transmission as well as the effects of glutamatergic ligands on the rewarding and reinforcing effects of cocaine.

In addition to elevating extracellular levels of monoamines, cocaine also increases extracellular levels of glutamate in various brain regions including the dorsal striatum [61], NAcc [62–71], septum [72], ventral pallidum [73,74], VTA [75,76] and cerebellum [77]. However, it should be noted that not all studies have observed cocaine-induced increases in extracellular glutamate, including studies in cocaine self-administering animals [78]. Others have found stimulatory effects of cocaine on extracellular glutamate only with high (i.e., 30 mg/kg i.p.) doses [63,65,66], which may cause neurotoxicity. Thus, the ability of cocaine to induce increases in extracellular glutamate is not a universally observed phenomenon. Nonetheless, immunohistochemical studies have shown that cocaine decreases glutamate immunoreactivity in presynaptic terminals several brain regions including the NAcc [79–81], suggesting that some of the observed elevations in extracellular glutamate in response to cocaine are derived from neuronal stores. Several reports suggest that environmental contexts and cues are important modulatory factors in the ability of cocaine to elevate extracellular levels of glutamate in the NAcc [67,82] but not the FC [83].

Glutamate mediates numerous neuronal effects of acute exposure to cocaine. Low doses of acutely administered cocaine enhance glutamate-evoked neuronal firing in the cortex, striatum, or NAcc, whereas higher or self-administered doses tend to inhibit glutamate-evoked neuronal activity in these regions [84–86]. However, the ability of high concentrations of locally administered cocaine to suppress glutamate-induced neuronal activity should be interpreted with caution, since cocaine exerts local anesthetic effects via blockade of voltage-gated sodium channels. Drugs of abuse including cocaine can produce elevated resting neuronal membrane potentials (i.e., "up" states) in regions such as the dorsal striatum, NAcc, and FC, and this phenomenon requires coordinated interactions between dopaminergic and glutamatergic transmission [87,88].

The ability of acute cocaine exposure to increase striatal neuropeptide expression and activate signaling molecules such as ERK is dependent on NMDA receptor activation [89–91]. Acute administration of cocaine has been shown to increase phosphorylation of the GluR1 subunit of the AMPA receptor in the striatum [92], induce a redistribution of AMPA and NMDA receptors in the VTA [93–95], and induce the formation of NR2B-D2 heteroreceptor complexes [96]. The expression of various iGluR subunits is reduced by acute cocaine. For example, in situ hybridization studies have shown that mRNA levels for GluR3, GluR4 and NR1 are decreased in the NAcc by acute cocaine exposure, as is NR1 mRNA expression in the striatum and VTA [97], perhaps as a compensatory response to increased glutamate overflow produced by cocaine. However, acute cocaine has been shown to increase NR1 mRNA expression in the hippocampus [98] and GluR2 mRNA in the striatum [99].

Repeated cocaine exposure can lead to a phenomenon called "behavioral sensitization" (sometimes termed "reverse tolerance"), which is a progressive increase in the behavioral (i.e., locomotor) response to cocaine in response to repeated exposure to the same dose. Behavioral sensitization to cocaine is paralleled by adaptive changes in mesolimbic dopamine system function as well as the responsiveness of this system to glutamate. For example, repeated exposure of rats to cocaine or amphetamine results in a transient enhanced responsiveness of VTA dopamine neurons to locally applied glutamate [100], and it was later determined that this phenomenon was a result of increased responsiveness of AMPA and not NMDA or mGluR receptors located on VTA dopamine neurons [101]. Such an effect is paralleled by an increase in expression of GluR1 receptor levels in the VTA, but not the substantia nigra, following repeated cocaine exposure [102–104]. Expression of NR1 in the VTA has also been reported

Table 1 – Commonly used glutamatergic ligands in preclinical addiction research

Ligand	Chemical name	Mode of action
AP5 (APV)	2-Amino-5-phosphonovaleric acid	NMDA antagonist (competitive)
Dizocilpine (MK-801)	(5*S*, 10*R*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5, 10-imine	NMDA antagonist (non-competitive)
Ifenprodil	2-(4-Benzylpiperidino)-1-(4-hydroxyphenyl)-1-propanol	NMDA antagonist (polyamine site) (some preference for NR2B)
GYKI 52466	4-(8-Methyl-9*H*-1,3-dioxolo[4,5-*h*][2,3]benzodiazepin-5-yl)-benzenamine	AMPA antagonist (non-competitive)
NBQX	2,3-Dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[*f*]quinoxaline-7-sulfonamide	AMPA/KA antagonist (competitive)
CNQX	6-Cyano-7-nitroquinoxaline-2,3-dione	AMPA/KA antagonist (competitive) (also NMDA glycine site antagonist)
DNQX	6,7-Dinitroquinoxaline-2,3-dione	AMPA/KA antagonist (competitive)
CPCCOEt	7-(Hydroxyimino)cyclopropa[*b*]chromen-1a-carboxylate ethyl ester	mGluR1 antagonist (allosteric)
LY367385	(*S*)-(+)-α-amino-4-carboxy-2-methylbenzeneacetic acid	mGluR1 antagonist (allosteric)
EMQMCM	(3-Ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methane sulfonate	mGluR1 antagonist (allosteric)
MPEP	2-Methyl-6-(phenylethynyl)pyridine	mGluR5 antagonist (allosteric)
MTEP	3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine	mGluR5 antagonist (allosteric)
LY379268	(1*R*, 4*R*, 5*S*, 6*R*)-4-Amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid	mGluR2/3 agonist (orthosteric)
DCPG	(*S*)-3,4-Dicarboxyphenylglycine	mGluR8 agonist (orthosteric)
TBOA	DL-Threo-β-benzyloxyaspartic acid	EAAT inhibitor
MS-153	(*R*)-(−)-5-Methyl-1-nicotinoyl-2-pyrazoline	EAAT activator

to be increased following repeated cocaine, but the expression of NR2A/B, GluR2/3 or GluR6/7 is unaltered [102–105]. Some investigators have not observed changes in iGluR expression in the VTA [97,106–108]. These discrepancies may be due to the type of detection methodology used (i.e., immunoblotting, radioimmunohistochemistry, or in situ hybridization), variations in cocaine dose, length of withdrawal period prior to analysis, or the inclusion of a final challenge administration of cocaine in order to demonstrate the maintenance of behavioral sensitization. Nonetheless, post-mortem analysis of human brain tissue samples from cocaine overdose victims did reveal an up-regulation of numerous iGluR subunits in the VTA [109,110], suggesting that cocaine, at least at high doses, alters iGluR subunit expression in the VTA.

In the primary target field of VTA DA neurons, the NAcc, it has been demonstrated that multiple cocaine exposures result in a sensitized increase in extracellular levels of glutamate [64,65] but see [111], paralleled by an accumulation of presynaptic glutamate immunoreactivity in this region [112]. Changes in glutamate receptor expression in the NAcc following repeated cocaine exposure are, however, complex and inconsistent across studies. Some investigators have reported no changes in expression of NR1, NR2A/B, GluR1–2, or KA receptor subunits in the NAcc within 24 h of discontinuation of cocaine treatment [102,103], or have reported decreases in NR1 and GluR3/4 expression [97,98]. However, at later time points, others have observed increases in NR1 expression in this region [97,103,113], but only in rats that exhibited signs of behavioral sensitization. Reductions in NR2B expression in the NAcc were observed after 24 h [114] but not 1 week [115] of cocaine withdrawal. In an elegant protein cross-linking study, it was demonstrated that repeated cocaine exposure increases the surface expression of GluR1–3 subunits in the NAcc at 3 weeks following discontinuation of treatment, but only in rats showing behavioral signs of sensitization [116]. Collectively, these data show that the effects of repeated cocaine exposure on iGluR subunit expression can vary considerably depending on many experimental factors, and that any lack of observed changes in overall protein expression may overlook more subtle adaptive changes such as increased surface expression of AMPA receptor subunits.

All of the aforementioned studies on the effects of repeated cocaine administration on iGluR expression utilized response non-contingent (i.e., passive, experimenter-administered) administration of the drug. Interestingly, a recent study by Hemby and colleagues examined the effect of active intravenous cocaine self-administration on changes in iGluR subunit expression in the NAcc [108]. It was found that during the early phases of cocaine withdrawal, NR1 and GluR5 expression were reduced in the VTA, no changes in any subunit examined were observed in the NAcc, and in the frontal cortex NR1 levels were increased and GluR2-6 and KA2 levels were decreased. Although it is difficult to compare these results with those reviewed above due to the many procedural differences involved, this study was one of the first to examine changes in iGluR subunit expression in addiction-related brain regions following active self-administration of the drug.

During protracted cocaine withdrawal, extracellular levels of glutamate and presynaptic glutamate immunoreactivity are decreased in the NAcc [36,37,64,67,69,79–81] but increased in the prefrontal cortex [117]. This reduction in extracellular levels of glutamate in the NAcc may be due to desensitization of presynaptic Group II mGluRs in their ability to regulate glutamate release [118–121] as well as a down-regulation of x_c^- function [36], which closely regulates extracellular glutamate levels. As a result, increases in NR1, GluR1–3, and Group I mGluR expression have been observed in the NAcc [97,103,104,122,123], suggesting that adaptations to reduced extracellular glutamate levels may occur. The observed decreases in extracellular glutamate during cocaine withdrawal have been shown to be critically involved in relapse-like behavior, since pharmacological restoration of basal extracellular glutamate

levels to those observed in non-withdrawn animals, as with agents such as *N*-acetylcysteine that promote the activity of x_c (see Fig. 4 and Section 13.2), inhibit the ability of cocaine priming to further increase extracellular levels glutamate levels in the NAcc. The ability of *N*-acetylcysteine to inhibit cocaine-induced increases in NAcc glutamate overflow is paralleled by blockade of cocaine-induced reinstatement [37,69], suggesting that an imbalance in glutamatergic transmission in the NAcc may induce a predisposition towards relapse.

Other changes brought on by repeated cocaine exposure include:

- an up-regulation of NMDA receptor binding in the regions such as the cortex, striatum, amygdala and hippocampus following repeated cocaine exposure [124–126] but see [127];
- a decrease in NR1 and/or NR2B/2C expression in regions such as the globus pallidus, subiculum, striatum, and cerebellum [98,105];
- an up-regulation of NR1 and a down-regulation of GluR2-7 and KA2 expression in cerebral cortex [97,108,128];
- increased phosphorylation of GluR1 in the prefrontal cortex [115];
- an increase in mGluR5 expression in the hippocampus [129];
- bidirectional alterations in the expression of NMDA and AMPA receptor subunit expression in the amygdala [130,131].

A role for glutamatergic transmission in the rewarding and reinforcing effects of cocaine has been clearly demonstrated by pharmacological studies utilizing iGluR antagonists. Systemic administration of NMDA antagonists attenuate cocaine reinforcement [132–135] and the acquisition and/or expression of a cocaine CPP [136,137]. Similar reductive effects on cocaine reinforcement have been reported following administration of inhibitors of glutamate carboxypeptidase II [138], which reduce free glutamate availability. The ability of iGluR antagonists to reduce cocaine reinforcement are likely mediated, at least in part, by NMDA and/or AMPA receptors in the NAcc and dorsal striatum, as evidenced by microinjection studies [49,139,140] but see [141].

Stimulation of AMPA receptors in the NAcc has been shown to reinstate previously extinguished cocaine-seeking behavior [141–143], and AMPA antagonists infused into the NAcc block reinstatement induced by priming injections of cocaine [142], cocaine-associated cues [144], or infusions of cocaine into the FC [145]. On the other hand, some studies have reported that NMDA receptor antagonists, whether administered systemically or into the NAcc shell, actually *induce* reinstatement of cocaine-seeking behavior [145–147]. The reason for the opposing effects of NMDA and AMPA antagonists on reinstatement are currently unclear, but may involve cocaine-induced increased AMPA receptor responsiveness (relative to NMDA) due to trafficking of AMPA subunits to the plasma membrane [116]. The FC has been identified as the primary source of glutamatergic afferents to the NAcc that mediate cocaine-primed reinstatement [68]. Together these data suggest a critical role for iGluRs in the NAcc in mediating the reinforcing effects of cocaine as well as the ability of exposure to cocaine or drug-associated cues to reinstate cocaine-seeking behavior (see also [148,149]). However, further research into identifying the unique, and possibly opposing, contributions of AMPA and NMDA receptors in the NAcc to reinstatement of cocaine-seeking behavior is needed.

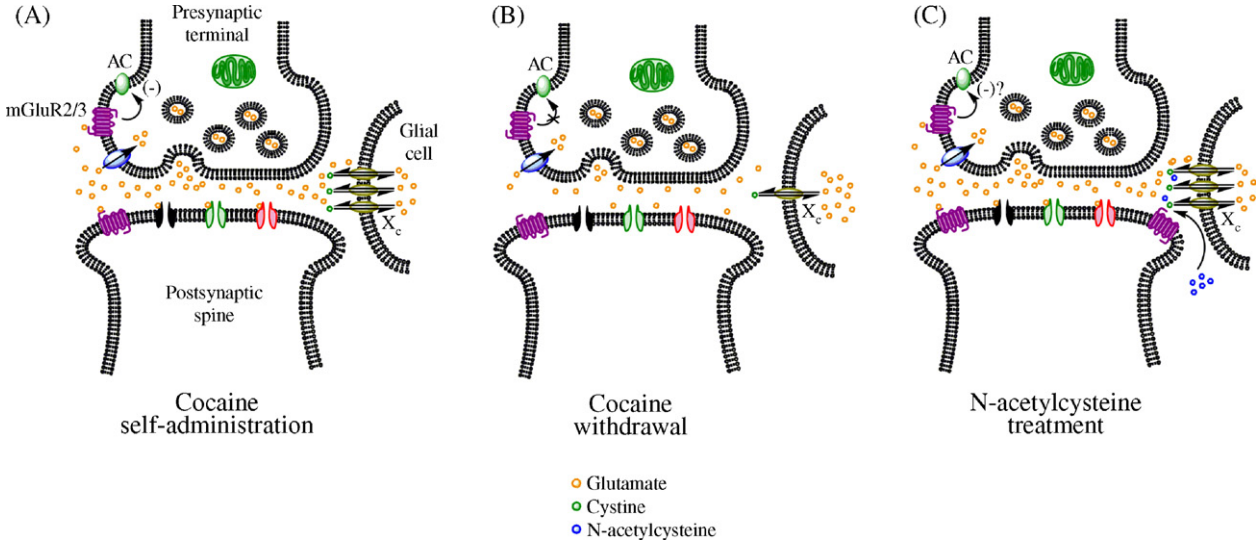

Fig. 4 – Hypothesized mechanism by which N-acetylcysteine (NAC) restores extracellular glutamate levels in the NAcc and prevents cocaine-induced reinstatement. (A) Cocaine self-administration induces glutamate release from prefrontal cortical neurons that synapse onto medium spiny neurons (MSNs) in the NAcc. (B) Repeated exposure to cocaine results in a desensitization of presynaptic Group II mGluRs and also down-regulates the efficacy of the cystine-glutamate exchanger (x_c), resulting in decreased extracellular glutamate levels during cocaine withdrawal. (C) NAC, a cystine pro-drug, is converted to cystine and drives x_c to transport glutamate from within glial cells into the extracellular environment. The resulting "normalization" of extracellular glutamate levels in the NAcc is believed to prevent further glutamate release produced by a priming injection of cocaine, thereby reducing subsequent reinstatement of cocaine-seeking behavior. See Section 13.2 for more detail.

Glutamatergic transmission in the VTA also plays a role in cocaine reward, reinforcement and reinstatement. For example, electrical stimulation of glutamatergic fibers in the ventral subiculum reinstates cocaine-seeking behavior in a manner dependent on glutamate transmission in the VTA [150]. Blockade of NMDA or AMPA receptors in the VTA blocks the development of cocaine CPP [151] and cue-induced reinstatement [152]. Expression and phosphorylation of GluR1 in the VTA also mediates the reinforcing effects of cocaine [153].

The basolateral amygdaloid nucleus (BLA) also plays a role in cue-induced reinstatement of cocaine-seeking behavior (reviewed in [154]). However, conflicting results have emerged as the role of glutamate transmission in this phenomenon. For example, infusion of NMDA into the BLA reinstates previously extinguished cocaine-seeking behavior [155], yet infusions of iGluR antagonists into this region do not attenuate cue-induced reinstatement [156]. Thus, while glutamatergic transmission in this region may play a role in reinstatement per se, iGluRs apparently do no mediate the ability of drug-associated cues to induce reinstatement. In addition, AMPA receptors in the NAcc mediate cocaine-seeking behavior only when BLA dopamine receptors are blocked [157].

mGluRs, particularly Group I and Group II mGluRs, are also involved in cocaine reward and reinforcement. Following a pivotal study by Chiamulera and colleagues who showed that mice carrying a targeted deletion of the mGluR5 gene do not self-administer cocaine [158], numerous investigators have shown that mGluR5 antagonists reduce cocaine reinforcement and reinstatement [159–165]. mGluR5 receptor antagonists also reduce the development and/or expression of cocaine CPP [166,167]. Dampening glutamate transmission via stimulation of presynaptic mGluR2/3 receptors or activating glutamate transporters attenuates cocaine reinforcement [168,169], cue- and cocaine-induced reinstatement [168,170], ''incubation'' of cocaine craving (i.e., a progressive increase in the magnitude of cue-induced reinstatement over time following cocaine self-administration) [171], and the development of cocaine CPP [172]. The NAcc and amygdala appear to be important mediators of some of these effects [144,169,171].

In addition to the aforementioned pharmacological evidence, studies utilizing genetically modified mice have also shed light on the role of glutamatergic transmission in cocaine addiction, as summarized below:

- Genetic deletion of GluR1 and/or GluR2 does not alter the acquisition of cocaine CPP [173,174], but impairs extinction of cocaine-seeking behavior [174]; however, another group of investigators showed a failure of GluR1 null mutant mice to develop cocaine CPP [175].
- Cocaine CPP is attenuated in mice engineered to express an NR1 subunit with reduced cation flux properties explicitly in D_1-containing neurons [176].
- Mice carrying a targeted deletion of the mGluR5 gene do not self-administer cocaine and are indifferent to its locomotor stimulant effects [158].
- Genetic deletion of mGluR2 enhances cocaine CPP [71].
- Altered behavioral and neurochemical responses to cocaine are observed in Homer1 or Homer2 knockout mice, as described below.

Homer proteins are a family of scaffolding proteins that link NMDA receptors, Group I mGluRs and IP_3-gated intracellular calcium stores to the postsynaptic density. A growing body of literature suggests that the expression of these proteins is regulated by cocaine and that they play an important role in the behavioral and neurochemical effects of this psychostimulant. Acute cocaine treatment induces a rapid but transient increase in Homer1a but not Homer1b/c or Homer2a/b expression in the dorsal striatum [177]. Chronic cocaine treatment, on the other hand, reduces Homer1b/c levels in the NAcc [119]. In addition, antisense knockdown of Homer1 expression in this region sensitizes rats to the locomotor stimulant effects of cocaine and also down-regulates GluR1 expression [178], suggesting that cocaine-induced down-regulation of Homer1 proteins may regulate its behavioral sensitizing effects. Subsequently, it was shown that mice carrying a targeted deletion of either the Homer1 or Homer2 gene demonstrate increased locomotor stimulant and rewarding effects (as measured by CPP) of cocaine as compared to wildtype controls [179–181], thus exhibiting a behavioral phenotype similar to that of cocaine-sensitized animals. In addition, Homer2 deficient mice exhibited a more rapid acquisition of cocaine IVSA and decreased basal extracellular glutamate levels in the NAcc (similar to cocaine withdrawn animals). Remarkably, many of these behavioral and neurochemical changes could be reversed by virally mediated restoration of Homer2 expression in the NAcc [180]. These findings highlight the importance of Homer proteins and the functional consequences of alterations in their expression due to repeated cocaine exposure.

5. Glutamate and amphetamines

Amphetamines are psychomotor stimulant drugs that promote the release of monoamines by reversing the directionality of vesicular and plasmalemmal monoamine transporters located in presynaptic terminals, thereby promoting the release of dopamine, norepinephrine and serotonin into the synaptic cleft. Although there are many amphetamine-related compounds, the primary analogues that will be focused on in this review are D-amphetamine (herein referred to as ''amphetamine''), methamphetamine, and methylenedioxymethamphetamine (MDMA, 'Ecstasy').

As with cocaine, the first observations that glutamate was involved in the psychomotor stimulant properties of amphetamine were reported in the late 1980s, when it was demonstrated that sensitization to the locomotor stimulant effects of amphetamine was blocked by co-administration of the NMDA antagonist MK-801 [46], and that infusion of iGluR antagonists into the NAcc reduced the motor stimulant effects of amphetamine [47]. The reader is directed to various reviews elsewhere for in depth details on the role of glutamate in amphetamine-induced locomotor activity and behavioral sensitization [52–60]. In addition, the reader is also directed to several recent reviews on the role of glutamate in amphetamine-induced neurotoxicity [182–184].

In addition to being monoamine-releasing agents, amphetamines also elevate extracellular levels of glutamate, as demonstrated by in vitro release and in vivo microdialysis studies in the cerebral cortex [66,185–190], dorsal striatum [187,191–202] but see [203], NAcc [66,190,204–207], hippocampus [187,208,209] and VTA [205,210,211]. However, it should be noted that some of these studies used doses of amphetamine that were in the neurotoxic range (i.e., 9–10 mg/kg i.p.) [193,204]. On the other hand, high doses of methamphetamine are often intentionally utilized to explore the hypothesis that prolonged increases in extracellular glutamate levels underlie the neurotoxic effects of this drug (cf. [192,195,196,201,202,212]). Presynaptic glutamate immunoreactivity has been shown to be decreased in various brain regions following methamphetamine administration [213,214], suggesting that some of the elevations in extracellular glutamate induced by this drug are derived from neuronal stores. Elevation of extracellular glutamate by amphetamines in various brain regions is not likely a result of alterations in EAAT function [215,216], although one study implicated EAATs in the ability of amphetamine to increase glutamate overflow in the VTA [211]. Some investigators have shown that local administration of high concentration of amphetamines actually reduce extracellular glutamate levels in certain brain regions [193,217,218] and suppress glutamate evoked neuronal activity in the NAcc and cerebral cortex [219,220].

Acute administration of amphetamines has been consistently shown to increase the expression immediate early genes such as c-fos and Zif268, various neuropeptide precursors, and induce phosphorylation of various transcription factors in the dorsal striatum, all of which are dependent on iGluR- and/or mGluR-mediated mechanisms [89,221–229]. Oddly, however, amphetamine-induced increases in the expression of immediate early genes in the NAcc appear to be NMDA receptor-independent [230]. Acute administration of methamphetamine has been shown to increase phosphorylation of the GluR1 subunit of the AMPA receptor in the striatum [92], which alters AMPA receptor channel conductance and promotes trafficking to the plasma membrane. With regards to VTA dopaminergic neurons, acute administration of amphetamines generally tends to inhibit the firing of these neurons by inducing somatodendritic release of dopamine, which in turn stimulates inhibitory D_2-like autoreceptors. However, acute amphetamine may actually excite VTA dopamine neurons by inhibition of mGluR-mediated inhibitory postsynaptic currents [231]. Amphetamine can also induce cellular hallmarks of neural plasticity in these neurons, such as increasing the AMPA component of evoked excitatory postsynaptic currents [232–234].

Repeated exposure of amphetamines can have markedly different effects on glutamate-mediated neuronal activity and function as compared with acute exposure. For example, as mentioned above, acute administration of amphetamine can suppress glutamate evoked neuronal activity in the NAcc and cerebral cortex [219,220]. However, repeated amphetamine administration results in enhanced neuronal responsiveness to locally applied glutamate in the VTA [100,101] and FC [235] but not NAcc [100]. It is unclear if the mechanisms underlying the enhanced responsiveness to glutamate are similar across these regions.

Repeated amphetamine exposure also results in various changes in other components of glutamate transmission. For example, repeated methamphetamine administration produces a reduction in NMDA NR1, NR2A and NR2B protein levels in the striatum [236] but increases vGluT1 levels in this region, which may facilitate the incorporation of glutamate into synaptic vesicles to promote long-lasting methamphetamine-induced increases in extracellular glutamate [202]. Repeated exposure to amphetamine also produces changes in AMPA receptor expression which can be either short- or long-lasting. In a series of studies conducted by Wolf and colleagues, it was shown that 5 days of amphetamine treatment produced decreases in mRNA and protein levels of GluR1, GluR2 and NR1 in the NAcc and increased NR1 expression in the frontal cortex at 14 but not 3 days following that last amphetamine exposure [237–239]. However, changes in GluR1 in the frontal cortex were only transient, being increased at 3 but not 14 days following the last amphetamine administration [237,238]. With regards to the VTA, repeated amphetamine treatment does not alter AMPA subunit expression [106,240], but does sensitize the ability of intra-VTA applied AMPA to increase in extracellular levels of glutamate in this region [241], suggesting a sensitizing effect of repeated amphetamine on AMPA receptor function in the VTA without alteration in subunit expression. However, many of these studies examined receptor protein levels in tissue homogenates by immunoblotting, or immunoreactivity or mRNA expression at the level of the cell body. Thus, it is possible that more subtle changes in receptor levels, such as increased surface expression of AMPA receptor subunits as has been observed following cocaine treatment [116], may be overlooked by use of these techniques.

Repeated amphetamine also alters the expression of mGluRs, causing transient increases mGluR1 expression in the dorsal and ventral striatum, but more persistent reductions in mGluR5 expression in these regions [242]. Repeated amphetamine also increases hippocampal and cortical mGluR5 expression [243,244]. Repeated amphetamine administration does not alter EAAT2 or EAAT3 expression in various regions including the midbrain, NAcc, dorsal striatum or FC [245,246]; however, methamphetamine has been shown to increase the expression of EAAT2 in the striatum [247].

Glutamate appears to play an important role in the rewarding and reinforcing effects of amphetamines. Reductions in glutamate transmission by administration of the glutamate release inhibitor riluzole [248], the glutamate transporter activator MS-153 [172], infusion of an AMPA/KA antagonist into the NAcc [249], and virally mediated overexpression of EAAT2 in the NAcc [250] all have been shown to attenuate the development of amphetamine CPP. However, it was also found that antagonism of mGluR2/3 receptors, which facilitates glutamate transmission, disrupts the ability of intra-NAcc amphetamine to establish a CPP [251], suggesting that excessive glutamatergic transmission may actually disrupt the neuronal communication that normally subserves the ability of amphetamine to establish a CPP. Our laboratory demonstrated that the development of amphetamine CPP was not attenuated by the mGluR5 antagonist MPEP [166]. However, others have shown that the expression of amphetamine CPP, but not MDMA CPP, is suppressed by MPEP [252].

With regards to amphetamine reinforcement and relapse-like behavior, surprisingly little attention has been given to the potential role of glutamate. Both dextromethorphan and the African tree shrub extract ibogaine, which have NMDA receptor antagonist properties, reduce methamphetamine reinforcement [253,254] and the establishment of amphetamine CPP [255]. However, ibogaine has been reported to have numerous other neurochemical effects including nicotinic acetylcholine receptor (nAChR) antagonism [256], and current evidence from studies with ibogaine congeners that are devoid of NMDA antagonist activity indicate that the inhibitory effects of ibogaine on amphetamine reward and reinforcement are likely mediated by antagonism of nAChRs rather than NMDA receptor blockde [257]. However, one recent study did show that stimulation of mGluR2/3 receptors attenuates enhanced amphetamine reinforcement in amphetamine-sensitized rats [258], suggesting that glutamatergic transmission may indeed regulate the reinforcing effects of amphetamines. Clearly, more research in this area is needed.

6. Glutamate and opiates

There are dozens of opiate alkaloid compounds that are used clinically for pain management, including morphine, codeine, hydrocodone, oxycodone, meperidine, and fentanyl. Many of these compounds exhibit potential for abuse and addiction. For the purposes of this review, we will focus on interactions between glutamate and just two of these opiate drugs: morphine, which is considered the ''gold standard'' of narcotic analgesics, and its illegal and highly addictive diacetylated form, heroin.

Opiate alkaloids bind with high affinity to one or more of several opioid receptor proteins, including the μ, δ and κ subtypes [259]. Opioid receptors are GPCRs that are negatively coupled to AC activity and normally subserve neurotransmission mediated by endogenous opioid peptides such as enkephalins, endorphins and dynorphins. There is a substantial amount of literature suggesting that abused opiates such as morphine and heroin interact with glutamatergic transmission. While many of these opioid–glutamate interactions take place in the spinal cord and brainstem in the mediation of nociception, here we will focus primarily on interactions in supraspinal regions of the brain known to be involved in addiction.

Most in vitro and in vivo studies have shown that morphine suppresses basal and evoked increases in extracellular glutamate in regions such as the cerebral cortex [260–266], dorsal striatum [262,267–269] but see [270,271], NAcc [272,273], globus pallidus and ventral pallidum [268,274–277] and hippocampus [278], but not the VTA [279]. The ability of morphine to dampen extracellular glutamate levels is likely mediated by opioid receptors located presynaptically on glutamatergic terminals. Morphine can also act postsynaptically to suppress glutamate-evoked neuronal excitation [280–283]. The resulting decrease in neuronal activity is reflected by other studies showing that the stimulatory effects of acute morphine on the expression of immediate early genes such as c-fos and c-jun in the dorsal and ventral striatum is blocked by NMDA and/or AMPA receptor antagonists [284–286].

Acute morphine administration induces neuronal plasticity in the VTA, as evidence by an increase in the AMPA/NMDA ratio of evoked EPSCs [232]. In the NAcc core, a reduction in the expression of NR1, NR2B, NR2C, GluR1–4, and GluR6 was observed 3 days after acute morphine exposure; however, 21 days following acute morphine exposure, expression of all iGluR subunits was reported to be increased [287]. Transient changes in components of glutamatergic signaling have also been described in the hippocampus following acute morphine exposure, with the expression of mRNA encoding NR1, NR2A and NR2B subunit proteins being reduced 4 h after administration, returning to preinjection levels by 24 h post-treatment [288].

More robust changes in glutamatergic signaling have been observed following repeated exposure to morphine. While acute exposure to morphine can suppress glutamate-evoked neuronal responses (see above), repeated exposure to morphine can result in tolerance to this effect, which can ultimately result in neuronal supersensitivity to glutamate [289–292]. Chronic morphine exposure reduces glutamate uptake in the FC, striatum and hippocampus [293], paralleled by decreases in striatal EAAT2 expression [294]. Reductions in [^{3}H]MK-801 or [^{3}H]glutamate binding in various brain regions have been reported following repeated morphine exposure [295–297], while [^{3}H]MK-801 binding is increased in the hippocampus [298]. Along these lines, the induction of LTP at mossy fiber synapses in the hippocampus has been observed following repeated morphine exposure [299], which may be a result of altered AMPA receptor dynamics [300], an increase in glutamate receptor number or binding sites [298] or a molecular rearrangement of the postsynaptic density complex [301]. There are several reports that repeated morphine exposure does not alter NR1, NR2A or NR2B expression in the hippocampus [113,130] or even decreases NR1 expression in this region [302]. These discrepancies are likely due to variations in dose, duration of morphine administration, and method of exposure (daily injections vs. continuous infusions via subcutaneous pellet or osmotic minipump implantation).

Rats self-administering morphine show an increase in plasma membrane levels of GluR1 in the basolateral amygdala [303], and during morphine withdrawal, expression of NR1 is increased in this region [130], which may contribute to the aversive motivational properties of opiate withdrawal [304]. Some investigators have reported that repeated morphine does not alter NR1, NR2A or NR2B expression in the FC [113] while others have reported that chronic morphine exposure decreases expression of these subunits in this region [302]. Similarly, some have reported that chronic morphine increases NR1 and NR2A expression in the NAcc [302,305] and produces a shift towards NR2A-mediated NMDA function, such as decreased glycine binding and faster rates of receptor desensitization [306]. Yet others have reported that chronic morphine has no effect on NMDA subunit expression in the NAcc [113,307]. As mentioned earlier, such discrepancies are likely due to dose, duration, and method of morphine exposure. Chronic morphine up-regulates mGluR5 expression in the limbic forebrain [308], which may be relevant to the ability of mGluR5 antagonists to attenuate the conditioned rewarding effects of morphine (see below).

One particular adaptation in glutamatergic signaling that may be important for the development of addiction to opiates is the reported up-regulation of the expression of the AMPA subunit GluR1 in the VTA by repeated morphine exposure [102]. In an elegant pair of studies, Nestler and colleagues showed that behavioral correlates of repeated morphine exposure, such as locomotor sensitization and CPP, can be mimicked in drug-naïve animals by virally mediated overexpression of GluR1 in the VTA [309], particularly in the rostral VTA [310]. Thus, the VTA may be a crucial site whereby repeated opiate exposure produces adaptive changes in glutamate neurotransmission that increase the propensity towards opiate addiction.

As opposed to the suppression of extracellular glutamate levels that is characteristic of acute morphine exposure, morphine withdrawal is characterized by increased overflow of glutamate in regions such as the locus coeruleus [311,312], NAcc [272,313], and hippocampus [278]. This withdrawal-induced increase in glutamate overflow is accompanied by reductions in Group II-mediated LTD in the NAcc [314], likely due to a desensitization of presynaptic mGluR2/3 receptors. However, in the dorsal striatum, extracellular levels of glutamate are reduced during morphine withdrawal [271], paralleled by an increased in EAAT2 expression [294]. Hippocampal synapses show increased surface expression of EAAT2 and parallel increases in glutamate uptake during morphine withdrawal [315]. Morphine withdrawal is also characterized by enhanced presynaptic inhibition of excitatory input into the VTA [316], which may result in reduced brain reward circuitry function that is characteristic of drug withdrawal [317].

Perhaps one of the most consistent findings in the literature on opiate–glutamate interactions is the ability of reduced glutamatergic signaling to attenuate the development of tolerance to the antinociceptive effects of morphine and to ameliorate the behavioral signs of morphine withdrawal. One of the first studies along these lines was published by Trujillo and Akil [318]. In this study, the NMDA receptor antagonist MK-801 not only blocked the development of tolerance to the antinociceptive effects of morphine, but also the development of physical dependence on morphine, as evidence by reduced naloxone-precipitated withdrawal symptoms. Since this study, numerous others have shown that morphine tolerance and/or withdrawal symptoms (including naloxone-precipitated CPA) are reduced by

- NMDA receptors antagonists [270,305,319–329];
- AMPA/KA receptor antagonists [322,330];
- genetic deletion of NR2A [331];
- genetic deletion of GluR1 [332];
- mGluR5 antagonists [326,333,334];
- stimulation of presynaptic Group II mGluRs [335–338];
- administration of a glutamate release inhibitor [339];
- activation of glutamate transporters [340];
- inhibition of the processing of the putative glutamate precursor peptide *N*-acetyl-aspartylglutamate [341,342].

On the contrary, facilitation of glutamatergic transmission, such as by administration of the glutamate transport inhibitor TBOA [343] or mGluR2/3 antagonists [344], actually exacerbates somatic signs of opiate withdrawal. There is a general consensus that the behavioral signs of opioid withdrawal are largely mediated by increased glutamatergic drive to the locus coeruleus [336,344–350], an area that provides noradrenergic innervation to much of the brain. Reductions in glutamate transmission in this region reduce the expression of morphine withdrawal symptoms [348–350]. However, blockade of NMDA or AMPA receptors in the VTA also attenuates the behavioral signs of morphine withdrawal [351,352], indicating that this region is also involved in generating symptoms of opiate withdrawal.

Glutamate is important for the rewarding properties of morphine, as measured by the CPP paradigm. Impairment of glutamatergic transmission by administration of NMDA and/or AMPA antagonists, either systemically [341,353,354] or into reward-related regions such as the NAcc [353,355], ventral pallidum [356], central amygdala [357] or VTA [355,358] attenuate the development and/or expression of morphine CPP. This is not due to drug substitution effects, since iGluR antagonists do not have morphine-like discriminative stimulus effects [359,360]. Likewise, reductions in glutamatergic transmission by systemic administration of a glutamate transporter activator [172], a glutamate release inhibitor [248], genetic inactivation of the NR2A subunit of the NMDA receptor [331] or virally mediated overexpression of EAAT2 in the NAcc [250] can attenuate the development of morphine CPP. Morphine-induced reinstatement of CPP can be attenuated by NMDA antagonists [361-363]. On the other hand, potentiation of glutamate transmission by the glutamate uptake inhibitor TBOA [343] or injection of NMDA into the CeA [357] facilitates the expression of morphine CPP. With regards to mGluRs, we found that doses of MPEP up to 20 mg/kg do not inhibit the development of morphine CPP in mice [166]. However, other investigators have found that higher doses of MPEP block the acquisition and/or expression of morphine CPP in rats [167,308,364]. Thus, there is ample evidence to support the notion that the functionality of glutamate transmission is positively correlated with the rewarding effects of morphine.

Heroin (diacetylmorphine) is abused primarily for its intense euphorigenic properties. There are, however, only a handful of studies examining interactions between this highly addictive opiate drug and glutamatergic signaling. One of the first studies demonstrating an interaction between heroin and glutamate was the observation that blockade of NMDA receptors in the NAcc with MK-801 attenuated the locomotor stimulant effects of heroin [48]. However, this same manipulation did not attenuate the reinforcing effects of heroin [49]. Infusions of NMDA antagonists into the VTA, in contrast, decrease heroin reinforcement, whereas administration of an AMPA/KA antagonist into this region actually increases heroin reinforcement [365], suggesting opposing roles of VTA NMDA and AMPA receptors in regulating the addictive properties of this opiate. Heroin administration is accompanied by delayed increases in extracellular levels of glutamate in the ventral pallidum [366], a region known to be involved in regulating heroin reinforcement [367]. Finally, cue- and/or context-induced reinstatement of heroin-seeking behavior is attenuated by stimulation of mGluR2/3 receptors, administered either systemically [368,369] or directly into the VTA [368] or NAcc [370], but not the dorsal striatum [370]. mGluR2/3 agonists have no effect on baseline heroin reinforcement [369]. These studies indicate that Group II mGluRs in both the

NAcc and VTA regulate the ability of contextual or other environmental cues to reinstate extinguished heroin-seeking behavior. Further research is clearly needed on the potential clinical utility of both iGluR and mGluR ligands in the treatment of heroin addiction.

7. Glutamate and nicotine

Although cigarette smoke contains several thousand different chemical compounds, nicotine is considered to be the primary component that promotes addiction to cigarettes. Nicotine binds with high affinity to nAChRs, which are pentameric ligand-gated cation channels comprised of various combinations of α and β type subunits. Nicotine is thought to exert is rewarding and reinforcing effects by activating VTA dopamine-containing neurons expressing nAChRs composed of the $\alpha_4\beta_2$ subunit combination [371–374]. Alternatively, there is also evidence suggesting that nAChRs containing the α_7 subunit are localized presynaptically on glutamatergic afferents to the VTA [375], and thus activation of these receptors by nicotine increases glutamate release in the VTA and activates iGluRs located postsynaptically on VTA dopamine neurons, with the end result of increasing the activity of the mesolimbic reward circuit [376–386].

Many studies have shown that nicotine elevates extracellular glutamate levels in a number of brain regions including the cerebral cortex [387–393], dorsal striatum [387,388,391,394,395], NAcc [376,396–399], hippocampus [400], hypothalamus [387], locus coeruleus [401,402] and cerebellum [403,404]. As a result, EPSCs and neural activity are increased by nicotine in many of these regions via iGluR-mediated mechanisms [382,389,405–423], including the induction of hippocampal LTP [424–426]. As a result, nicotine may induce long-lasting synaptic plasticity in numerous brain regions, which may promote addiction to this substance.

Repeated exposure to nicotine can produce adapative changes in the expression of various proteins related to glutamate neurotransmission. Rats and mice repeatedly administered nicotine, either passively or by active self-administration, show decreased levels of NR2A and NR2B levels in the striatum [427], and increased levels of these proteins in the FC [428]. Consistent with these latter findings, a microarray study revealed that in the post-mortem cerebral cortex of human cigarette smokers, a significant increase in the expression of GluR1 and NR2A is observed [429]. Chronic nicotine self-administration in rats also increases GluR2/3 expression in the VTA but does not induce changes in NR2A, NR2B, or GluR2/3 levels in the NAcc [428]. An up-regulation of the glutamate transporter EAAT2 has been reported in the cerebellum in response to chronic nicotine exposure [430]. The expression of Group I mGluRs and Homer1 and Homer2 mRNA in the amygdala, NAcc and VTA are altered by nicotine [431], although many of these changes are only transient. Finally, a proton magnetic resonance spectroscopy analysis of smokers, former smokers and controls showed no differences in concentrations of glutamate in the hippocampus or anterior cingulate cortex [432]. Although the results of this study were negative, they represent a novel attempt at examining changes in glutamate transmission in the living human brain as a result of nicotine addiction.

Some of the adaptive changes in glutamate transmission produced by nicotine may be age-related, which may provide a neural basis for the enhanced vulnerability to nicotine addiction during adolescence in both humans and animals [433–435]. For example, repeated exposure of adolescent mice to nicotine produces a down-regulation of the GluR2/3 levels in the striatum, whereas opposite effects are observed in adult exposed animals [427]. Thus, nicotine may produce age-dependent adaptations in glutamatergic transmission, and further research on this topic is needed to determine the glutamatergic substrates underlying enhanced vulnerability to nicotine addiction during the adolescent stage of development.

Pharmacological studies on nicotine reinforcement, relapse, and withdrawal have provided important developments in possible glutamate-based interventions for the treatment of nicotine addiction. NMDA antagonists such as MK-801 or memantine block the development and expression of locomotor sensitization to nicotine [436] as well the acquisition of nicotine IVSA [135]. Blockade of mGluR5 receptors has been shown to decrease the reinforcing effects of nicotine but not food [159,160,437,438]. mGluR5 antagonists also decrease the break-point for nicotine reinforcement on a progressive ratio schedule [163]. Blockade of mGluR1 or mGluR5 receptors also attenuates cue- and nicotine-induced reinstatement of nicotine-seeking behavior [160,439,440]. However, stimulation of mGluR2/3 receptors or blockade of mGluR5 receptors does not block the ability of nicotine to lower ICSS thresholds [159,441], and mGluR5 antagonism does not block the development of a nicotine CPP [166]. Thus, although glutamatergic ligands such as mGluR5 antagonists may be of some clinical benefit in reducing cigarette smoking or relapse during attempts to quit [442], they may not significantly attenuate the effects of nicotine on brain reward function.

Glutamatergic ligands also modulate the nicotine withdrawal syndrome. One early study showed that activation of mGluR2/3 receptors suppresses nicotine withdrawal symptoms [443]. However, other investigators have shown that mGluR2/3 agonists, administered either systemically or directly into the VTA, actually elicit withdrawal-like elevations in ICSS thresholds in nicotine-dependent rats [444]. Thus, there appears to be a disconnect between glutamatergic modulation of the behavioral signs of nicotine withdrawal and nicotine modulation of brain reward function. AMPA/KA antagonists such as NBQX can also precipitate withdrawal-like elevations in ICSS thresholds in nicotine-dependent rats [444]. In addition, mGluR5 antagonists such as MPEP can actually increase somatic signs of nicotine withdrawal [438]. This, dampening glutamate transmission may be beneficial in reducing the reinforcing effects of nicotine, but may actually exacerbate nicotine withdrawal symptoms.

8. Glutamate and cannabinoids

The primary psychoactive ingredient in marijuana is Δ9-tetrahydrocannabinol (THC). THC acts as an agonist at the type 1 cannabinoid (CB_1) receptor, which is expressed primarily in the brain, and has lower affinity for CB_2 receptors,

which are expressed in more restricted areas of the brain but are abundant in the periphery. Both CB_1 and CB_2 receptors are GPCRs that are negatively coupled to AC activity and also modulate the function of various ion channels [445]. Endogenous CB receptor ligands include anandamide and 2-arachidonylglycerol. There is now substantial evidence from animal models that the endogenous cannabinoid system is involved in numerous aspects of drug addiction and alcoholism (see [446–448] for recent reviews).

CB_1 receptors are present at high densities on presynaptic terminals of glutamatergic synapses [449–451]. In vitro studies have shown that THC and other CB_1 receptor agonists inhibit glutamate-mediated neurotransmission and/or decrease glutamate overflow in numerous brain regions including the cerebral cortex [452,453], dorsal striatum [450,454–457], NAcc [449,458–461], globus pallidus [462], hippocampus [453,463–473], amygdala [453,474], hypothalamus [475,476], substantia nigra [477], VTA [478], locus coeruleus [479] and cerebellum [480–482], primarily by inhibiting glutamate release from the presynaptic terminal. Cannabinoid-induced reductions in glutamatergic transmission are a candidate mechanism by which cannbinoids impair the induction of LTP [483,484]. However, two microdialysis studies have shown that CB_1 agonists actually increase extracellular levels of glutamate in the FC [485,486]. These findings are in contrast to those cited above where cannabinoids suppress glutamatergic transmission in the cortex. The reasons for the discrepancy are currently unclear, but may be a result of the type of experimental technique used (slice preparation versus in vivo microdialysis) and route of drug administration (i.e., bath application versus systemic injection, the latter of which does not result in steady-state concentrations of the drug in the brain).

Little is known about the effects of chronic cannabinoid exposure on glutamatergic transmission. Few studies, if any, have examined the effect of chronic cannabinoid administration on the expression of elements of glutamate transmission, such as iGluR, mGluR and EAAT protein levels. However, tolerance to the ability of THC to alter synaptic plasticity in several brain regions has been demonstrated as a result of repeated THC administration [487,488], suggesting the possibility of some degree of alteration of glutamatergic signaling by chronic cannabinoid exposure.

One of the first studies showing that THC may interact with mGluR function was published by Nah and colleagues, who showed that THC inhibited glutamate-stimulated increases in IP_3 in cultured hippocampal neurons [489]. There is now substantial evidence that mGluR and CB1 receptors interact to modulate synaptic plasticity (reviewed in [490,491]).

The effects of CB_1 agonists such as THC on glutamatergic transmission in regions of the brain's reward circuitry may mediate the addictive properties of THC. For example, in prefrontal cortical slices, Auclair and colleagues found that CB_1 receptor agonists inhibit glutamatergic synaptic transmission between layer V afferents and layer V, and favor LTD at the expense of LTP at the same synapses [452]. Given the prominent role of the prefrontal cortex in addictive behaviors, the disruption of glutamatergic activity in this area may be associated with addiction to THC. Robbe and et al. [449,460] found that CB_1 receptors are present on large fibers making synaptic-like contacts with GABAergic medium spiny neurons in the NAcc, and that the synthetic CB_1 agonists WIN 55,212 and CP55940 inhibited glutamatergic transmission at the synapses between the prelimbic cortex and the NAcc. These authors suggested that cannabinoids can indirectly affect NAcc dopamine *overflow* via this mechanism. For instance, the glutamatergic afferents from the cortex to the NAcc control the firing of the GABAergic medium spiny neurons, which in turn inhibit the dopaminergic neurons of the VTA. Via the reduction of excitatory transmission in the NAcc, cannabinoids may disinhibit midbrain dopaminergic, thereby increase their firing rate and trigger an increase in extracellular levels of dopamine in the NAcc [449,460]. A similar reduction in glutamatergic transmission by THC has also been shown in the shell of the NAcc [459].

The effects of CB_1 agonists have also been studied in the amygdala. Activation of CB_1 via WIN 55,212 reduces basal synaptic transmission and pharmacologically isolated AMPA receptor-mediated postsynaptic currents in the lateral amygdala of mice [474]. This ability of cannabinoids to reduce glutamatergic transmission in the amygdala may underlie the ability of THC to alter emotional or drug-related memories.

To our knowledge, there are no studies published examining the effects of glutamatergic ligands on the reinforcing effects of THC or relapse-like behavior, likely because reliable self-administration of THC is difficult to obtain in laboratory animals [492].

9. Glutamate and alcohol

Ethanol was long thought to exert its actions on the brain solely via potentiation of GABAergic transmission and/or increases in plasma membrane fluidity. However, in the late 1980s and early 1990s, a series of reports were published indicating that ethanol also acts by inhibiting neuronal NMDA receptor function [493–499]. The NMDA receptor is now considered one of the primary molecular targets for the actions of ethanol in the brain. Studies with recombinant NMDA receptors have shown that NR2B-containing receptors are particularly sensitive to inhibition by ethanol, and NR2C- and NR3-containing receptors are slightly less sensitive to ethanol [500–506]. Ethanol appears to inhibit NMDA receptor function via a non-competitive mechanism [507] and induces the phosphorylation and internalization of NR2 subunits [508,509]. NMDA receptors in many brain regions are sensitive to inhibition by ethanol, including the cerebral cortex [510,511], NAcc [512,513], septum [514,515], amygdala [516,517], hippocampus [511,515,518–521], locus coeruleus [522–524], VTA [525,526] and cerebellum [511,515,519,527]. As a result, ethanol inhibits the induction of several forms of neural plasticity such as LTP in the hippocampus [528–531], dorsal striatum [532] (but also see [509]) and bed nucleus of the stria terminalis [533] while enhancing LTD in the hippocampus [534]. The ability of ethanol to inhibit NMDA receptor function is dependent on various factors including the NR1 splice variant that is co-assembled with NR2 subunits [535], extracellular Mg^{2+} and glycine concentrations [536–540], intracellular Ca^{2+} concentrations [541], and NMDA receptor phosphorylation by proteins kinases such as Fyn [542–544], PKA [545] but see [546], and PKC [547] as well as by the phosphorylation regulator DAARP-32 [548].

As a result of the ability of ethanol to inhibit NMDA receptor function, NMDA antagonists such as MK-801 can potentiate the effects of acute ethanol such as the duration of ethanol-induced loss-of-righting reflex [549–552] and stimulation of locomotor activity [553–555]. NMDA antagonists can also produce ethanol-like discriminative stimulus effects in both animals and humans [556–575].

In response to chronic inhibition of NMDA receptor function, repeated ethanol exposure induces an up-regulation of various NMDA receptor subunits including the NR1, NR2A and NR2B subunits in the cerebral cortex and hippocampus [576–597]. However, the effects of chronic ethanol exposure on NR1 expression have been less consistent than those on NR2A and NR2B, likely a result of the numerous splice variants of the NR1 subunit that exist [590]. Changes in NR2B expression have been linked to methylation of the NR2B gene [598,599]. Chronic ethanol up-regulates NR1 expression in the VTA and amygdala [600,601], regions that are critical for the reinforcing effects of ethanol. In addition to up-regulating NMDA subunit expression, chronic ethanol also increases NMDA receptor functionality (i.e., conductance, cation influx, etc.) [587,592,595,601–608] and synaptic clustering of the receptor [609].

As a result of ethanol-induced up-regulation of NMDA receptor expression, the central nervous system enters a state of hyperexcitability upon acute withdrawal from ethanol exposure [610,611]. In animals and humans, this CNS hyperexcitability manifests itself as a propensity towards seizure-like activity, which can be suppressed by NMDA antagonists [550,589,602,612–619]. Following prolonged ethanol withdrawal, NMDA receptor expression and functionality are reduced [620].

Ethanol also appears to inhibit the function of AMPA and KA receptors [507,512,523,524,608,621–639], although these receptors appear to be less sensitive to inhibition by ethanol than NMDA receptors, requiring concentrations of 50 mM or greater. Like other drugs of abuse, ethanol increases the AMPA/NMDA ratio of EPSCs in the VTA [232]; however, this effect was shown after an extremely low dose of ethanol (20 mg/kg i.p.), and it is not known if this effect is observed following administration of more pharmacologically relevant doses of ethanol. Nonetheless, chronic ethanol has been reported to up-regulate the expression of the GluR1 subunit in the VTA [600] and the GluR2/3 subunit in the cerebral cortex [585] and hippocampus [640] without altering KA subunit expression. Chronic ethanol also up-regulates Ca^{2+} influx mediated by AMPA receptors [641,642]. Interestingly, AMPA/KA receptors in the central amygdala have recently been reported to be important for the conditioned rewarding effects of ethanol [517].

Although ethanol primarily acts on ion channels, there is also evidence that ethanol alters Group I mGluR function. Minami and co-workers showed a preferential inhibition of mGluR5-stimulated Ca^{2+}-mediated Cl^{-} currents by ethanol, albeit at high concentrations of 100–190 mM [643]. Chronic ethanol also inhibits mGluR-mediated phospholipase C activity [644] and down-regulates the expression of various mGluRs such as mGluR1, mGluR3, mGluR5 and mGluR7 in the hippocampus [645].

Numerous studies have shown that glutamate receptor ligands alter the reinforcing effects of ethanol. Infusion of NMDA receptor antagonists systemically [569,617,646–651], into the cerebral ventricles [652], or directly into regions such as the NAcc [653] or dorsal striatum [509] attenuates oral ethanol consumption in rats. Some, but not all, NMDA receptors antagonists also attenuate the alcohol deprivation effect [654], cue-induced reinstatement of alcohol-seeking behavior [655,656], the acquisition of ethanol CPP [650,657,658] and sensitization to the locomotor stimulant effects of low doses of ethanol [659–663]. Surprisingly, NMDA antagonists such as MK-801, while producing ethanol-like discriminative stimulus effects, do not reinstate ethanol-seeking behavior [664]. AMPA/KA receptor antagonists also attenuate operant ethanol reinforcement [665] and cue-induced reinstatement [655,666]. However, some of these studies have shown that NMDA or AMPA/KA ligands also attenuate sucrose or saccharin reinforcement [665], indicating that such compounds may not be selective for reducing ethanol intake, but may rather attenuate general appetitive responding.

Attenuation of glutamatergic transmission by mGluR ligands also appears to reduce the rewarding and reinforcing effects of ethanol as well as relapse-like behaviors. The mGluR1 antagonist CPCCOEt has been reported to reduce operant ethanol self-administration as well as acute ethanol-stimulated dopamine and glutamate release in the NAcc in mice [667]; however, another group of investigators found no effect of this ligand on ethanol self-administration in the same mouse strain [668]. The reason for this discrepancy are likely attributable to numerous procedural differences between the two studies, as discussed in [667]. The mGluR2/3 agonist LY379268 attenuates ethanol consumption and stress- and cue-induced reinstatement of ethanol-seeking behavior [669,670]. However, locomotor suppressant effects of this ligand have been observed [669], and thus the reductive effects of this ligand on ethanol consumption and relapse-like behavior must be interpreted with caution. The mGluR5 antagonists MPEP and/or MTEP have been shown to reduce voluntary ethanol consumption, reinforcement and relapse in a variety of rat and mouse strains [667,668,671–676]. The ability of MPEP to reduce ethanol consumption is absent in mice lacking PKCε [674] indicating that this PKC isozyme is an important signaling target of mGluR5 and is involved in the regulation of ethanol consumption via this receptor. MPEP also attenuates the expression [667] but not the acquisition [166] of ethanol CPP, attenuates ethanol-stimulated dopamine and glutamate release in the NAcc [667], and can modulate the discriminative stimulus effects of self-administered ethanol [677]. Stimulation of mGluR8 receptors with DCPG also reduces ethanol consumption and cue-induced reinstatement of ethanol-seeking behavior [669]. However, as with LY379268, locomotor suppressant effects of this ligand have been observed [669], and thus the reductive effects of this ligand on ethanol consumption and relapse-like behavior must be interpreted with caution.

Mice carrying mutations in genes encoding various components of glutamatergic transmission have yielded novel insight into the mechanisms of action of ethanol and the role of various glutamatergic signaling components in ethanol-related behaviors [678], as summarized below:

- Mice carrying a gene encoding the NR1 subunit with reduced affinity for glycine demonstrate reduced anxiolytic and motor impairing effects of ethanol [679].
- Mice engineered to express NR2A subunits without the C-terminal tail ($NR2A^{\Delta C/\Delta C}$) displayed decreased ethanol-induced inhibition of NMDA receptor function in the hippocampus and evidence for increased behavioral sensitivity to ethanol [680].
- Mice lacking the NR2A subunit (previously known as ε1) do not develop tolerance to the hypnotic effects of high doses of ethanol and do not acquire ethanol CPP [681–683].
- Mice lacking the AMPA subunit GluR1 showed patterns of ethanol consumption, ethanol-induced depression of locomotor activity, and hypnotic effects of high doses of ethanol that are similar to that of wildtypes [684].
- Mice lacking the GluR3 subunit of the AMPA receptor show reduced cue-induced reinstatement of alcohol-seeking behavior as compared with wildtypes but normal basal levels of ethanol consumption [666].
- Mice lacking mGluR4 demonstrate normal ethanol consumption patterns, withdrawal severity, and hypnosis induced by high doses of ethanol, but do not demonstrate a locomotor stimulant effect of lower doses of ethanol [685].
- Mice lacking Fyn, a tyrosine kinase that phosphorylates (amongst other things) the NR2B subunit of the NMDA receptor, fail to show tolerance to the ability of ethanol to inhibit NMDA receptor function in the hippocampus, and are also hypersensitive to the hypnotic effects of ethanol [542,686,687] but do not seem to display altered ethanol consumption or CPP [687,688], although one of these studies demonstrated reduced ethanol consumption in Fyn-deficient mice [686].
- Mice lacking the gene encoding the NMDA-Group I mGluR scaffolding protein Homer2 show a reduced preference for a 12% ethanol solution, an absence of CPP for higher doses of ethanol, an absence of sensitization to the locomotor stimulant effects of ethanol, a lack of ethanol-induced stimulation of extracellular dopamine and glutamate levels in the NAcc [689]. Many of these phenotypes were reversed by virally induced restoration of Homer2 expression in the NAcc.

Microdialysis studies have shown that ethanol, particularly at low doses, elevates extracellular glutamate levels in the hippocampus [690], amygdala [516,691] and NAcc [667,690,692,693], whereas at higher doses ethanol can reduce glutamate overflow in these regions [690,694–696] and in the cingulate cortex [697]. The precise mechanisms whereby ethanol alters extracellular glutamate levels remains uncertain, and may be perhaps due to ethanol-induced changes in glutamate uptake by glial cells [698–700]. However, not all investigators have found that acute ethanol increases extracellular glutamate in the NAcc [701–704]. Repeated exposure to ethanol may be necessary achieve this effect [516,700], and it may be dependent on the strain of animal used [704,705] or the effect may be delayed by several hours into the acute withdrawal phase [705]. More consistently, withdrawal from chronic ethanol exposure is characterized by elevated extracellular glutamate levels in regions such as the dorsal striatum [706,707], NAcc [399,708] and hippocampus [709,710]. This phenomenon appears to increase over the course of repeated withdrawal periods [709], paralleling the ''kindling'' effect of multiple withdrawal episodes on seizure-like activity [711].

Thus, a paradoxical effect of ethanol on glutamatergic transmission exists, with acute exposure to low doses of ethanol as well as withdrawal from chronic exposure increasing extracellular levels of this neurotransmitter, while ethanol simultaneously acts to inhibit the function of one of its primary cognate receptors (i.e., the NMDA receptor).

10. Glutamate and abused inhalants

Abused inhalants comprise a wide variety of compounds that range from gasoline to industrial solvents and cleaning agents. Most members of this class of drugs are simple hydrocarbon or substituted hydrocarbon compounds such as toluene, hexane, benzene and trichloroethane [712,713]. The use of inhalants for their intoxicating effects is widely recognized as a problem of drug abuse, and is particularly prevalent among teenagers and children because of the simplicity of obtaining these compounds. Recent research has shown that nearly 20% of children in middle school and high school have experimented with inhaled substances [714]. While there are numerous volatile compounds that are abused, toluene (methylbenzene) is considered the prototypical compound for this class of drugs. Thus, a considerable amount of research on the neurobiological substrates of inhalant abuse has focused on toluene.

Like other drugs of abuse, toluene increases the activity of the mesolimbic reward circuitry [715–717]. One of the first demonstrations of an interaction between toluene and glutamatergic transmission was reported by Woodward and co-workers [718], who revealed that toluene inhibited the function of recombinant NMDA receptors expressed in *Xenopus* ooctyes. Cells expressing the NR1/NR2B subunit combinations were the most sensitive to inhibition of NMDA-induced currents by toluene, with a reported EC_{50} value of 0.17 mM. Cells expressing NR1/NR2A or NR1/NR2C subunit combinations of the NMDA receptors showed less sensitivity to inhibition of NMDA-induced currents by toluene than those expressing the NR1/NR2B subunit combination. In contrast, cells expressing the AMPA/KA subunits GluR1, GluR1/2 or GluR6 showed no inhibition of kainate-induced currents by toluene at concentrations up to 9 mM. This was the first evidence that abused inhalants such as toluene act by inhibiting iGluR function, particularly NMDA receptors. Acute toluene exposure reduces glutamate-stimulated increases in potassium channel activity via mGluR1 [719], indicating that toluene may also interact with mGluR function as well as iGluR function.

The ability of toluene to inhibit NMDA receptor function was later replicated in cultured hippocampal neurons [720], and it was also demonstrated that prolonged (4-day) exposure of cultured hippocampal neurons to toluene produced an up-regulation of NMDA receptor function, with increased whole-cell current responses to NMDA, increased density of NR1 subunits, and an increase in expression of the NR2A and NR2B subunits. These results suggest that chronic exposure to the abused inhalant toluene induces compensatory responses in

the functional expression of NMDA receptors, similar to that observed following chronic ethanol exposure.

Comparable effects of chronic toluene exposure have been demonstrated in vivo in rodents. Exposure of rats to 500 ppm toluene vapor for 16 h per day for 3 months up-regulated nonspecific glutamate binding in numerous brain regions [721]. In a study by Williams et al. [722], adult male rats that were exposed to toluene vapor (8000 ppm) for 30 min per day for 10 days demonstrated increased NR1, NR2B and GluR2/3 subunit levels in the medial prefrontal cortex, increased NR2B expression in the NAcc, and decreased NR1 subunit expression in the substantial nigra. Together, these findings suggest that, like ethanol, chronic toluene exposure up-regulates NMDA (and possibly AMPA) receptor expression and function in many, but not all, regions of the brain.

To our knowledge, only one study to date has examined the effects of toluene exposure on extracellular glutamate levels in vivo. Using microdialysis techniques, Win-Shwe et al. [723] demonstrated that an acute administration of toluene (150 and 300 mg/kg i.p.) dose-dependently increased extracellular glutamate levels in the hippocampus of mice, with glutamate levels returning to baseline values within 1 h of administration. Thus, as with ethanol, a paradoxical effect of toluene on glutamatergic transmission exists, with acute exposure of toluene increasing extracellular levels of this neurotransmitter while simultaneously acting to inhibit the function of one of its primary cognate receptors (i.e., NMDA receptors).

11. Drugs of abuse and synaptic plasticity

There is now overwhelming evidence that drugs of abuse induce various forms of synaptic plasticity, such as LTP and LTD, within the reward circuitry of the brain. Accordingly, there is a growing consensus that repeated exposure to drugs of abuse produces lasting neuroadaptive changes within this circuitry, which eventually results in the pathological drug seeking that is characteristic of addiction (see [43,59,724–730] for reviews). One of the first demonstrations that abused drugs induce electrophysiological indices of synaptic plasticity in reward-related brain regions was the finding that acute exposure to cocaine depressed excitatory transmission (as measured by the amplitude of glutamate-evoked EPSCs) in the NAcc [731,732]. Similar effects were observed in the VTA following acute amphetamine exposure [733]. Jones and colleagues also showed that acute amphetamine also blocked the induction of LTD by glutamatergic synapses onto VTA dopamine neurons [734]. However, by analyzing the individual components of glutamate-evoked EPSCs (i.e., NMDA- and AMPA-mediated currents), Ungless and colleagues demonstrated that a single exposure to cocaine induced LTP in VTA dopamine neurons, as characterized by an increase in the AMPA–NMDA ratio of glutamate-evoked EPSCs [95]. This effect was transient, as it was evident at 5 but not 10 days following the exposure to cocaine. It was subsequently demonstrated that similar effects are observed following acute exposure to other drugs of abuse, including morphine, nicotine, amphetamine, ethanol, as well as acute exposure to stress [232,233]. The increase in the AMPA component of the EPSCs is likely due to increased trafficking of AMPA receptor subunits to the plasma membrane, which is a well-known regulator of excitatory synaptic strength [20,21,735–739]. However, not all studies have observed increased membrane insertion of AMPA receptors following acute drug exposure [233]. Repeated exposure of animals to cocaine also facilitates the induction of LTP in VTA dopamine neurons, which is a possibly a result of cocaine-induced decreases in GABAergic inhibition of these neurons [740]. Similarly, it was recently reported that opiate drugs such a morphine inhibit the formation of LTP in local GABAergic inhibitory synapses onto VTA dopamine neurons [741].

Drug-induced synaptic plasticity has also been observed in the NAcc. Thomas and colleagues [742] demonstrated that repeated administration of cocaine to mice, which resulted in behavioral sensitization, resulted in LTD in the NAcc (measured one day after a final challenge with cocaine to demonstrate the continued expression of behavioral sensitization). This LTD was characterized by decreases in the AMPA–NMDA ratio of EPSCs evoked by stimulation of prefrontal glutamatergic afferents to the NAcc shell. These observed changes are important since AMPA receptors in the NAcc shell modulate brain reward function as assessed by ICSS [743]. Others have reported that repeated amphetamine attenuates the induction of PFC-NAcc LTP via dopaminergic mechanisms [744], but this effect is transient, as LTP in the NAcc could be established 8–10 days after discontinuation of amphetamine treatment.

While all of the aforementioned studies have examined changes in synaptic transmission after passive (i.e., experimenter-administered) exposure to drugs of abuse, a recent study examined the effects of active cocaine self-administration on synaptic plasticity in brain reward circuitry. Martin et al. [745] demonstrated that in rodents self-administering cocaine intravenously, LTD in the NAcc core and shell was abolished following one day of abstinence, but this effect was still evident in the core 21 days into abstinence. These data are in contrast to those of Thomas et al. [742], who showed that repeated passive exposure to cocaine induced LTD in the NAcc shell. Thus, the effects of drugs of abuse on synaptic plasticity in reward-related regions of the brain are often transient, and may also be dependent on whether the drug is administered in a response-contingent or non-contingent manner.

While glutamatergic transmission is often considered a ''prime mover'' in terms of its role in synaptic plasticity, particularly drug-induced plasticity, it should not be construed that other neurotransmitter systems within the brain's reward circuitry do not play an equal if not more important role. As the mesolimbic reward circuit is primarily dopaminergic and receives a significant amount of glutamatergic input (see Fig. 3), it should not be surprising that there is a great deal of convergence of dopamine and glutamate signaling within this system that mediates drug-induced synaptic plasticity [43,87,726,728,730,746,747]. For example, glutamatergic afferents (i.e., from the FC) make synaptic contacts into the ''heads'' of dendritic spines localized on MSNs in the NAcc, the primary type of neuron in this region. Dopaminergic afferents arising from the VTA form synapses onto these very same spines, although these synapses tend to be localized towards the ''neck'' of the spine. In accord with the close proximity of these converging dopaminergic and glutamatergic inputs, there is a great deal of biochemical cross-talk

between these entities. For example, activation of D_1 receptors on MSNs (i.e., due to drug-induced increases in extracellular dopamine in the NAcc) activates PKA, which phosphorylates GluR1 subunit and facilitates the insertion of AMPA receptors into the neuronal membrane [748–750]. Similar effects have been observed in the prefrontal cortex [751] and hippocampus [752]. This dopamine-induced increase in trafficking of AMPA receptors to the plasma membrane has a subsequent facilitatory effect on the induction of synaptic plasiticity in these neurons [20,21,735–739], which can lead to long-term adaptations in the brain reward circuitry.

12. Glutamate and extinction learning—relevance for addiction

It has become increasingly apparent that the brain circuits, neurotransmitters, and signal transduction mechanisms that underlie drug addiction have considerable overlap with those that underlie normal learning and memory processes. As a result, numerous theories have emerged that hypothesize drug addiction to be a disorder of learning and memory [43,729,753–760], where certain behaviors and drug–environment associations become ''overlearned''. In other words, with repeated drug exposure, drug-taking behaviors become compulsive and automatic (i.e., instrumental overlearning) and the associations between drugs and specific environmental cues and contexts becomes overly salient (i.e., associative overlearning). These types of overlearning often lead to drug craving and relapse [148,761,762]. Attempts at extinguishing the salience of drug-associated cues by exposure therapy have been met with limited success [763,764], likely because of the high degree of context specificity in extinction learning [765,766]. In addition, most behavioral or pharmacological treatments for drug addiction are primarily aimed at reducing drug use, withdrawal symptoms, or relapse, with little attention being given to the process of extinction. Thus, there is a great need to develop therapeutic interventions whereby instrumental and associative ''overlearning'' that occurs in the process of addiction is subsequently extinguished.

Both learning and memory and drugs of abuse induce various forms of neuronal plasticity including LTP and LTD mediated by glutamatergic transmission [43,724,725,728–730,767–770]. Unfortunately, most of what is known about extinction learning has been derived from studies on aversive conditioning with footshock or appetitive conditioning with natural rewards. As a result, it would overly simplistic to assume that the neural substrates of extinction of drug-seeking behavior are synonymous with those that mediate extinction of other types of conditioned behaviors. There do, however, appear to be a number of commonalities. For example, extinction of conditioned fear has been reported to be facilitated by the NMDA receptor partial agonist D-cycloserine either administered systemically (reviewed in [771,772]) or directly into the BLA [773–775]. Similarly, recent reports demonstrate that extinction of a cocaine CPP is also facilitated by D-cycloserine, administered either systemically [776,777] or into the BLA [776]. Thus, it is possible that the neural substrates that subserve both extinction of drug-seeking behavior and extinction of other conditioned behaviors are somewhat overlapping.

Exinction has long been viewed as a process of ''forgetting'', or a disintegration of the association between previously neutral stimuli and an emotional or subjective state. However, there is increasing evidence that extinction is not merely a process of forgetting, but actually a form of new and active learning. Although scientists investigating fear conditioning arrived at this realization as many as 10–15 years ago [778,779], only recently has the notion that extinction of drug-seeking behavior is also a form of new and active learning come to light. In an eloquent series of studies, Self and colleagues have demonstrated that extinction training procedures following cocaine self-administration produce various hallmarks of neuronal plasticity in the NAcc. First, extinction training was shown to restore cocaine-induced deficits in tyrosine hydroxylase immunoreactivity in the NAcc shell, whereas in animals that did not undergo extinction training, the levels of the enzyme remained reduced following cocaine self-administration [780]. Subsequently, these investigators showed that extinction training induces an up-regulation in the expression of the GluR1 and GluR2/3 subunits of the AMPA receptor in the NAcc [781,782] and that virally mediated up-regulation of these AMPA subunits in this region facilitates extinction learning [782]. Consistent with this, GluR1 deletion in mice results in resistance to extinction following cocaine or food self-administration [174]. Self and colleagues also demonstrated that extinction training also normalizes cocaine-induced deficits in levels of the NR1 subunit of the NMDA receptor in the NAcc core [781]. Another group of investigators led by Marshall showed that inhibition of extracellular signal-regulated kinase (ERK) in the NAcc core region results in a lasting attenuation of drug-induced reinstatement of cocaine CPP as well as cocaine-induced phosphorylation of several signaling molecules including ERK, CREB, Elk-1 and c-fos [783]. The authors suggest that these particular molecular substrates of learning and memory in the NAcc are necessary for reconsolidation of drug-associated memories. Finally, it was recently demonstrated that rats that have undergone extinction training show differences in Fos expression in various brain regions, particularly in AMPA receptor expressing cells, as compared with animals that have not undergone extinction training [784]. Collectively, these studies suggest that a considerable amount of neuroplasticity occurs in the brain during extinction following drug self-administration (or passive exposure, in the case of CPP), and that agents that potentiate glutamatergic transmission, such as D-cycloserine, might be of clinical benefit in facilitate extinction learning in drug addicts attempting to abstain from drug use.

13. Glutamatergic medications for the pharmacological management of drug addiction and alcoholism

13.1. *Acamprosate*

Acamprosate (calcium acetylhomotaurine) is a derivative of homotaurine (a nonspecific GABA agonist) that is *N*-acetylated to facilitate penetration across the blood–brain barrier, and is

formulated as a calcium salt to increase absorption from the gastrointestinal tract (see Fig. 5). Acamprosate was developed in Europe in the 1980s as a pharmacological agent to reduce alcohol consumption, craving and relapse in alcoholic patients. Only one study in animals showing that acamprosate reduced voluntary ethanol consumption in rats [785] was published prior to the first demonstration of its clinical efficacy in reducing the incidence of relapse in alcoholics [786]. Over the years, acamprosate has demonstrated moderate efficacy in reducing overall alcohol consumption and subjective measures of alcohol craving, and promoting abstinence, as reviewed in recent meta-analyses [787–792]. It should be noted, however, that a large multicenter study of over 600 subjects found that acamprosate was no more effective than placebo in reducing the incidence of relapse in a medically managed care setting [793]. The reasons for these negative findings, particularly in light of the numerous previous clinical trials showing moderate efficacy of acamprosate, are still being debated.

Despite years of use as a treatment for alcoholism, the neuropharmacological mechanisms underlying the actions of acamprosate are still unclear. Originally, acamprosate was thought to exert its effects via a GABAergic mechanism, since the drug has a chemical structure similar to that of GABA (see Fig. 5). However, subsequent studies have failed to find any direct evidence of acamprosate binding to recombinant $GABA_A$ receptors, or an ability of acamprosate to enhance $GABA_A$ receptor function [794–796]. Thus, acamprosate has not been classified as a GABAergic compound. Nonetheless, acamprosate may indirectly increase GABAergic neurotransmission by blocking inhibitory presynaptic $GABA_B$ autoreceptors [796] and/or by increasing extracellular levels of taurine [797,798], an endogenous sulfonated amino acid that can potentiate $GABA_A$ receptor-mediated chloride flux.

The first studies suggesting that acamprosate exerts its actions through glutamatergic mechanisms were reported by Zeise at al. [799,800]. These investigators demonstrated that locally applied acamprosate reduced the excitation of neuronal firing evoked by iontophoretic application of L-glutamate onto cortical neurons in vivo, and inhibited EPSCs evoked by glutamate and NMDA in rat forebrain slices. These data suggested that acamprosate may functionally antagonize excitatory amino acid neurotransmission and therefore reduce neuronal excitability. In support of this, subsequent studies have shown that acamprosate antagonizes NMDA-evoked postsynaptic currents in cultured hippocampal neurons and *Xenopus* oocytes expressing recombinant NMDA receptors [801], up-regulates NMDA receptor subunit expression in a pattern similar to that observed following treatment with the non-competitive NMDA antagonist MK-801 [801,802], and reduces NMDA receptor-mediated Ca^{2+} influx in cultured rat midbrain neurons [803]. However, not all electrophysiological studies have provided evidence that acamprosate acts as an NMDA receptor antagonist, as some investigators have found no effect of acamprosate on NMDA-mediated synaptic transmission in the CA1 region of the hippocampus [804], while others have found that acamprosate actually potentiates NMDA receptor function in the CA1 region of the hippocampus [795] or in the NAcc [796]. Thus, the action of acamprosate on NMDA receptors appears to be inconsistent, and is perhaps dependent on factors such as brain region examined, NMDA receptor subunit composition, state of neuronal excitation, and the presence of various endogenous NMDA receptor neuromodulators such as polyamines [805].

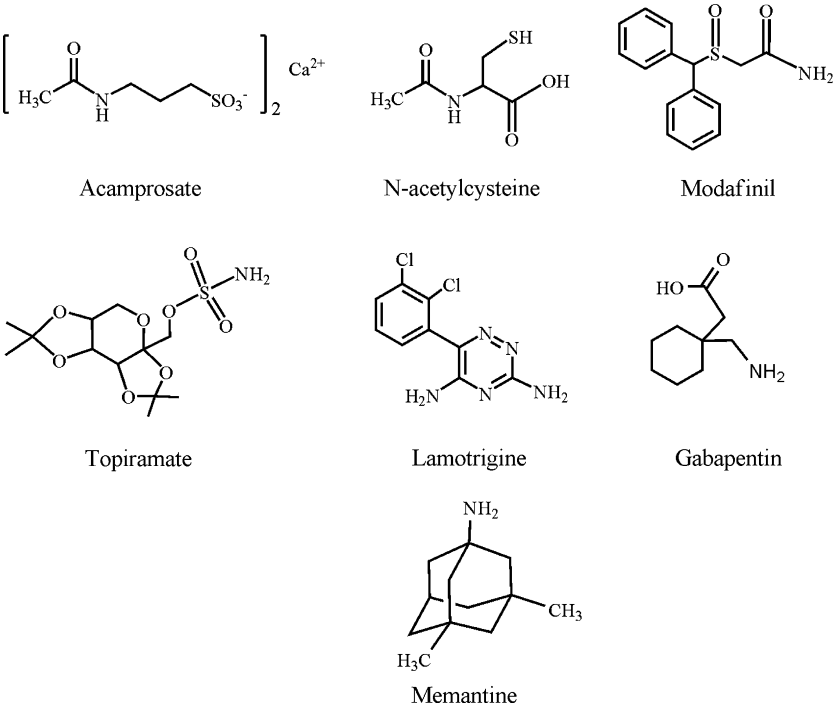

Fig. 5 – Chemical structures of medications that act on glutamatergic transmission that have shown positive effects in the treatment of drug addiction and/or alcoholism in humans.

Nonetheless, several binding studies have confirmed an interaction of acamprosate with the spermidine-, glutamate- and/or MK-801-sensitive binding site of the NMDA receptor [806–808]. Thus, there is a general consensus that acamprosate is an NMDA receptor modulator [805,809].

In addition to an apparent interaction of acamprosate at ionotropic glutamate receptors, recent in vitro studies demonstrated that acamprosate inhibits the binding of and neurotoxic effects of trans-ACPD (Group I and II mGluR agonist), as well as the neurotoxic effects of ethanol withdrawal, in a manner similar to the mGluR5 antagonist SIB-1893 [808,810]. These data suggest that acamprosate may act on metabotropic as well as ionotropic glutamate receptors. This is an important observation, given the important role of mGluR5 in regulating alcohol consumption and relapse (see Section 9). However, additional studies are needed to confirm a functional interaction between acamprosate and individual mGluR subtypes.

Despite its elusive mechanism of action, acamprosate is believed to restore the imbalance between excitatory and inhibitory neurontransmission caused by chronic alcohol exposure. Chronic exposure to alcohol produces an up-regulation of NMDA receptor function and a down-regulation of $GABA_A$ receptor function, resulting in an imbalance between excitatory and inhibitory amino acid transmission. During acute withdrawal from alcohol exposure, glutamate release is increased [709,710] to further induce a state of CNS hyperexcitability. It is believed that through its modulatory effects on NMDA receptor function, suppression of glutamate release when the organism is in a hyperglutamatergic state (see also [811]), and possible enhancement of GABAergic transmission (though this remains controversial), acamprosate may restore the imbalance between excitatory and inhibitory amino acid transmission in the brain following chronic alcohol consumption [805,812].

To date, very few animal or human studies have examined the potential efficacy of acamprosate in treating addiction to other drugs of abuse. Acamprosate was shown to be ineffective in preventing the development of morphine CPP in mice [813] and did not alter heroin reinforcement or stress- or heroin-induced reinstatement of heroin-seeking behavior in rats [814]. Thus, based on these animal studies, acamprosate is likely to have limited use in the treatment of opiate addiction. However, there have been several studies by our laboratory suggesting that acamprosate may be of potential benefit in the treatment of cocaine addiction. We found that acamprosate prevented the development [813] and cocaine-induced reinstatement [815] of a cocaine CPP in mice, and have recently demonstrated that acamprosate attenuates cocaine- and cue-induced reinstatement of cocaine-seeking behavior in rats without affecting basal levels of cocaine IVSA [816]. A pilot Phase II clinical trial was recently initiated to examine the effects of acamprosate on cocaine use, craving and acute withdrawal symptoms in humans (http://www.clinicaltrials.gov identifier: NCT00385268). However, measurement of rates of relapse following abstinence are not planned in this study, for which our animal studies indicate acamprosate might be most effective. The results of this clinical trial (and future trials on relapse) are eagerly awaited, since if they are positive, they may not only lead to approval of one of the first medications specifically for the treatment of cocaine addiction, but will also provide some predictive validity for the use of CPP, IVSA and reinstatement procedures in the screening of potential medications to treat drug addiction.

13.2. *N-Acetylcysteine*

N-Acetylcysteine (NAC) is an *N*-acetylated derivative of the naturally occurring amino acid cysteine (see Fig. 5). NAC is used worldwide as a mucolytic agent and to treat acetaminophen overdose, and has numerous mechanisms of action including increasing glutathione synthesis. Because NAC is a cystine pro-drug, it can serve as a substrate for x_c, which exchanges extracellular cystine molecules for intracellular glutamate molecules in glia, thereby elevating extracellular glutamate levels in many tissues including the brain [34,817]. Numerous animals studies have shown that acute cocaine exposure elevates extracellular levels of glutamate in regions such as the NAcc, but during withdrawal from repeated cocaine exposure, extracellular levels of glutamate are decreased in this region relative to drug-naïve animals, likely due a desensitization of presynaptic mGluR2/3 autoreceptors and decreased activity of x_c (see Section 4 and Fig. 4). However, by providing a source of extracellular cysteine (which is converted to cystine) and increasing the activity of x_c, administration of NAC "restores" extracellular levels of glutamate to those observed in drug-naïve animals and prevents the ability of a subsequent cocaine challenge to further increase glutamate levels in the NAcc. The resulting behavioral effect is a blockade of the ability of acute cocaine to reinstate cocaine-seeking behavior [37,69].

Taking these findings from animal studies to the clinic, Kalivas and colleagues have conducted two preliminary investigations into the efficacy of NAC to reduce cocaine use, craving, withdrawal symptoms and relapse in human cocaine addicts. In a small safety and tolerability study, it was demonstrated that NAC was well tolerated by cocaine addicts and produced slight trends in reductions in self-reports of cocaine craving and withdrawal symptoms [818]. A follow-up 4-week pilot open-label trial confirmed that NAC is well tolerated by cocaine addicts and actually produces significant reductions in cocaine use [819]. Although these results provide encouraging data that NAC may be of potential use in the treatment of cocaine addiction, additional larger placebo-controlled clinical trials are needed to confirm these results.

13.3. *Modafinil*

Modafinil is a central nervous system stimulant that was originally designed as a wakefulness- and vigilance-enhancing drug for the treatment of narcolepsy and excessive daytime sleepiness caused by sleep apnea or shiftwork. Modafinil is sometimes prescribed as an off-label treatment for attention-deficit/hyperactivity disorder. Although its mechanism of action is not fully understood, it does not appear to act as a monoamine releaser as is the case for amphetamine-like stimulants. Modafinil may act by stimulating α-adrenoceptors, suppressing GABA release, weakly inhibiting the dopamine transporter, or stimulating hypothalamic orexin-containing neurons [820]. Modafinil also elevates extracellular levels of glutamate in numerous brain regions including the dorsal

striatum, thalamus, hippocampus, and hypothalamus [821–823] without affecting glutamate synthesis [824]. Modafinil is not considered to have abuse potential, although reports of non-medical use are increasing [820], and as a result modafinil is currently classified as a Schedule IV controlled substance.

Two clinical reports have shown some potential efficacy of modafinil in the treatment of cocaine addiction. In a small placebo-controlled drug-interaction study by Dackis and colleagues, it was reported that modafinil actually blunted the euphorigenic effects of intravenous cocaine in cocaine addicts [825], a findings that was later independently replicated [826]. A double-blind placebo-controlled study of treatment-seeking cocaine-dependent outpatients showed that modafinil significantly reduced daily cocaine use and prolonged abstinence [827]. Although these data provide potentially promising evidence that modafinil might be of use in the treatment of cocaine addiction, it is possible that some of the effects observed might be due to decreases in peak plasma concentrations of cocaine in the presence of modafinil [828]. Studies on the efficacy of modafinil in preventing relapse to cocaine use are needed. Nonetheless, these results show promise for modafinil as a potential treatment for cocaine addiction.

It is somewhat counterintuitive that a drug like modafinil, which increases extracellular glutamate levels similar to other psychostimulants (see Sections 4 and 5), results in reductions in cocaine intake, whereas numerous animal studies have shown that blockade of glutamatergic neurotransmission (i.e., by administration of iGluRs or mGluR5 receptor antagonists) reduces cocaine reinforcement. It is possible that the increases in extracellular glutamate levels produced by modafinil ''normalize'' the reduced extracellular glutamate observed during cocaine withdrawal and therefore attenuate the ability of cocaine to further increase glutamate release, akin to the effect observed with NAC (see Section 13.2 and Fig. 4). Further studies are needed to test this hypothesis.

13.4. *Topiramate*

Topiramate has been used as an anticonvulsant for over a decade, and has more recently been approved for the treatment of migraine. Topiramate is also sometimes prescribed for psychiatric conditions such as bipolar disorder and post-traumatic stress disorder. Like many anticonvulsant drugs, however, topiramate has multiple mechanisms of action, including inhibition of voltage-gated Na^+ and Ca^{2+} channels and activation of $GABA_A$ receptors [829–831]. In addition, it has recently been observed that topiramate also blocks GluR5-containing AMPA receptors [832,833].

Within the past few years it has become apparent that topiramate may be a novel therapeutic agent for the treatment of drug addiction. Topiramate attenuates the somatic symptoms of withdrawal from various drugs of abuse [834,835]. Several recent clinical trials have demonstrated efficacy of topiramate in attenuating alcohol craving or consumption [836–839], and has been shown to promote abstinence from cocaine [840], nicotine [841,842] and MDMA [843]. Since topiramate has numerous mechanisms of action, it is unknown whether its reductive effects on drug and alcohol use are a result of its interactions with AMPA receptors. However, it should be noted that since AMPA receptors play a critical role in mediating cocaine-seeking behavior and relapse (see Section 4), this mechanism of action may provide a possible neurochemical basis for the ability of topiramate to reduce relapse to cocaine use.

13.5. *Lamotrigine*

Similar to topiramate, lagotrimine is an anticonvulsant that inhibits voltage-gated Na^+ and Ca^{2+} channels [829-831]. Recently lamotrigine has shown some promise as a mood stabilizer. Through inhibition of presynaptic Na^+ and Ca^{2+} channels, lamotrigine prevents the release of various neurotransmitters, including glutamate [844–853]. Lamotrigine inhibits the somatic signs of withdrawal from various drugs of abuse [834,835]. Recent clinical studies show that lamotrigine also appears to exhibit efficacy in reducing craving for and use of cocaine [854–857], although it does not seem to alter the subjective effects of cocaine [858]. Similar reductive effects of lamotrigine on craving for and use of alcohol [859] and abused inhalants [860] have also been reported. These findings suggest that lamotrigine may be of clinical benefit in the treatment of addiction to cocaine, alcohol or abused inhalants. As with the multimodal actions of other anticonvulsants, it is difficult to determine whether the positive clinical effects of lamotrigine are due to its glutamate release-inhibiting properties, but this mechanism of action would fit well with the preclinical literature reviewed presently.

13.6. *Gabapentin*

Similar to its fellow anticonvulsants topiramate and lagotrimine, gabapentin inhibits presynaptic voltage-gated Na^+ and Ca^{2+} channels [829–831], and as such prevents the release of various neurotransmitters, including glutamate [632,861–866]. Gabapentin has been used successfully in the alleviation of somatic symptoms of drug withdrawal, particularly alcohol withdrawal [867–873]. Similar protective effects of gabapentin on animals or in vitro models of CNS hyperexcitability during alcohol withdrawal have been observed [874,875].

The results of clinical studies on possible therapeutic uses of gabapentin for cocaine addiction have been mixed. Some studies demonstrated that gabapentin does not reduce the use of cocaine [856,876,877], while other studies have shown some positive results [878–880]. Gabapentin has been reported to attenuate the discriminative stimulus effects of cocaine [881]. However, gabapentin does not reduce methamphetamine use [882], has limited effects on promoting abstinence from smoking [883], and does not appear to reduce craving for or the subjective effects of alcohol [884,885]. Thus, despite its glutamate release-inhibiting properties, gabapentin may not be of much clinical use in the treatment of drug addiction or alcoholism other than alleviating the symptoms of alcohol withdrawal.

13.7. *Memantine*

Memantine is a noncompetitive NMDA receptor antagonist that is used for the treatment of cognitive decline in Alzheimer's disease. In addition to its actions at NMDA receptors, memantine also blocks $5\text{-}HT_3$ receptors as well as

nAChRs. Memantine is one of the few NMDA receptor antagonists that is generally well tolerated by humans and does not appear to have abuse potential [886]. Clinical studies have shown that memantine is efficacious in reducing withdrawal symptoms in detoxified alcoholics [835] and opiate addicts [887], consistent the NMDA hyperactivity hypothesis of alcohol withdrawal (see Section 9). Several clinical trials have reported that memantine was superior to placebo in attenuating on-going drinking and/or craving for alcohol in alcoholics [888–890]. This amelioration of craving for alcohol may be a result of the ethanol-like subjective effects that are produced by memantine [888,889]. However, a larger placebo-controlled study indicated that memantine does not appear to reduce on-going drinking behavior in alcohol-dependent patients [891]. Also, memantine has been reported to increase the subjective and cardiovascular effects of cocaine without altering the choice to self-administer cocaine [892,893]. These data suggest that memantine may be of use in the treatment of alcohol or opiate withdrawal, but the disparate results that have been reported on its ability to reduce on-going alcohol consumption and/or alcohol craving need to be further evaluated. In addition, based on its inability to reduce the choice to self-administer cocaine and its potentiation of the subjective effects of this psychostimulant, memantine is likely to be ineffective in the treatment of cocaine-dependence, though large-scale clinical trials are needed to verify this.

14. Genetic linkages between glutamatergic neurotransmission and addiction in humans

Despite overwhelming evidence that glutamatergic transmission is involved in drug addiction and alcoholism, and the widely accepted notion that addiction has a strong genetic component, only a handful of genetic alterations in components of glutamate transmission (such as single nucleotide polymorphisms, SNPs) have been successfully linked to or associated with addictive behaviors. One of the first findings in this area was reported by Sander and colleagues, who found an increased allelic frequency of a silent SNP in exon 5 of the EAAT2 gene (G603A) in a population of German alcoholics with co-morbid antisocial personality disorder, but not in alcoholics without the co-morbid psychiatric diagnosis [894]. Thus, in this population, the EAAT2 SNP may not have been associated with alcoholism per se, but in tendencies towards risk-taking behaviors that are occasionally found in alcoholic individuals. An additional study found an association between the G603A allele and alcoholic cirrhosis [895].

As reviewed in Section 9, one of the molecular targets of alcohol is the NMDA receptor, the function of which is inhibited by alcohol. Indeed, non-alcoholics with a family history of alcoholism have altered subjective responses to NMDA antagonists such as ketamine as compared with non-alcoholics without a family history of alcoholism [896]. Accordingly, several groups of investigators have attempted to identify allelic variations in the genes encoding one or more of the NMDA receptor subunit proteins that may confer susceptibility to alcoholism. However, the results of these studies have been mixed. Two groups of investigators have shown that alcoholics with a history of alcohol withdrawal seizures and delirium tremens were more likely to carry a G2108A SNP in exon 7 of the NR1 subunit gene than controls [897,898]. An association of delirium tremens was also demonstrated to be associated with a Ser310Ala polymorphism in the GluR7 KA receptor gene [899], although this same polymorphism was not associated with alcoholism per se [900]. With regards to other iGluR subunits, findings have been less consistent. For example, a decreased allelic frequency of a C2664T SNP in exon 13 of the NR2B subunit gene in early-onset alcoholics has been demonstrated [897], while other groups of investigators have shown no association between alcoholism and a C2873T SNP in the NR2B gene, even in early onset alcoholics [901], or a C366G SNP in this gene [895]. Given the present set of data, it appears that genetic variations in iGluR subunit genes may be related to the presence of delirium tremens or alcohol-withdrawal seizures in alcoholic patients, but further research is needed to clarify whether such polymorphisms are associated with risk for alcoholism itself.

Group II and Group III mGluRs are often localized to presynaptic glutamatergic terminals where they regulate glutamate release via classic inhibitory autoreceptor mechanisms (see Fig. 2). Therefore, genetic mutations in these mGluRs may result in a lack of inhibitory feedback tone on the presynaptic glutamatergic terminal, resulting in excessive glutamate release and the possibility of seizures. Preuss and colleagues hypothesized that since mice carrying a targeted deletion of the mGluR7 gene show increased seizure susceptibility [902], polymorphisms in one or more presynaptic mGluRs might confer susceptibility to delirium tremens during alcohol withdrawal. However, these investigators found no association of a Tyr433Phe polymorphism in the mGluR7 gene or a C2756T polymorphism in mGluR8 gene and seizures or delirium tremens in a population of alcoholic patients [903].

In addition to alcoholism, there is evidence for a genetic component of cocaine addiction. As discussed in Section 4, the postsynaptic scaffolding Homer family of proteins plays a role in the behavioral and neurochemical responses to cocaine [30,904]. A recent genetic linkage study attempted to determine the presence of polymorphisms in Homer genes in African-American cocaine addicts [905]. Of the seven polymorphisms analyzed (four in the Homer1 gene, three in the Homer2 gene), only one SNP (ID #rs6871510, localized to the Homer1 gene) was detected to occur more frequently in cocaine addicts. While this study represents a potentially exciting and important link between cocaine addiction and glutamatergic signaling, replication studies in other cocaine addict populations are needed, as are studies to determine precisely how this polymorphism alters signal transduction by the NMDA-Group I mGluR-Homer complex.

15. Summary, conclusions and future directions

All drugs of abuse alter glutamate transmission via one mechanism or another. Psychostimulants and nicotine enhance extracellular levels of glutamate, opiates and cannabinoids reduce synaptic overflow of glutamate, and alcohol has mixed effects on extracellular levels of this amino acid.

Pharmacological agents that attenuate glutamatergic signaling, either by receptor antagonism, release inhibition, or enhancement of cellular uptake, tend to reduce the reinforcing and rewarding effects of most drugs of abuse, and can also attenuate the reinstatement of drug-seeking behavior, an established animal model of relapse. On the contrary, enhancement of glutamatergic transmission appears to promote the extinction of drug-seeking behavior, likely by facilitating new learning about drug availability, expectancies, or drug-cue associations. Thus, pharmacological compounds that antagonize glutamate transmission, including those already being used or tested in humans, are likely candidates that may be of use in the pharmacological management of excessive drug intake and relapse prevention. On the contrary, drugs that potentiate glutamatergic transmission and therefore promote synaptic plasticity and "new" learning may be of benefit in the facilitation of extinction learning.

Given that glutamate transmission is one of the primary neurochemical substrates of synaptic plasticity, and the overwhelming evidence reviewed here that all drugs of abuse interact with glutamate transmission, it is not surprising that drugs of abuse can cause long-lasting neuroadaptions of glutamate systems in the brain. These adaptations somehow lead to compulsive drug use, loss of volitional control over drug intake, and hypersalience of drug-associated environmental cues or contexts, all of which are characteristic of addiction. The question is—where do we go from here? From a scientific perspective, much more needs to be done to fully characterize the changes in glutamate systems that are caused by volitional intake of drugs of abuse in experimental animals, particularly in the context of drug intake patterns that mimic those taken by drug addicted humans. From treatment perspective, future research should focus on which changes in glutamate transmission can be most safely and effectively targeted by pharmacological or genetic interventions that either counteract the adaptive changes in the brain produced by prolonged intake of drugs of abuse, or promote new synaptic plasticity that can help the individual regain volitional control over drug intake and extinguish drug-associated memories and cravings.

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