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Cocaine-induced neuroadaptations in glutamate transmission

Potential therapeutic targets for craving and addiction

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A growing body of evidence indicates that repeated exposure to cocaine leads to profound changes in glutamate transmission in limbic nuclei, particularly the nucleus accumbens. This review focuses on preclinical studies of cocaine-induced behavioral plasticity, including behavioral sensitization, self-administration, and the reinstatement of cocaine seeking. Behavioral, pharmacological, neurochemical, electrophysiological, biochemical, and molecular biological changes associated with cocaine-induced plasticity in glutamate systems are reviewed. The ultimate goal of these lines of research is to identify novel targets for the development of therapies for cocaine craving and addiction. Therefore, we also outline the progress and prospects of glutamate modulators for the treatment of cocaine addiction.

Keywords: nucleus accumbens; reinstatement; relapse; synaptic plasticity; pharmacotherapy; receptor

Introduction

Cocaine abuse remains a major public health problem in the United States.[1] According to the National Survey on Drug Use and Health, it has been estimated that 34.15 million Americans ages 12 and older have used cocaine once in their lifetime and 2.1 million are current users of cocaine.[1] One hallmark of cocaine addiction and the paramount issue in its treatment is the high rate of relapse to drug taking after detoxification.[2,3] Despite decades of focused preclinical and clinical studies that have advanced our understanding of the anatomical and neurochemical bases of drug addiction, a safe and efficacious pharmacotherapy for cocaine craving remains to be discovered.

Cocaine craving and relapse of cocaine-taking behavior in abstinent human addicts are precipitated by three major stimuli: a stressful life event, an environmental stimulus previously associated or paired with the drug-taking event, or reexposure to the pre-viously self-administered drug itself.[4–8] Relapse to drug taking/seeking in humans is typically modeled in laboratory animals, including rodents and non-human primates, as follows: after a period of drug self-administration and the subsequent extinction of the drug-reinforced behavior, the ability of stress exposure, drug-associated stimuli, or reexposure to the drug itself to reinstate drug-seeking behavior is assessed.[9] For example, after extinction of cocaine self-administration, systemic or intravenous administration of relatively low doses of cocaine reinstate operant responding in the absence of drug reinforcement in both nonhuman primates and rodents.[5,10–13] Although the reinstatement model has good face validity in that similar stimuli reinstate cocaine seeking in animals that precipitate relapse in humans, the predictive validity of the reinstatement paradigm remains to be determined mainly because a successful pharmacotherapy for cocaine addiction has not been identified.[14] As the most commonly used animal model of relapse, the

reinstatement model has proven invaluable for elucidating the cellular and molecular mechanisms as well as the neural circuitry underlying cocaine-seeking behavior.

The reinforcing and rewarding effects of cocaine are mediated, in part, through the mesocorticolimbic dopamine system.[15] However, a growing body of evidence has emerged indicating that cocaine indirectly influences glutamate transmission in the limbic system, producing persistent changes in neuronal function that alter the behavioral effects of cocaine. Recent studies have suggested that drug addiction is a disorder in which long-term neural adaptations in dopamine and glutamate systems result from, and contribute to, drug-associated learning.[16] Furthermore, many similarities have been observed between the cellular and molecular mechanisms underlying addiction and neuronal plasticity associated with learning and memory.[17,18] Thus, drugs of abuse, including cocaine, induce synaptic modifications in motivational networks through coordinated signaling of dopamine and glutamate systems that in turn lead to maladaptive behaviors, including cocaine craving and relapse.[19–23] Therefore, studies further defining the cellular and molecular mechanisms underlying cocaine-induced plasticity in neuronal circuits that mediate drug-seeking behavior are essential to identify novel drug targets for cocaine craving and addiction.

Traditionally, research into the neurobiology of cocaine addiction has focused almost exclusively on the mesocorticolimbic dopamine system.[15,24–26] However, a substantial body of literature has emerged supporting a role for glutamate in drug-associated learning and other adaptive processes that mediate addictive behaviors in laboratory animals, including the reinstatement of cocaine-seeking behavior.[27–32] Here, we focus on the mechanisms underlying cocaine-induced behavioral and neuronal plasticity, with particular emphasis on the role of glutamate transmission in the nucleus accumbens, the primary input nucleus of the limbic portion of the basal ganglia.[33] Recent studies describing cocaine-induced synaptic plasticity in the nucleus accumbens are presented along with the molecular mechanisms regulating glutamate receptor–mediated signaling and localization/expression of glutamate receptor subunits. Furthermore, the effect of cocaine-induced neuroplasticity in excitatory synapses within the ac-

cumbens is discussed with relation to preclinical cocaine self-administration studies, including the reinstatement paradigm, although important evidence from other models (such as behavioral sensitization) is presented as well. Finally, a summary of findings from clinical studies examining the efficacy of glutamate-modulating drugs for cocaine relapse is discussed. A more complete understanding of how cocaine-induced synaptic plasticity in the mesocorticolimbic dopamine system alters neuronal ensembles to produce reinstatement of drug-seeking behavior could lead to the development of novel, targeted pharmacotherapies for cocaine addiction and relapse.

Neuronal circuitry mediating reinstatement of cocaine seeking

Dopaminergic modulation of the limbic system

Drugs of abuse produce their reinforcing effects through actions in the limbic component of the basal ganglia, a circuit of nuclei that is responsible for the influence of motivational, emotional, contextual, and affective information on behavior (Fig. 1). Cocaine is a crystalline tropane alkaloid that binds to dopamine, norepinephrine, and serotonin transporters, thereby blocking reuptake of biogenic amines in the brain.[34] Despite this binding profile, a growing literature indicates that dopamine is the biogenic amine primarily involved in cocaine reinforcement and the reinstatement of cocaine seeking.[15,35]

Limbic nuclei, including the amygdala, hippocampus, and medial prefrontal cortex (mPFC), send major glutamatergic projections to the nucleus accumbens, which is subdivided into the shell and core subregions.[36–38] The nucleus accumbens sends segregated efferent GABAergic projections to the ventral pallidum and ventral tegmental area/substantia nigra.[39–43] Both the ventral pallidum and ventral tegmental area, in turn, send GABAergic efferent projections to the medial dorsal thalamus.[44,45] Glutamatergic projections from the medial dorsal thalamus to the mPFC close this limbic circuit.[46–51] Dopaminergic neurons in the ventral tegmental area innervate the nucleus accumbens, amygdala, hippocampus, mPFC, and ventral pallidum, and changes in dopaminergic transmission play a critical role in modulating the flow of
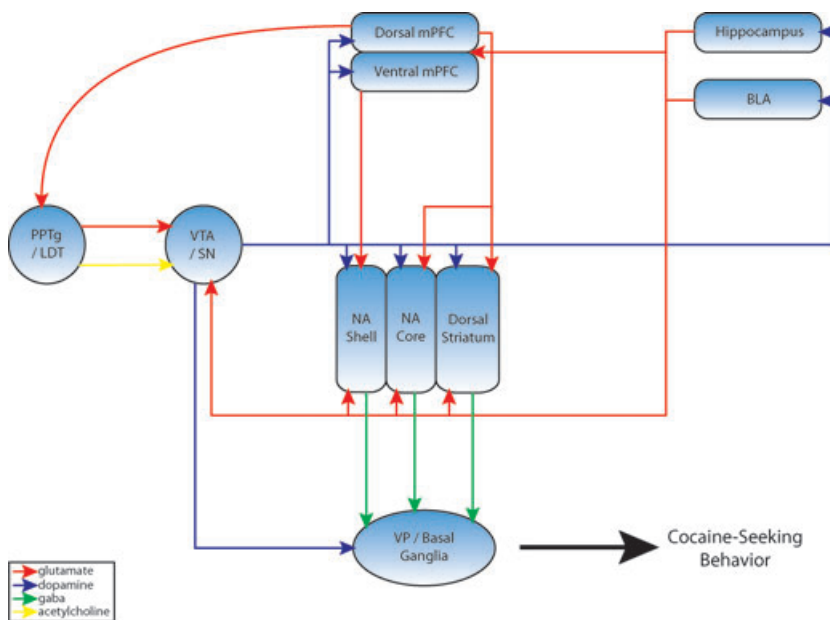
Figure 1. Proposed neuronal circuitry mediating cocaine priming–induced reinstatement of drug-seeking behavior. The medial prefrontal cortex (mPFC) sends segregated glutamatergic afferents to the nucleus accumbens (NA). These include excitatory projections from the dorsal mPFC (anterior cingulated cortex and dorsal prelimbic cortex) and ventral mPFC (ventral prelimbic cortex and infralimbic cortex) to the NA core and shell, respectively. The core and shell subregions of the accumbens also receive excitatory glutamatergic projections from both cortical (hippocampus) and subcortical (basolateral amygdala [BLA]) nuclei. Dopaminergic projections from the ventral tegmental area (VTA) and substantia nigra (SN) modulate the flow of emotional, declarative, and procedural memories through circuits centered on the NA, mPFC, BLA, and hippocampus. The activity of VTA and SN dopamine cells is regulated by excitatory glutamatergic projections from the pedunculopontine tegmental nucleus (PPTg)/laterodorsal tegmental nucleus (LDT), mPFC, hippocampus, and BLA, as well as inhibitory GABAergic/peptidergic projections from the NA and ventral pallidum (VP). Excitatory cholinergic afferents from the PPTg/LDT also synapse on midbrain dopamine neurons. The NA functions to translate the rewarding/reinforcing effects of drugs of abuse into drug-seeking behavior by processing, consolidating, and integrating information from limbic nuclei with motor functions of basal ganglia structures including the VP, thalamus, and motor cortex. (In color in *Annals* online.)

information through the limbic circuit comprising these interconnected nuclei.[48,52–57]

Nucleus accumbens: core and shell subregions

The nucleus accumbens can be divided according to histochemical criteria into two functionally discrete subregions, known as the core and shell.[43,58–63] Growing evidence suggests that heterogeneity in ventral striatal subregions imparts distinct functional differences to the nucleus accumbens. For example, the nucleus accumbens shell, which is classified as a part of the limbic system, is implicated in the primary rewarding effects of drugs of abuse[64–70] as well as regulating instrumental responding in the presence of motivationally relevant stimuli.[71–75] Alternatively, the nucleus accumbens core, which is considered part of the basal ganglia, mediates the incentive value of reward-conditioned stimuli and contributes to drug-associated, cue-induced cocaine seeking.[76–80] Neuronal circuits centered on the nucleus accumbens shell, nucleus accumbens core, and neostriatum are interconnected and can process information via parallel as well as integrated feedforward connections.[81–83] Moreover, information can flow through the striatal complex hierarchically from the shell to the core and to the

neostriatum.[36,50,81] Thus, the nucleus accumbens serves as a functional interface between limbic and motor systems processing affective and motivational information from the limbic system and integrating it with the basal ganglia.[84]

Nucleus accumbens: dopamine and cocaine reinstatement

An extensive literature indicates that increased dopamine transmission through D1- and D2-like dopamine receptors plays a critical role in priming-induced reinstatement of cocaine seeking.[35,85,86] For example, D2-like dopamine receptor agonists administered systemically or into the nucleus accumbens shell reinstate cocaine seeking.[11,12,87–94] Consistent with these results, systemic or intra-accumbal shell administration of a D2-like dopamine receptor antagonist attenuates cocaine priming–induced reinstatement of drug-seeking behavior.[12,90,91,95–98] In contrast, the precise contribution of D1-like dopamine receptors to reinstatement behavior is not clear. On their own, systemically administered D1-like dopamine receptor agonists do not reinstate cocaine-seeking behavior.[11,12,88,90,99] However, systemically administered D1-like dopamine receptor agonists and antagonists both attenuate drug-seeking behavior induced by a priming injection of cocaine.[11,12,90,100–102] When administered into the nucleus accumbens shell, D1-like dopamine receptor agonists reinstate drug-seeking behavior.[23,91,93,94] Consistent with these results, intra-accumbal shell administration of a D1-like dopamine receptor antagonist attenuates drug seeking induced by a priming injection of cocaine.[13,91] Taken together, these results indicate that D1- and D2-like dopamine receptors play critical roles in cocaine reinstatement and that D1-like dopamine receptors expressed in nuclei other than the nucleus accumbens shell may have different roles in drug-seeking behavior.

Converging neurotransmitter systems: corticostriatal glutamate afferents and mesostriatal dopamine afferents

There is considerable evidence that activation of the dopaminergic pathway from the ventral tegmental area to the mPFC contributes significantly to the reinstatement of cocaine seeking.[103–107] Increases in extracellular dopamine levels in the mPFC appear to promote cocaine seeking by stimulating glutamatergic pyramidal neurons that project from the mPFC to the nucleus accumbens.[105,108,109] Interestingly, there are two largely segregated glutamatergic afferents to the nucleus accumbens arising from the mPFC. Thus, the dorsal subregion of the mPFC (anterior cingulate cortex and dorsal prelimbic cortex) projects mainly to the accumbens core, whereas the ventral subregion of the mPFC (ventral prelimbic cortex and infralimbic cortex) sends glutamatergic projections to the accumbens shell.[110–114]

Within the nucleus accumbens and neostriatum, glutamatergic and dopaminergic afferent projections converge on the same spines of medium spiny GABAergic projection neurons.[56,115–118] This convergence of glutamate and dopamine neurotransmitter systems at synaptic and extrasynaptic sites within the nucleus accumbens facilitates a unique synaptic triad whereby dopamine modulates excitatory input to the accumbens from the mPFC, hippocampus, and amygdala.[119] Recent studies indicate that D2 dopamine receptors located on glutamatergic terminals regulate glutamate release in the striatum, and thus reinforce specific corticostriatal synapses by filtering less salient synaptic connections[120–123] (however, see Ref. 124). Also, stimulation of the ventral tegmental area leads to a D2-like dopamine receptor–mediated attenuation of the response of nucleus accumbens neurons to limbic input from the mPFC.[125] Taken together, these results indicate that excitatory input from cortical and subcortical structures to the nucleus accumbens is filtered and integrated by dopamine-mediated mechanisms, thereby shaping information output to the basal ganglia.

Glutamatergic neurotransmission

Glutamate is the major excitatory amino acid neurotransmitter in the central nervous system. Approximately 80–90% of synapses in the brain are glutamatergic, and it has been estimated that up to 90% of neurons in the brain use glutamate as a neurotransmitter.[126] In the brain, glutamate is synthesized in presynaptic nerve terminals from glucose via the Krebs cycle and from glutamine that is synthesized in glial cells, released into the extracellular fluid, and transported into nerve terminals where it is converted into glutamate by the mitochondrial enzyme glutaminase. Within the

nerve terminal, glutamate is loaded into synaptic vesicles by vesicular glutamate transporters (VGLUTs), multimeric protein complexes that function as proton–glutamate antiporters.[127] To date, three different VGLUTs have been cloned (VGLUT1–3). Whereas VGLUT1 and 2 are expressed in functionally distinct populations of glutamatergic neurons, VGLUT3 is localized in serotonin and possibly dopamine neurons, cholinergic interneurons in the striatum, and GABAergic interneurons of the hippocampus and cortex, which suggests a novel role for glutamate.[128–130] Upon depolarization of the presynaptic terminal, glutamate is released into the synaptic cleft, where it passively diffuses and binds to presynaptic, postsynaptic, and perisynaptic glutamate receptors. There are two main families of glutamate receptors: ligand-gated ionotropic glutamate receptors that mediate fast excitatory neurotransmission and metabotropic glutamate receptors that modulate pre- and postsynaptic responses through G protein activation of second-messenger systems.[131] Glutamate signaling is terminated by a family of high-affinity, Na^+-dependent excitatory amino acid transporters (EAATs 1–5) that have distinct anatomical and cellular distributions as well as unique pharmacological profiles.[132] For example, EAAT1 and 2 are expressed on glial cells and neuronal EAATs (2–5) have specialized roles at presynaptic terminals (EAAT2 and 5) and postsynaptic membranes (EAAT3 and 4).[132] In contrast to EAAT1 and 2, the Na^+-independent cystine–glutamate antiporter maintains basal levels of extrasynaptic glutamate by exchanging extracellular cystine for intracellular glutamate in glial cells.[133]

Nucleus accumbens glutamate and cocaine reinstatement

A growing body of literature indicates that cocaine indirectly influences glutamate transmission in the limbic system, including the nucleus accumbens, producing persistent changes in neuronal function that alter the behavioral effects of cocaine.[30,31,134,135] Thus, maladaptive forms of neuroplasticity in the nucleus accumbens contribute to cocaine-seeking behavior, and reversing these cocaine-induced neuroadaptations in glutamatergic transmission may prevent relapse of cocaine taking.

Basal levels of extracellular glutamate are decreased in the nucleus accumbens during withdrawal from repeated cocaine exposure

As a dopamine, serotonin, and norepinephrine reuptake inhibitor, cocaine does not act directly on glutamatergic neurons.[34] Acute systemic administration of cocaine has little or no effect on extracellular glutamate levels in the nucleus accumbens[136] (however see Refs. 137 and 138). In contrast, withdrawal from repeated exposure to cocaine reduces basal extracellular glutamate levels in the nucleus accumbens.[35,136,139] It was subsequently shown that the decrease in basal accumbal glutamate during withdrawal from chronic cocaine exposure resulted from decreased activity of the cystine–glutamate antiporter.[139,140] Consistent with these results, normalization of extracellular accumbal glutamate levels in animals with a history of cocaine self-administration with *N*-acetylcysteine (NAC), a cysteine prodrug that increases activity of the cystine–glutamate antiporter, prevented reinstatement of drug seeking induced by a priming injection of cocaine.[140] Taken together, these results indicate that repeated cocaine treatment promotes neuroadaptations in glutamatergic transmission in the nucleus accumbens that influence the persistence of craving and drug-seeking behavior.

Glutamate release in the nucleus accumbens of cocaine-experienced rats promotes reinstatement of cocaine seeking

Multiple studies indicate that a cocaine challenge injection administered to rats pretreated with repeated cocaine injections results in increased glutamate release in the nucleus accumbens core.[108,136,141–144] During withdrawal from repeated cocaine exposure, a challenge injection of cocaine also decreased presynaptic glutamate immunoreactivity in the accumbens core, but not the accumbens shell, suggesting that different neuroadaptations occur in these brain regions after repeated cocaine exposure.[145–147] Similarly, cocaine priming–induced reinstatement of drug seeking was associated with increased glutamate release in the core of the nucleus accumbens, an effect that was attenuated by pharmacological inactivation of the mPFC.[108] Consistent with these results, administration of an α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonist into the nucleus accumbens blocked the

reinstatement of cocaine seeking induced by administration of cocaine directly into the mPFC.[105] Infusion of an AMPA receptor antagonist directly into the nucleus accumbens core or γ-aminobutyric acid (GABA) receptor agonists directly into the dorsal mPFC also alters GABA levels in the ventral pallidum after a challenge injection of cocaine in animals withdrawn from chronic cocaine exposure.[148] These findings, collectively, suggest that activation of the glutamatergic projection from the mPFC to the nucleus accumbens promotes cocaine seeking, a finding supported by brain imaging studies of human cocaine addicts, which demonstrate that cocaine craving is associated with metabolic activation of the mPFC.[149,150] These findings also demonstrate that stimulation of AMPA glutamate receptors in the nucleus accumbens plays a critical role in cocaine seeking.

Glutamate receptors and cocaine self-administration/seeking

The ionotropic family of glutamate receptors consists of three subfamilies of tetrameric receptors named for the agonists that bind to them: *N*-methyl-D-aspartate (NMDA) receptors, AMPA receptors, and kainate receptors (Fig. 2). Agonist binding induces a conformation change in NMDA, AMPA, and kainate receptors that increases the probability of channel opening. Different subunit compositions of ionotropic glutamate receptors produce functionally diverse NMDA, AMPA, and kainate receptors that are expressed differently throughout the brain.[151]

Ionotropic glutamate receptors: NMDA receptors

NMDA receptors are a heteromeric ligand-gated ion channels that are composed of three different subunits (NMDAR1–3) and are permeable to Ca^{2+}, K^+, and Na^+. There are multiple subtypes of NMDA receptors that differ in their subunit composition and in their biophysical and pharmacological properties. Eight different splice variants of the NR1 subunit originate from a single gene. In contrast, six separate genes encode four different NR2 subunits (NR2A–D) and two genes encode two NR3 subunits (NR3A and B).[151] Although the exact stoichiometry of NMDA receptors *in vivo* is unclear, at least one NR1 subunit and one NR2 subunit are required for

functional NMDA receptors *in vitro*.[152] The NMDA receptor is unique among all other neurotransmitter receptors in its requirement for the simultaneous binding of two different agonists (coagonists) for activation, glutamate and glycine or D-serine.[153] At least one NR1 subunit and one NR2 subunit are required for functional NMDA receptors because glutamate and glycine bind to these respective subunits. In addition to binding coagonists, NMDA receptor activation requires membrane depolarization via AMPA receptor activation in order to remove the voltage-dependent block provided by Mg^{2+} at resting state.[154] Furthermore, distinct recognition sites for endogenous and exogenous ligands regulate NMDA receptor function.[151,152] NMDA receptors are expressed in different cell types, including microglia, astrocytes, oligodendrocytes, and neurons[152,155–157] as well as on presynaptic and postsynaptic membranes in the nucleus accumbens.[158,159] An emerging literature indicates that nucleus accumbens NMDA receptors play a role in the drug-induced neural plasticity underlying maladaptive behaviors, including addiction.[17,160–163]

Effect of repeated cocaine exposure on NMDA receptor expression in the nucleus accumbens

Studies examining NMDA receptor subunit mRNA and protein expression in the nucleus accumbens of animals receiving noncontingent injections of cocaine and in animals self-administering intravenous injections of cocaine report inconsistent findings.[30] For example, some reports have demonstrated no change in the expression of NR1 and NR2A/B receptor subunits in the nucleus accumbens after 24 h of withdrawal from repeated cocaine exposure,[164,165] whereas others have reported decreased expression of accumbal NR1 subunits at similar time points.[166,167] In contrast, NR1 receptor subunit expression is increased in the nucleus accumbens after longer periods of withdrawal in animals that developed behavioral sensitization.[164,166,168] Moreover, nucleus accumbens NR1 subunit expression is increased after protracted withdrawal periods in animals that previously self-administered cocaine.[160,169] Behavioral sensitization to the locomotor-activating effects of cocaine is also associated with increased expression of NR2B in the nucleus accumbens shell after 24 h, but not
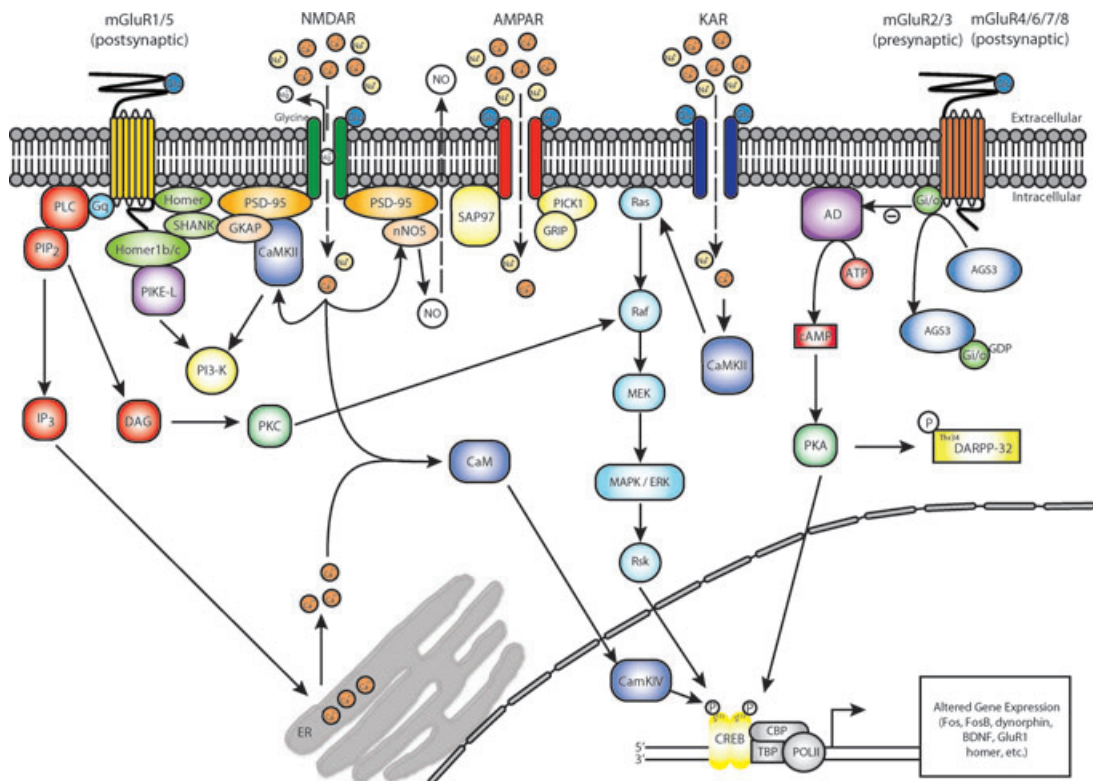
Figure 2. Glutamate receptor–mediated signaling. Glutamate released into the synaptic cleft binds to and activates ionotropic glutamate receptors (NMDA, AMPA, and kainate [KA] receptors) on postsynaptic membranes. Extracellular glutamate also binds to and activates perisynaptic metabotropic glutamate receptors located on presynaptic (mGluR2/3 autoreceptors) or postsynaptic (mGluR1/5s heteroreceptors) membranes. Influx of Na^+, Ca^{2+}, and K^+ ions through activated AMPA/KA receptors depolarizes a neuron and subsequently relieves the Mg^{2+} block from voltage-sensitive NMDA receptors and activates voltage-gated Ca^{2+} channels (not shown). In addition to propagating action potentials, influx of cations through ionotropic glutamate receptors activates several intracellular signaling pathways including, but not limited to, Ras, CaMKII, and protein kinase A (PKA). Group I (mGluR1/5) and group II (mGluR2/3) metabotropic glutamate receptors are coupled via G_q and $G_{i/o}$, respectively, to intracellular enzymes. Stimulation of mGluR1/5s activates phospholipase C (PLC), which catalyzes the production of inositol-1,4,5-triphosphate (IP_3) and diacylglycerol (DAG) from phosphatidylinositol-4,5-bisphosphate (PIP_s). The resulting increase in cytoplasmic IP_3 triggers release of Ca^{2+} from intracellular stores, including the endoplasmic reticulum (ER). Stimulation of mGluR2/3s inhibits adenylyl cyclase (AC) activity, thus decreasing intracellular levels of cAMP and PKA. The cytoplasmic proteins PSD-95, glutamate receptor–interacting protein (GRIP), and Homer anchor glutamate receptors to the PSD complex. For example, Shank–Homer interactions link mGluR1/5s to NMDA receptors through PSD-95 and guanylate kinase–associated protein (GKAP). GluR1-containing AMPA receptors may be linked to mGluR1/5s through interactions between Homer and phosphoinositide 3 kinase (PI3-K) enhancer (PIKE-L). Metabotropic glutamate receptor–mediated signaling is influenced by regulators of G protein signaling (RGS), including activator of G protein signaling 3 (AGS3). AGS3 binds to and stabilizes the inactive guanosine diphosphate (GDP)–bound G_i conformation, preventing GDP release and thereby inhibiting G_i-mediated signaling. PKA phosphorylates dopamine- and cyclic AMP–regulated phosphoprotein (DARPP-32) at Thr34, which enhances extracellular signal–regulated kinase (ERK) signaling by inhibiting phosphatase activity. Activation of ionotropic and metabotropic glutamate receptors ultimately leads to phosphorylation of transcription factors, including cAMP response element–binding protein (CREB) at Ser133, changes in gene expression, and persistent changes in synaptic plasticity. See text for more detail on how repeated cocaine administration influences glutamate receptor–mediated signaling in the nucleus accumbens. (In color in *Annals* online.)

1 week, of withdrawal from cocaine, suggesting that changes in glutamate receptor subunit expression are time dependent.[170,171] However, in rats that undergo withdrawal from cocaine, NR1 receptor subunit expression is decreased in the accumbens shell.[172] Postmortem studies of human cocaine overdose victims reveals increased expression of NR1.[173] Collectively, these studies indicate that after a period of forced abstinence from cocaine administration there is increased expression of NMDA receptor subunits in the nucleus accumbens.

Nucleus accumbens NMDA receptors and cocaine reinforcement

NMDA receptors have been demonstrated to contribute to the reinforcing effects of cocaine. Systemic administration of noncompetitive NMDA receptor antagonists blocks the acquisition of cocaine self-administration behavior[174] and attenuates responding for cocaine on a fixed-ratio (FR) schedule of reinforcement.[175–178] Although these results indicate that blocking NMDA receptor–mediated signaling enhances the reinforcing efficacy of cocaine, MK-801 administration dose-dependently modulates breakpoint ratios (i.e., low doses potentiate and high doses attenuate the rewarding effects of cocaine) in rodents responding for cocaine under a progressive-ratio schedule of reinforcement.[179] Interestingly, pharmacological antagonists of the NMDA receptor may have different effects on cocaine self-administration behavior owing to unique binding sites and modulatory kinetics.[177] When administered directly into the nucleus accumbens, NMDA receptor antagonists attenuate responding for cocaine under a second-order schedule of reinforcement.[180–182] However, NMDA receptor antagonists have reinforcing properties and thus abuse liability, because rats will self-administer pharmacologically diverse NMDA receptor antagonists directly into the nucleus accumbens shell.[64]

Nucleus accumbens NMDA receptors and the reinstatement of cocaine seeking

There also is evidence that accumbal NMDA receptors play a role in the reinstatement of cocaine seeking. Administration of a NMDA receptor agonist directly into the nucleus accumbens reinstated cocaine seeking in rats.[143,144] However, intra-accumbal administration of a NMDA receptor agonist increased

responding on an inactive lever, a nonspecific operant response not associated with drug infusion, suggesting that increased responding on the active lever may be due to a generalized increase in locomotor activity.[143] In a subsequent study, it was found that systemic administration of a relatively low dose of an NMDA receptor antagonist neither prevented cocaine-primed reinstatement nor induced reinstatement when administered alone.[144] In contrast, other studies have shown that systemic,[183] intra-accumbal shell,[105,161] or intra-accumbal core[161] administration of an NMDA receptor antagonist reinstates cocaine-seeking behavior. Taken together, these results suggest that NMDA receptors in the nucleus accumbens modulate the reinstatement of cocaine seeking.

The extant literature examining the role of accumbal NMDA receptors in cocaine reinstatement does not provide an obvious interpretation of why NMDA receptor agonists and antagonists produce similar behaviors when administered directly into the nucleus accumbens.[35,144] However, there are several plausible mechanisms to explain this discrepancy. For example, cocaine administration increases extracellular levels of acetylcholine in the cortex.[184] Similarly, NMDA and a competitive NMDA receptor antagonist both increase extracellular acetylcholine levels in the mPFC when administered directly into the nucleus accumbens.[185–187] Thus, one potential explanation for the similar behavioral effects of NMDA receptor agonists and antagonists involves acetylcholine release in the mPFC. It is also possible that the behavioral effects of NMDA receptor antagonists are mediated by presynaptic NMDA receptors in the accumbens. Although NMDA receptors are expressed predominantly on postsynaptic membranes, there is some evidence that these receptors are also expressed on corticostriatal terminals.[158] Furthermore, systemic administration of an NMDA receptor antagonist increases extracellular glutamate levels in the nucleus accumbens.[188] Therefore, it is possible that NMDA receptor antagonists administered into the nucleus accumbens promote cocaine seeking by blocking presynaptic NMDA receptors on glutamatergic afferents, thereby increasing extracellular glutamate levels[188] and indirectly activating postsynaptic AMPA receptors to reinstate cocaine-seeking behavior.[105,143,144] This hypothesis has not yet been examined experimentally. Finally, extracellular dopamine levels are

increased in the nucleus accumbens after systemic, intra-accumbal, or intra-mPFC administration of NMDA receptor antagonists.[188–191] Several studies have clearly demonstrated that increased dopaminergic transmission in the shell and medial core subregions of the accumbens reinstates cocaine seeking.[13,91,93,94,97] On the basis of these studies, it is possible the NMDA receptor antagonists promote the reinstatement of cocaine seeking, in part, by increasing extracellular dopamine levels in the nucleus accumbens. Taken together, these results reveal that the functional role of nucleus accumbens NMDA receptors in the reinstatement of cocaine seeking is complex, and further studies are needed to determine the precise mechanism(s) by which NMDA receptor agonists and antagonists promote cocaine-seeking behavior.

Ionotropic glutamate receptors: AMPA and kainate receptors

Similar to NMDA receptors, AMPA receptors are heterotetrameric ligand-gated ion channels that are ubiquitously expressed throughout the brain, including the nucleus accumbens.[158,159] Multiple subtypes of AMPA receptors with distinct pharmacological profiles are composed from different combinations of subunits termed GluR1–4 (or GluRA–D), GluRδ1, and GluRδ2.[151,192] AMPA receptor subunits exist in two functionally different variants, flip or flop, that are generated by alternative splicing, differently expressed throughout the brain and characterized by distinct desensitization kinetics.[193–195] In contrast to NMDA receptors, AMPA receptor activation is voltage independent. AMPA receptors are permeable to cations, including Ca^{2+}, Na^+, and K^+. The conversion of a glutamine (Q) codon to an arginine (R) renders GluR2-containing AMPA receptors impermeable to calcium.[196–198] Because most GluR2 subunits are edited in this manner, GluR2-containing AMPA receptors are calcium impermeable.[199] Interestingly, the relative expression of GluR2 subunit mRNA and protein in neurons is not static and may be remodeled by administration of cocaine.[200,201] In the nucleus accumbens, GluR1 and GluR2 subunits are expressed in virtually all medium spiny neurons.[202] In contrast, GluR3 and GluR4 subunit expression in the nucleus accumbens is relatively low.[202–204]

Similar to AMPA receptors, kainate receptors are heterotetrameric ligand-gated ion channels that mediate fast excitatory synaptic transmission.[205,206] Kainate receptors are voltage-independent protein complexes that are composed of combinations of five subunits: GluR5–7, KA1, and KA2.[151,207] Functional homomeric or heteromeric kainate receptors are formed from combinations of GluR5–7, whereas KA1 and KA2 form heteromeric receptors only by partnering with any of the GluR5–7 subunits.[205,207] Kainate receptors are permeable to Na^+; K^+; and, depending on editing and/or alternative splicing of GluR5 and GluR6 subunit mRNAs, Ca^{2+}.[208–211] In addition to influencing cation permeability, mRNA editing and alternative splicing mechanisms regulate trafficking and subcellular localization of kainate receptor subunits.[212–216] Kainate receptors are expressed presynaptically and postsynaptically in the nucleus accumbens, where they regulate neurotransmitter release and neuronal excitability, respectively.[158,159,205]

In contrast to AMPA receptors, the precise role of kainate receptors in synaptic plasticity remains unclear; however, there is emerging evidence that kainate receptors mediate some forms short- and long-term synaptic plasticity in the brain.[205,207,211,217,218] Moreover, a specific role for kainate receptors in drug-induced plasticity is difficult to determine because of a lack of pharmacological compounds that discriminate between these two classes of ionotropic glutamate receptors.[219] The most commonly used non-NMDA glutamate receptor antagonist, CNQX, exhibits relatively little selectivity between kainate and AMPA receptors and, at higher concentrations, binds to the glycine site on NMDA receptors.[220–222] Recently, selective kainate receptor agonists and antagonists have been developed,[219,223,224] which should prompt studies into the specific role of kainate receptors in the reinforcing effects of cocaine as well as cocaine craving and relapse.

Role of nucleus accumbens AMPA/kainate receptors in cocaine self-administration and extinction

Modulation of AMPA/kainate glutamate receptors influences cocaine self-administration behavior, indicating that the reinforcing and rewarding effects of cocaine are mediated, in part, through

AMPA receptor–mediated signaling. Thus, systemic administration of an AMPA/kainate receptor antagonist decreases or has no effect on responding for cocaine on an FR schedule of reinforcement.[143,175] Similarly, infusion of an AMPA/kainate receptor antagonist directly into the core, but not the shell, decreases cocaine self-administration under a second-order schedule of reinforcement, suggesting that AMPA receptors in these two subregions of the nucleus accumbens have dissociable roles in cue-induced cocaine seeking.[225] However, intra-accumbal core administration of an AMPA receptor agonist also decreased responding for cocaine on an FR schedule of reinforcement, suggesting that increased accumbens AMPA receptor signaling augments the reinforcing effects of cocaine.[143] Thus, future studies are required to elucidate the precise role of intra-accumbal AMPA/kainate receptors in the reinforcing effects of cocaine and whether basal levels of extracellular glutamate influence the reinforcing efficacy of cocaine in these behavioral models.[143]

During extinction, when animals learn that drug-seeking behavior is no longer reinforced in the absence of drug reward, AMPA receptor subunit expression is altered, suggesting that extinction training induces plasticity in glutamatergic systems that influence cocaine reinstatement.[226] For example, GluR1 and GlurR2/3 subunit expression was increased in the nucleus accumbens shell of cocaine-experienced rats that had undergone 1 week of extinction training.[227] Viral-mediated overexpression of GluR1 and GluR2 AMPA receptor subunits in the nucleus accumbens shell facilitated extinction of lever responding for cocaine and was sufficient to attenuated stress-induced reinstatement of cocaine seeking.[227] These data indicate that extinction-induced plasticity in the nucleus accumbens shell is a compensatory response to decreased basal extracellular glutamate levels during withdrawal from cocaine. However, in rats that undergo withdrawal from cocaine, rather than active extinction, GluR1 subunit expression is decreased in the accumbens shell.[172] Collectively, these results suggest that increases in AMPA receptor expression in the nucleus accumbens shell during extinction opposes stress-induced reinstatement of cocaine seeking and that active inhibitory learning, not passive withdrawal, is required for these neuroadaptations.

Effect of repeated cocaine exposure on AMPA receptor expression in the nucleus accumbens

Studies examining glutamate receptor subunit mRNA and protein expression in the nucleus accumbens of animals receiving noncontingent injections of cocaine and in animals self-administering intravenous injections of cocaine report inconsistent findings.[30] For example, some reports have demonstrated no change in the expression of GluR1–2 or kainate receptor subunits in the nucleus accumbens after 24 h of withdrawal from repeated cocaine exposure,[164,165,201] whereas others have reported decreased expression of accumbal GluR3/4 subunits at similar time points.[166,167] In contrast, GluR1 and GluR2/3 subunit expression is increased in the nucleus accumbens after longer periods of forced abstinence in animals that developed behavioral sensitization.[164,166,168,201] After protracted periods of forced abstinence among animals that previously self-administered cocaine, nucleus accumbens GluR1, GluR2, and GluR2/3 subunit expression are increased after protracted withdrawal periods in animals that previously self-administered cocaine.[160,169] Similar results were observed after the extinction of cocaine self-administration behavior.[227] Cocaine self-administration followed by a period of forced abstinence is also associated with increases in phospo-GluR1 in the accumbens core and shell, although the magnitude of this increase is less than that occurring after the acute administration of cocaine.[172] Consistent with these preclinical studies, postmortem studies of human cocaine overdose victims reveals increased expression of GluR2/3 and a trend toward increased GluR1 subunit proteins in the nucleus accumbens.[173] Collectively, these studies indicate that repeated exposure to cocaine followed by a period of forced abstinence, when extracellular glutamate levels are decreased in the nucleus accumbens,[136,140] is associated with increases in the expression of AMPA receptor subunits in the nucleus accumbens, which may result in a predisposition toward cocaine craving and relapse.

Nucleus accumbens AMPA/kainate receptors and the reinstatement of cocaine seeking

Several studies have shown that accumbal AMPA/kainate receptors contribute significantly to

the reinstatement of cocaine seeking. Thus, administration of an AMPA receptor agonist directly into the nucleus accumbens promotes reinstatement of cocaine seeking, whereas intra-accumbal administration of an AMPA/kainate receptor antagonist blocks reinstatement induced by a systemic priming injection of cocaine[143,144,228] or conditioned stimuli previously paired with cocaine taking.[229] Although these microinjection studies did not distinguish between the core and shell subregions of the nucleus accumbens, there is evidence that increased glutamate transmission in both the core and shell contributes to the reinstatement of cocaine seeking. Thus, increased extracellular glutamate release in the nucleus accumbens core was observed during cocaine priming–induced reinstatement of drug seeking,[108] whereas administration of an AMPA/kainate receptor antagonist into the accumbens shell inhibited the reinstatement of cocaine seeking prompted by administration of cocaine into the mPFC.[105] Recent evidence indicated that administration of an AMPA/kainate receptor antagonist into the accumbens core or shell attenuated the reinstatement of cocaine seeking.[230] Consistent with these results, microinjection of AMPA directly into the accumbens core or shell reinstates cocaine seeking.[231] Moreover, suppression of GluR1 transcription in either the accumbens core or shell impaired the reinstatement of drug seeking induced by a cocaine priming injection.[231] Collectively, these data indicate that increased glutamate transmission through AMPA/kainate receptors in both the core and shell of the nucleus accumbens promotes the reinstatement of cocaine-seeking behavior.

AMPA receptor trafficking and cocaine-induced plasticity

A growing body of evidence indicates that the dynamic trafficking of AMPA receptors plays a critical role in neuronal plasticity.[27,192,232–235] In terms of cocaine-induced neuronal plasticity, the ratio of cell surface to intracellular GluR1 and GluR2/3 AMPA receptor subunits in the nucleus accumbens is increased after 3 weeks, but not 1 day, after the last of a series of repeated cocaine injections.[236] Increases in synaptic insertion of GluR1, GluR2, and possibly GluR3 subunits in the nucleus accumbens should contribute to cocaine-induced behavioral plasticity as well as augment

long-term potentiation (LTP),[27] a change in synaptic plasticity that has been demonstrated in the nucleus accumbens after repeated cocaine injections.[237] However, repeated cocaine injections and cocaine self-administration also decrease the magnitude of long-term depression (LTD) in the nucleus accumbens.[238–240] More recent studies suggest that cocaine-induced changes in the synaptic strength of excitatory cortico-accumbal synapses are bidirectional.[204,241] That is, although repeated cocaine administration, followed by a period of forced abstinence, enhances AMPA receptor-mediated synaptic transmission[241] and AMPA receptor transport to the cell surface in the nucleus accumbens,[204] these effects are reversed 24 h after a systemic challenge injection of cocaine.[204,241] Consistent with these findings, cocaine self-administration followed by extinction results in decreased GluR2–pSer880 in the nucleus accumbens shell, whereas a cocaine challenge injection prompts an increase in accumbens shell GluR2–pSer880.[230] Recent results suggest a behavioral correlate of this form of bidirectional plasticity in that the expression of behavioral sensitization to cocaine is associated with transient decreases in the behavioral hyperactivity induced by intra-accumbal AMPA administration.[242] Taken together, these findings highlight one mechanism by which cocaine-induced plasticity in the nucleus accumbens regulates expression of sensitization to the incentive motivational effects of cocaine.[204,236]

Cocaine-induced bidirectional plasticity in the synaptic strength of excitatory cortico-accumbal synapses indicates that a prior history of cocaine alters the magnitude or direction of plasticity within a given neuron or synapse in response to a subsequent priming injection of cocaine, a process referred to as metaplasticity.[243,244] Furthermore, dynamic regulation of AMPA receptors by intracellular proteins that regulate subunit trafficking and synaptic plasticity controls Ca^{2+} permeability of synaptic AMPA receptors.[245] Experience-dependent modification of neural circuitry, including neural adaptations to drugs of abuse, are believed to underlie all forms of behavioral plasticity and are mediated, in part, by AMPA receptor trafficking.[23,192,246–249] Thus, recent findings suggest that cocaine-induced plasticity in excitatory synapses within the nucleus accumbens initiates adaptive changes in neuronal ensembles that lead to drug-seeking behavior and alters subsequent physiological responses to cocaine,

including increased trafficking and surface expression of AMPA receptors, during extended withdrawal.

AMPA receptor trafficking and cocaine-induced reinstatement of drug seeking

Blocking AMPA glutamate receptor–mediated signaling in the nucleus accumbens core or shell attenuates cocaine priming–induced reinstatement of drug seeking.[105,108,230] Consistent with these results, decreased GluR1 subunit mRNA expression in the nucleus accumbens core or shell blocks cocaine priming–induced reinstatement.[231] However, cocaine priming–induced reinstatement of drug-seeking behavior was associated with increased phosphorylation of GluR1 AMPA receptor subunits on Ser831, an amino acid residue phosphorylated by calcium/calmodulin-dependent kinase II (CaMKII) and protein kinase C (PKC), and enhanced cell surface expression of GluR1-containing AMPA receptors in the accumbens shell.[23] Consonant with these findings, impairing the transport of GluR1-containing AMPA receptors to the cell surface in the nucleus accumbens shell attenuated the ability of a priming injection of cocaine to reinstate drug-seeking behavior.[23] The reinstatement of cocaine seeking is also associated with increased phosphorylation of GluR2 AMPA receptor subunits at Ser880, a PKC phosphorylation site, in the accumbens shell.[230] PKC-induced phosphorylation of GluR2 subunits at Ser880 and the subsequent association of GluR2 with protein interacting with C kinase (PICK1) results in rapid internalization of GluR2-containing AMPA receptors.[246,250–253] However, there is a growing body of evidence that PICK1 also contributes significantly to the insertion of GluR2-containing AMPA receptors into synapses under certain circumstances.[245,254] Although these results appear contradictory, these findings were observed in different cell types in the hippocampus and cerebellum. For example, activity-dependent interactions between GluR2 and PICK1 result in endocytosis of GluR2-containing AMPA receptors within Purkinje cells in the cerebellum.[250,255] In contrast, PICK1 regulates the insertion of GluR2-containing AMPA receptors into synapses in cerebellar stellate cells.[245,254] Disrupting interactions between GluR2 AMPA receptor subunits and PICK1 in the nucleus accumbens shell with a peptide that mimics C terminus residues of GluR2 subunits, including Ser880, attenuates cocaine-seeking behavior, which suggests that impairing the trafficking of GluR2-containing AMPA receptors in the nucleus accumbens disrupts the reinstatement of drug seeking.[230] Similarly, intra-accumbal administration of a peptide that specifically blocks activity-dependent but not constitutive endocytosis of GluR2-containing AMPA receptors attenuates the expression of behavioral sensitization to amphetamine.[256] These results indicate that enhanced behavioral responses after repeated cocaine exposure (reinstatement or behavioral sensitization) are associated with the internalization of GluR2-containing AMPA receptors in the core and shell of the nucleus accumbens. In contrast, the reinstatement of cocaine seeking was coincident with increases in the surface expression of GluR1-containing AMPA receptors in the nucleus accumbens shell.[23] Thus, removal of GluR2-containing AMPA receptors from synapses in the nucleus accumbens shell attenuates cocaine-seeking behavior,[230] and increases in GluR1-mediated excitatory transmission in the accumbens shell promote cocaine priming– and cue–induced reinstatement of drug seeking.[23,257] Taken together, these findings suggest that the reinstatement of cocaine-seeking behavior is mediated by different trafficking of AMPA receptor subunits in the nucleus accumbens shell, including increased surface expression of GluR2-lacking AMPA receptors.[257]

Metabotropic glutamate receptors

Metabotropic glutamate receptors (mGluRs) are coupled to intracellular signaling pathways via G proteins and upon activation generate slow synaptic responses and regulate neuronal plasticity.[258,259] Eight different mGluR subunits have been identified to date and classified into three main subfamilies on the basis of sequence homology, pharmacology, and coupling to intracellular effectors.[260,261] These functional subfamilies include group I mGluRs (mGluR1 and 5), which stimulate phospholipase C (PLC), resulting in the generation of diacylglycerol (DAG) and inositol triphosphate (IP_3), which activate PKC and Ca^{2+} release from intracellular stores; group II mGluRs (mGluR2 and 3); and group III mGluRs (mGluR4, 6–8), which inhibit adenylate cyclase

activity and subsequently decrease cAMP levels.[262,263] Group I and II mGluRs are widely distributed throughout the brain, including the nucleus accumbens.[264–273] Group I mGluRs are expressed predominantly on postsynaptic membranes, just lateral to the postsynaptic density; however, there is some evidence for presynaptic localization of mGluR1 and mGluR5.[274–278] mGluR2s are generally expressed at extrasynaptic sites on presynaptic terminals, where they have been demonstrated to attenuate excitatory amino acid neurotransmission.[279–282] In contrast, mGluR3s are localized on both pre- and postsynaptic locations on neurons as well as more widespread distribution in glial cells.[282,283] Recent studies have demonstrated that altered mGluR signaling mediates, in part, cocaine-induced neuroadaptations[284–288] and that activation of mGluR signaling may reverse cocaine-induced synaptic plasticity.[289]

Effect of repeated cocaine exposure on mGluR expression in the nucleus accumbens

Several studies have examined mGluR mRNA and protein expression in the nucleus accumbens after repeated exposure to cocaine. For example, expression of mGluR5 mRNA is increased and expression of mGluR2/3 is decreased in the nucleus accumbens after 3 weeks of withdrawal from repeated, but not acute, cocaine administration.[166,290] Because extracellular basal glutamate levels are decreased after repeated cocaine administration,[136] it is likely that increased mGluR5 expression and decreased mGluR2/3 expression in withdrawn animals reflects a compensatory change in response to hypoglutamatergic transmission. These results are consistent with recent findings demonstrating that an acute injection of cocaine did not alter total accumbal expression of mGluR5 protein but was sufficient to reduce surface expression of mGluR5 in the nucleus accumbens, which suggests that trafficking of mGluRs plays a critical role in cocaine-induced synaptic plasticity.[284] Consistent with this hypothesis, recent evidence indicates that mGluR2/3 and mGluR5 proteins are redistributed to the synaptosomal membrane fraction after a period of extended, but not acute, forced abstinence.[290]

Nucleus accumbens mGluRs and cocaine reinforcement

A few studies have assessed the role of mGluRs in cocaine self-administration behavior. Systemic administration of an mGluR2/3 glutamate receptor agonist attenuates cocaine self-administration through a mechanism that probably involves decreased synaptic glutamate transmission after stimulation of presynaptic mGluR2/3s.[291] Constitutive mGluR5–knockout mice do not self-administer cocaine and are insensitive to the locomotor stimulant properties of cocaine.[292] Similarly, administration of the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) decreases self-administration of cocaine, suggesting that mGluRs may be viable targets for the development of therapeutics for cocaine addiction.[293–297]

Nucleus accumbens mGluRs and reinstatement of cocaine seeking

Recent evidence suggests that mGluRs may also contribute to cocaine priming–induced reinstatement of drug seeking. Systemic administration of an mGluR5 antagonist attenuated the ability of a priming injection of cocaine[295] or cocaine-associated cues[298] to reinstate cocaine seeking. Consistent with this finding, intra-accumbal shell administration of an mGluR5 antagonist attenuated cocaine priming–induced reinstatement.[299] mGluR2/3s have also been shown to play a role in cocaine seeking. For example, systemic administration of an mGluR2/3 agonist attenuates cue-induced[300] and cocaine priming–induced[291,301] reinstatement of drug-seeking behavior. However, systemic and intra-accumbal core administration of an mGluR2/3 receptor agonist attenuates food seeking as well, suggesting that activation of accumbal mGluR2/3s impairs general responding for drugs of abuse and natural reinforcers.[301]

Role of the cystine–glutamate antiporter in cocaine seeking

In addition to decreasing basal levels of extracellular glutamate in the nucleus accumbens, withdrawal from repeated cocaine exposure decreases activity of the cystine–glutamate exchanger, an antiporter protein expressed on glial cells that

exchanges extracellular cystine for intracellular glutamate.[140,302] These results indicate that one potential mechanism underlying cocaine priming–induced reinstatement is decreased cystine–glutamate exchanger activity, a neuroadaptation that results in decreased extracellular glutamate levels.[303] Normalization of exchanger activity by administering cystine directly into the nucleus accumbens or NAC (a cystine prodrug) systemically attenuates the ability of a priming injection of cocaine to reinstate drug-seeking behavior.[140,304] Similarly, inhibiting cysteine–glutamate exchange in the nucleus accumbens promotes cocaine-induced drug seeking.[303] Moreover, increasing cystine–glutamate exchanger activity prevented both the decrease in basal extracellular glutamate levels during withdrawal from repeated cocaine and the subsequent increase in glutamate levels and the reinstatement of cocaine seeking associated with a systemic priming injection of cocaine.[140] Mechanistically, the reduction in extracellular glutamate levels in the nucleus accumbens core after repeated exposure to cocaine provides less tonic activation of mGluR2/3 autoreceptors on glutamatergic terminals in the nucleus accumbens, such that synaptic levels of glutamate are increased after a challenge injection of cocaine owing to less mGluR2/3-mediated inhibitor feedback.[305,306] Taken together, these results indicate that the reinstatement of cocaine seeking is promoted, in part, by reducing cystine–glutamate exchange in the nucleus accumbens.

Cocaine-induced metaplasticity, *N*-acetylcysteine, and mGluRs

The finding that withdrawal from repeated cocaine administration and subsequent reexposure to cocaine results in bidirectional synaptic plasticity in the nucleus accumbens[204,241] suggests that cocaine craving and relapse are regulated, in part, by cocaine-induced metaplasticity in excitatory synapses within the accumbens. Metaplasticity, as it relates to addiction, may involve drug-induced neuroadaptations in the physiological or biochemical state of glutamatergic networks or synapses that ultimately alters their ability to generate synaptic plasticity, such as LTP and LTD.[244,307] Recently, it was shown that withdrawal from repeated cocaine administration alters the capacity of subsequent stimuli to induce neuroplasticity at excitatory synapses

in the nucleus accumbens.[287] This study demonstrated that the ability of PFC stimulation to produce LTP or LTD in nucleus accumbens core GABAergic projection neurons is impaired after 3 weeks of extinction training in cocaine-experienced animals, indicating that withdrawal from repeated cocaine exposure shifts the threshold necessary for generating a plastic response in the accumbens.[287] Furthermore, systemic administration of NAC reversed cocaine-induced metaplasticity in the accumbens and restored the capacity of PFC stimulation to induce LTP and LTD at excitatory synapses in the accumbens core.[287] The ability of NAC to restore synaptic plasticity and reverse cocaine-induced metaplasticity in cortico-accumbal synapses is due to presynaptic mGluR2/3- and postsynaptic mGluR5-mediated effects on LTP and LTD, respectively.[287,308] Taken together, these results suggest that drugs, such as NAC that reverse cocaine-induced metaplasticity, may prevent cocaine craving and relapse. However, the precise relationship between altered synaptic plasticity and susceptibility to relapse remains to be determined.

Homer, mGluR signaling, and repeated cocaine

Intracellular scaffolding proteins called Homer proteins regulate mGluR1/5 signaling and trafficking in the brain.[309–311] Homer proteins are enriched at excitatory synapses, where they bind to several synaptic proteins in the postsynaptic density and link mGluR1/5s to ionotropic glutamate receptors.[311–313] After 3 weeks of withdrawal, mGluR1/5s, Homer1b/c, and Homer2a/b protein expression were decreased in the medial nucleus accumbens shell of cocaine-experienced rodents.[278,314] Constitutive Homer1- or Homer2-knockout mice have behavioral phenotypes similar to those of animals pretreated with repeated injections of cocaine.[315] Moreover, Homer2-knockout mice acquired cocaine self-administration behavior faster than wild-type control subjects and had reduced basal extracellular glutamate levels in the accumbens because of altered function of mGluR1s and the cystine–glutamate exchanger.[315] Interestingly, Homer2 function converges with regulators of G protein signaling (RGS) function at synapses in the striatum, indicating that altered expression of AGS3 and Homer proteins during

withdrawal from repeated cocaine use mediates persistent changes in cortico-accumbal glutamatergic projections.[316–318] The behavioral and neurochemical parallels between constitutive Homer2-knockout mice and wild-type mice with a history of repeated cocaine administration suggests that Homer2 plays a critical role in regulating accumbens glutamate levels and cocaine-induced behavioral sensitization.[319,320] Consistent with these results, overexpressing Homer isoforms in the nucleus accumbens attenuates expression of cocaine-induced behavioral sensitization as well as increased extracellular accumbens glutamate levels after a challenge injection of cocaine.[321] Expression of Homer isoforms in the nucleus accumbens is differently regulated by acute versus chronic cocaine injections, and this cellular response is mediated by D1-like dopamine receptors, and not D2-like dopamine, AMPA, or NMDA receptors.[322] Thus, Homer proteins regulate signaling and trafficking of metabotropic and ionotropic glutamate receptors in the nucleus accumbens, as well as extracellular levels of glutamate. Homer proteins may contribute to enduring molecular plasticity in excitatory synapses in the accumbens after repeated cocaine exposure.

Nucleus accumbens synaptic plasticity and reinstatement of cocaine-seeking behavior

As previously described, increases in dopamine and glutamate transmission in the nucleus accumbens independently promote the reinstatement of cocaine seeking.[35,85] Although the downstream signaling effects and neuroadaptations that contribute to this behavior are not well defined, there has been recent progress in this area, which is outlined in the following sections.

Cocaine seeking and interactions between accumbens dopamine and glutamate systems

The cellular mechanisms underlying D1-like dopamine receptor–mediated reinstatement of cocaine seeking in the nucleus accumbens are poorly defined. Stimulation of G protein-coupled D1-like dopamine receptors increases synthesis of cAMP and activates protein kinase A (PKA), which contribute to the reinforcing effects of cocaine and reinstatement of cocaine-seeking behavior.[323,324] One

intracellular effector targeted by PKA is the L-type Ca^{2+} channel, which plays a critical role in psychostimulant-induced behavioral and neuronal plasticity.[325,326] L-type Ca^{2+} channels in turn activate a family of protein kinases including CaMKII, an enzyme that regulates both the initiation and expression of psychostimulant-induced behavioral sensitization.[325,327] In striatal neurons, activation of D1-like dopamine receptors enhances AMPA receptor–mediated excitatory postsynaptic potentials,[328] an effect that is suppressed by administration of an L-type Ca^{2+} channel antagonist.[329] Consistent with these findings, blocking L-type Ca^{2+} channels decreases glutamate-mediated burst firing of accumbal neurons.[330] Collectively, these results suggest that cocaine-induced neuronal plasticity in dopamine and glutamate systems is mediated, in part, through activation of L-type Ca^{2+} channels and CaMKII.

A recent study examined this hypothesis and demonstrated that stimulating D1-like dopamine receptors in the medial nucleus accumbens shell promotes the reinstatement of cocaine seeking by serially stimulating L-type Ca^{2+} channels and phosphorylation of CaMKII on Thr286.[23] Furthermore, reinstatement of cocaine-seeking behavior was associated with an increase in phosphorylation of the AMPA receptor subunit GluR1 on Ser831, an amino acid residue phosphorylated by CaMKII and PKC, and enhanced cell surface expression of GluR1-containing AMPA receptors in the accumbens shell.[23] Consistent with these findings, impairing the transport of GluR1-containing AMPA receptors to the cell surface within the nucleus accumbens shell attenuated the ability of a priming injection of cocaine to reinstate drug-seeking behavior.[23] These results indicate that D1-like dopamine receptor stimulation–dependent activation of L-type Ca^{2+} channels and CaMKII facilitates the reinstatement of cocaine seeking by promoting the transport of GluR1-containing AMPA receptors in the nucleus accumbens shell to the plasma membrane (Fig. 3). The mechanisms underlying CaMKII-dependent AMPA receptor transport, however, are unclear and may include targets other than GluR1.[249,331] Thus, CaMKII activity in the nucleus accumbens shell may be an essential link between dopamine and glutamate systems involved in the neuronal plasticity underlying cocaine craving and relapse.
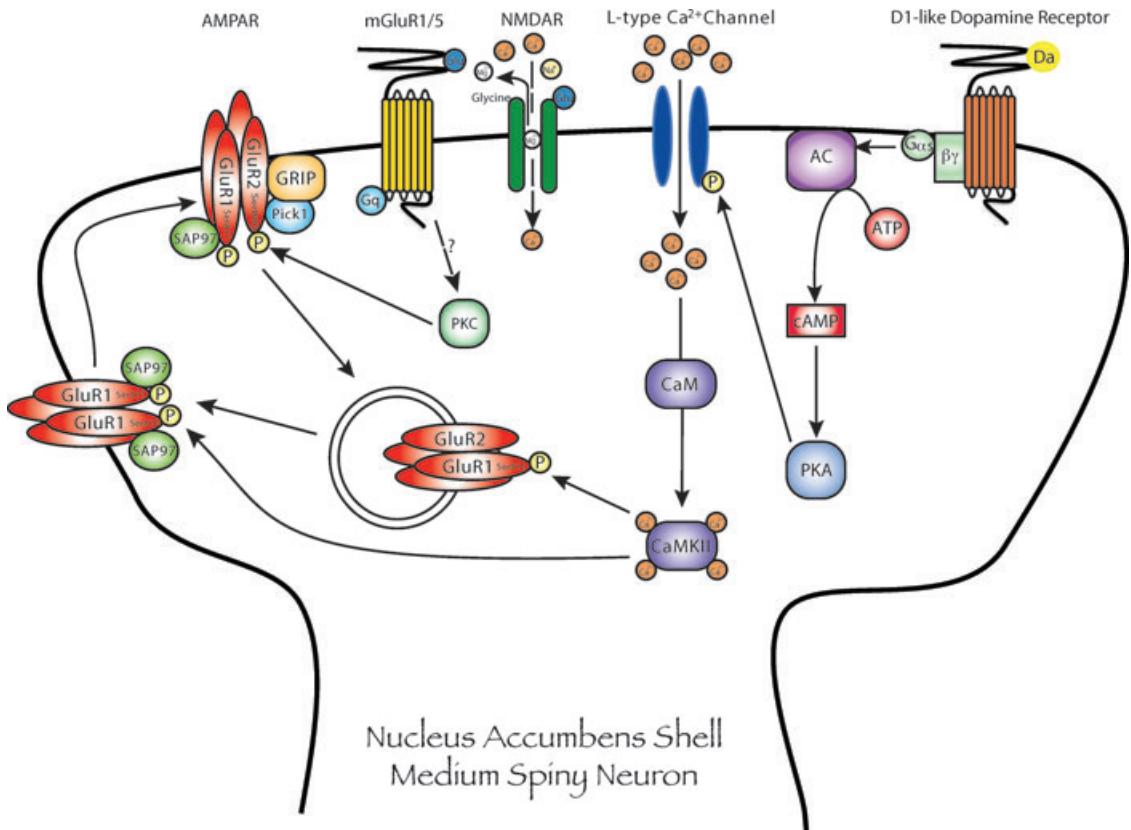
Figure 3. Link between nucleus accumbens shell dopamine and glutamate systems, via L-type Ca^{2+} channels and Ca^{2+}/calmodulin kinase II (CaMKII), which is proposed to underlie the reinstatement of cocaine seeking. In brief: stimulation of D1-like dopamine receptors serially activates L-type Ca^{2+} channels and CaMKII. In addition to phosphorylation of CaMKII, reinstatement of cocaine seeking is associated with phosphorylation of GluR1 AMPA receptor subunits at Ser831, a known CaMKII and protein kinase C (PKC) phosphorylation site, as well as increased surface expression of GluR1-containing AMPA receptors in the nucleus accumbens shell. However, cocaine priming–induced reinstatement was not associated with an increase in GluR1 phosphorylation on Ser845, a known protein kinase A (PKA) phosphorylation site. Interfering with PDZ domain–containing proteins, such as synapse-associated protein (SAP) 97, and GluR1 subunits impairs trafficking of GluR1-containing AMPA receptors to the cell surface and attenuates cocaine seeking. Reinstatement of drug seeking is also associated with increased phosphorylation of GluR2 subunits at Ser880, a known PKC phosphorylation site that promotes internalization of GluR2-containing AMPA receptors. Although the receptor systems that activate PKC signaling during the reinstatement are unknown, one possibility is mGluR1/5s that are coupled to PKC via PLC. Consistent with the theory that PKC phosphorylation promotes internalization of GluR2-containing AMPA receptors after a priming injection of cocaine, disruption of accumbens shell protein interacting with C kinase (PICK1) function, which involves binding to GluR2 subunits and their rapid internalization, attenuates the reinstatement of cocaine seeking. Taken together, these results suggest that the reinstatement of cocaine-seeking behavior is associated with dynamic trafficking of AMPA receptor subunits between the cell surface and cytoplasmic compartments within the accumbens and that these molecular adaptations underlie cocaine-induced synaptic plasticity. (In color in *Annals* online.)

Nucleus accumbens, cocaine-induced molecular neuroplasticity, and the reinstatement of cocaine seeking

Repeated cocaine administration has profound cellular and molecular effects on nucleus accumbens dopamine and glutamate systems. Cocaine-induced neuroadaptations in reward-related circuitry mediate maladaptive behaviors, including the reinstatement of drug-seeking behavior.[35] Aberrant neuroplasticity in learning and memory circuits within corticolimbic-striatal networks plays a critical role in the development and persistence of addictive behaviors.[16,17,20,27,134,332] In addition to altered expression of ionotropic and mGluR subtypes in the nucleus accumbens, chronic cocaine exposure also regulates expression and function of intracellular effectors that mediate synaptic plasticity and more permanent modifications in chromatin structure and protein expression. Recent studies have begun to examine the cellular and molecular components that mediate enduring cocaine-induced molecular plasticity in nucleus accumbens glutamate systems and how these alterations influence reinstatement of drug-seeking behavior.

Emerging evidence indicates that pre- and postsynaptic adaptations in glutamatergic projections from the mPFC to the nucleus accumbens facilitate glutamate release in response to a priming injection of cocaine and promote reinstatement of drug seeking. Preclinical studies suggest that repeated cocaine administration reduces signaling through $G_{i\alpha}$-coupled receptors and that this deficit plays a critical role in cocaine addiction.[333–336] Stimulation of transmembrane metabotropic G protein-coupled receptors activates heterotrimeric G proteins that, in turn, regulate intracellular effectors and transmit neuronal signals across plasma membranes. RGS proteins are accessory proteins that modulate signal transfer from G protein-coupled receptors to G protein and/or the activation state of G_α proteins by stimulating GTPase activity or blocking activation of signal transduction cascades by G proteins.[337–339] Chronic cocaine administration increases RGS9 protein expression in the nucleus accumbens.[317] Furthermore, withdrawal from chronic cocaine exposure increases expression of AGS3, an activator of G protein-coupled signaling that binds $G_{i\alpha}$ and thus decreases signaling through $G_{i\alpha}$-mediated signaling cascades, in the mPFC

and accumbens core.[316] AGS3 antisense oligonucleotides administered directly into the mPFC reversibly inhibit AGS3 expression and restore D2-like dopamine receptor–mediated $G_{i\alpha}$ signaling in the mPFC after chronic cocaine exposure, which provides further evidence that AGS3 reduces $G_{i\alpha}$ signaling in the mPFC.[316] Moreover, AGS3 antisense administration during extinction training attenuated cocaine priming–induced reinstatement of drug seeking.[316] Taken together, these results suggest that elevated AGS3 levels during withdrawal decrease $G_{i\alpha}$-mediated signaling (D2-like dopamine receptors, mGluR2/3s, and μ opioid receptors) and shift the signaling bias in the mPFC to favor $G_{s\alpha}$-mediated signaling (D1-like dopamine receptors, β-adrenergic receptors, and corticotropin-releasing factor receptors).[340] Thus, persistent changes in RGS proteins in the mPFC indicate that stable molecular changes occur in glutamatergic projection neurons to the nucleus accumbens and that these adaptations contribute to the propensity to reinstate cocaine-seeking behavior after withdrawal from cocaine self-administration.

Repeated noncontingent cocaine injections also increases adenylyl cyclase and cyclic-AMP dependent PKA expression in the nucleus accumbens of rodents[341] and nonhuman primates.[342] Consistent with these results, PKA expression was increased in the nucleus accumbens or rats after withdrawal from cocaine self-administration.[160] Administration of a PKA inhibitor directly into the nucleus accumbens reinstates cocaine seeking.[323] Although administration of a PKA activator into the accumbens facilitates cocaine reinstatement, this effect may reflect a generalized increase in behavioral activation, because operant responding was increased on both active and inactive levers[323]; however, see Ref. 324. In contrast, administration of a PKA inhibitor decreased cocaine self-administration under a progressive-ratio schedule of reinforcement.[324] These discrepant findings may be due to different dosing regimens and/or schedules of reinforcement that reflect motivational or regulatory aspects of drug-taking behavior.[343] Furthermore, prominent sex differences exist in basal and cocaine-induced alterations in PKA signaling within the nucleus accumbens.[344,345] Regardless, it is difficult to interpret the role of PKA signaling in priming-induced reinstatement because these behavioral effects could be

modulated by pre- and/or postsynaptic effects that modulate dopamine and glutamate transmission in the accumbens.[323,346,347] It is clear that stimulation of D1-like dopamine receptors in the nucleus accumbens activates PKA and increases insertion of AMPA receptor subunits into the plasma membrane.[235,348,349] Thus, cocaine-induced neuroadaptations in PKA-mediated signaling probably promote dysfunctional synaptic plasticity by altering trafficking and surface expression of AMPA receptors in the nucleus accumbens.

Recent evidence indicates that PKC may mediate drug-induced neuroadaptations in synaptic plasticity within the nucleus accumbens during the reinstatement of cocaine seeking. PKC-dependent increases in phosphorylation of GluR2 subunits in the accumbens shell, and possibly core, are associated with cocaine-seeking behavior and suggest that internalization/trafficking of GluR2-containing AMPA receptors in the accumbens is one mechanism underlying cocaine-induced metaplasticity.[230] These findings support those of previous studies demonstrating a role for PKC in psychostimulant-mediated behaviors. For example, repeated cocaine administration increases the phosphorylation of some, but not all, isoforms of PKC in the nucleus accumbens.[350,351] Furthermore, intra-accumbal administration of a PKC inhibitor attenuated amphetamine-induced conditioned place preference (CPP)[352] and systemic administration of a PKC inhibitor attenuated cocaine-induced CPP.[353] Similarly, administration of a PKC inhibitor directly into the accumbens blocked the expression of behavioral sensitization to cocaine.[354] PKC mRNA expression is increased in limbic areas, including the accumbens, after 5 days of withdrawal from self-administered cocaine.[355] Although the precise role of accumbens PKC isoforms in cocaine priming–induced reinstatement of drug seeking is unknown, preliminary studies suggest that persistent changes in PKC expression after repeated cocaine exposure may lead to enduring changes in glutamate transmission. In addition to regulating AMPA receptor trafficking, psychostimulants may also influence the trafficking and functional regulation of dopamine,[356–358] serotonin,[359,360] and norepinephrine[361,362] transporters through PKC- and PKA-dependent signaling mechanisms, although this hypothesis as it relates to cocaine craving and relapse has yet to be tested.

CaMKs have also been demonstrated to play a role in the persistent behavioral effects of repeated cocaine administration. For example, administration of a CaMKII inhibitor directly into the nucleus accumbens blocks expression of cocaine-induced behavioral sensitization.[327,354] Furthermore, reinstatement of cocaine-seeking behavior is associated with CaMKII-mediated phosphorylation and surface expression of GluR1 subunits in the nucleus accumbens.[23] The molecular bases for the physiological and behavioral effects of psychostimulant-induced activation of CaMKII may involve disruption of D2-like dopamine receptor–NR2B signaling interactions[363] and/or increased trafficking of GluR1-containing AMPA receptors to the cell surface.[23,364] Recent evidence suggests that CaMKIV also regulates cocaine-mediated behaviors. For example, mice selectively lacking CaMKIV expression in dopaminergic neurons display increased cocaine-induced CPP and behavioral sensitization.[365] Moreover, a significant association between a single-nucleotide polymorphism in the human CaMKIV promoter and cocaine addiction has been identified, further supporting a role for this enzyme in cocaine craving and relapse.[365] These results indicate that CaMKII and CaMKIV activity may have distinct influences on addictive behaviors, effects that are due, in part, to different regulation of CREB protein–dependent transcription.[365–367] However, the precise role of CaMK proteins in the long-term plasticity associated with vulnerability to relapse in human cocaine addicts remains to be determined.

Repeated cocaine administration produces enduring neuroadaptations in several intracellular effectors that mediate dopamine and/or glutamate signaling in the nucleus accumbens. In addition to the aforementioned proteins, long-term molecular and synaptic plasticity in the accumbens after chronic cocaine exposure are also mediated, in part, by changes in the extracellular signal–regulated kinase signaling pathway,[135,368,369] brain-derived neurotrophic factor,[135,370] cyclin-dependent kinase 5,[371,372] and gene expression.[373,374] Identifying and reversing these and other cocaine-induced neuroadaptations may lead to more targeted pharmacotherapies that enhance or block specific forms of neuroplasticity that underlie maladaptive learning and memory processes, such as cocaine craving and addiction.

Glutamate-modulating drugs, cocaine craving, and relapse

Collectively, the studies presented here indicate that altered glutamate transmission in the nucleus accumbens mediates the reinforcing effects of cocaine as well as the reinstatement of cocaine-seeking behavior. With the importance of cocaine-induced neuroadaptations in neuronal and synaptic plasticity within glutamatergic circuits that mediate normal reward learning,[17,27] recent approaches to developing novel pharmacotherapies for cocaine addiction have focused on drugs that inhibit/modulate glutamate transmission.[134,375] The results of these clinical and preclinical studies are summarized in the following.

Cystine–glutamate exchanger substrate: *N*-acetylcysteine

The efficacy of NAC, a drug commonly used to treat acetaminophen overdose,[376] in treating addictive behaviors has been tested for cocaine relapse,[377,378] nicotine addiction,[379] and gambling.[380] As reviewed in the preceding, NAC has been shown to normalize decreased glutamate levels in the nucleus accumbens of cocaine-experienced animals during withdrawal from drug use and attenuate reinstatement of cocaine-seeking behavior.[139,304] Recent clinical trials demonstrate that NAC is well tolerated; reduces cocaine use; and, according to subjective patient reports, decreases desire to use cocaine.[377,378] However, NAC treatment does not significantly reduce cocaine craving and thus may not prevent relapse in abstinent cocaine addicts.[381] Although the results of these preliminary studies are promising, clinical trials with larger sample sizes are needed to fully realize the therapeutic efficacy of NAC in treating maladaptive, compulsive behaviors, such as drug addiction.

Modafinil

Modafinil is a stimulant that is currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of narcolepsy, shift-work sleep disorder, and obstructive sleep apnea.[382,383] Preclinical studies of modafinil suggest a similar pharmacological profile to psychostimulants including amphetamines; however, not all its neurochemical and behavioral effects overlap with those of amphetamine.[384] For example, modafinil binds to sites on both dopamine and norepinephrine transporters *in vivo*, and clinically relevant doses of modafinil increase extracellular dopamine levels.[385,386] The molecular mechanisms that regulate the wake-promoting effects of modafinil have recently been attributed to activation of D1-like and D2-like dopamine receptors.[387] Furthermore, modafinil increases histamine release,[388] stimulates hypothalamic orexin neurons,[389,390] increases glutamate release, and inhibits both GABA release[391] and firing of midbrain dopamine neurons through a D2-like dopamine receptor–mediated mechanism.[392] Although humans will self-administer modafinil more than placebo under certain conditions,[393] most clinical studies suggest that modafinil has low abuse liability even among current drug users.[394–396] Modafinil pretreatment does not affect cocaine self-administration in rodents, which suggests that this compound does not have reinforcing effects.[397] In contrast, very high doses of modafinil produced reinforcing and discriminative stimulus effects in non-human primates.[398] However, the effects of chronic modafinil administration on the reinforcing effects of cocaine have not been studied using animal models.

Modafinil pretreatment reduces cocaine-induced euphoria and craving in human cocaine users without producing adverse effects.[399–401] Furthermore, cocaine-dependent patients reported that modafinil decreased cocaine-associated subjective measures after a drug-taking event.[402] A recent clinical study demonstrated that modafinil pretreatment decreased high-dose cocaine self-administration as well as the intoxicating and cardiovascular effects of smoked cocaine.[403] Collectively, these clinical results are promising and need to be confirmed by larger studies.

Partial NMDA receptor agonist: D-cycloserine

D-Cycloserine is an antibiotic that crosses the blood–brain barrier, binds with high affinity to the glycine modulatory site on the NMDA receptor and thus functions as a partial NMDA receptor agonist *in vivo*.[404–406] D-Cycloserine facilitates fear extinction in laboratory animals and humans patients with anxiety disorders.[407–409] Consistent with these results, administration of D-cycloserine enhances extinction of cocaine-induced CPP, a

behavioral effect that was persistent.[410–412] Taken together, these results suggest that D-cycloserine administration reduces the conditioned reinforcing properties of drug-associated stimuli through facilitation of extinction learning. However, a recent study demonstrates that administration of D-cycloserine directly into the basolateral amygdala augments cue-induced reinstatement of cocaine seeking.[413] This study indicates that D-cycloserine administration enhances reconsolidation of cocaine-associated memories and thereby promotes reinstatement of drug-seeking behavior.[413] Moreover, high doses of D-cycloserine reinstated cocaine-induced CPP.[412] It remains to be determined how different dosing regimens of D-cycloserine affect addictive behaviors in preclinical as well as clinical studies.

Noncompetitive NMDA receptor antagonists: memantine and amantadine

Memantine is a noncompetitive NMDA receptor antagonist that is used to treat cognitive decline associated with Alzheimer's disease.[414,415] In addition to blocking NMDA receptors, memantine also blocks 5-HT$_3$ receptors.[416] Memantine does not have reinforcing effects in cocaine-dependent humans, which suggests that it does not have abuse liability.[417] Memantine also increases the subjective and cardiovascular effects of cocaine without altering the choice to self-administer cocaine.[418,419] Administration of memantine attenuates cocaine self-administration in rats[177] and nonhuman primates.[420] However, memantine administration does not attenuate the reinforcing effects of cocaine in mice,[178] and higher doses of memantine increase cocaine self-administration behavior in nonhuman primates.[420] Memantine may not be a likely pharmacotherapy for cocaine craving and relapse on the basis of its inability to decrease cocaine self-administration behavior and its potentiation of the subjective effects of cocaine. Large-scale clinical trials are needed to determine the efficacy of memantine administration in treating cocaine addiction.

Amantadine is a noncompetitive NMDA receptor antagonist with weak dopaminergic effects that is used to treat Parkinson's disease and influenza A.[421] Amantadine has been proposed as a therapeutic for cocaine dependence.[422] Amantadine induces presynaptic release of dopamine and nore-

pinephrine in the brain and blocks reuptake of these monoamines.[423] In addition to these neurochemical effects, amantadine inhibits the release of acetylcholine in the striatum[424] and increases extracellular dopamine levels in the striatum[425] through NMDA receptor–mediated mechanisms. Amantadine attenuates cocaine-mediated behaviors in animals undergoing withdrawal from continuous cocaine exposure.[426] Although preliminary, clinical studies have demonstrated the amantadine treatment may reduce cocaine craving and use in current cocaine users[427,428] (but see Refs. 429 and 430). However, amantadine's therapeutic benefit may be realized only in cocaine addicts experiencing severe withdrawal symptoms.[431]

Anticonvulsants: topiramate and lamotrigine

Topiramate is an anticonvulsant drug approved by the FDA for treating migraines.[432] In addition to activating GABA$_A$ receptors and blocking voltage-gated Na$^+$ and Ca^{2+} channels, topiramate blocks mGluR5-containing AMPA receptors.[433–436] When tested in rodents, topiramate administration did not substitute for the discriminative-stimulus properties of cocaine, nor did it attenuate the reinforcing effects of cocaine.[437] Recent clinical studies demonstrate that cocaine-dependent patients receiving topiramate were more likely to abstain from cocaine use than control subjects.[438] Further studies are needed to determine the efficacy of topiramate in preventing relapse of cocaine-taking behavior and the neurochemical basis for these behavioral effects.

Similar to topiramate, lamotrigine is an anticonvulsant drug that blocks voltage-gated Na$^+$ and Ca^{2+} channels.[433,439,440] By inhibiting presynaptic Na$^+$ and Ca^{2+} channels, lamotrigine prevents the release of neurotransmitters including glutamate.[441–445] Recent clinical studies demonstrate that lamotrigine reduces cocaine craving,[446–448] although this treatment does not alter the subjective effects of cocaine.[449] In light of the growing literature demonstrating a role for glutamate in cocaine priming–induced reinstatement, these results indicate that one mechanism by which anticonvulsants reduce cocaine craving and relapse in human addicts is through their ability to inhibit glutamate release.

Gabapentin

Gabapentin is an anticonvulsant that is currently FDA approved for treating seizures, anxiety, and neuropathic pain.[450] Similar to other anticonvulsants, gabapentin inhibits presynaptic voltage-gated Na^+ and Ca^{2+} channels and thus prevents release of neurotransmitters, including glutamate.[433,451–454] Gabapentin is also an agonist that binds to specific $GABA_B$ receptor subtypes in the brain.[455] Preclinical and clinical studies of gabapentin indicate that it may be of little clinical use for treating cocaine addition. For instance, gabapentin administration does not affect cocaine-induced behavioral sensitization,[456,457] the reinforcing effects of cocaine, or cocaine-induced reinstatement of drug seeking.[458,459] Although some clinical studies have shown that cocaine-dependent subjects treated with gabapentin have less cocaine use and craving,[460–462] other studies demonstrated that gabapentin treatment did not affect cocaine use.[448,463–466] Furthermore, only high doses of gabapentin decrease the discriminative stimulus effects of low doses of smoked cocaine, which suggests that gabapentin is not an efficacious treatment in human cocaine addicts.[467]

L-type Ca^{2+} channel antagonist: diltiazem

Diltiazem is an L-type Ca^{2+} channel blocker that is commonly prescribed to treat hypertension, angina, and selective cardiac arrhythmias.[468] Calcium influx through L-type Ca^{2+} channels plays an important role in psychostimulant-induced behavioral and neuronal plasticity.[327] Several studies have shown that L-type Ca^{2+} channels modulate cocaine-regulated behaviors other than behavioral sensitization. For example, systemic administration of L-type Ca^{2+} channel antagonists impairs cocaine self-administration,[469–471] cocaine-induced CPP,[472] and psychostimulant-induced behavioral sensitization.[326,354,473,474] Consistent with these results, repeated administration of an L-type Ca^{2+} channel agonist directly into the ventral tegmental area cross-sensitizes to a subsequent challenge injection of cocaine.[475] However, systemic administration of L-type Ca^{2+} channel antagonists does not attenuate the reinforcing effects of cocaine in nonhuman primates.[471,476] Furthermore, injection of diltiazem directly into the nucleus accumbens shell facilitates cocaine-induced CPP and suggests that

different brain regions mediate the rewarding and aversive effects of L-type Ca^{2+} channels.[477] These results highlight the important role of calcium influx through L-type Ca^{2+} channels in a broad range of behaviors regulated by cocaine.

Recent evidence suggests that L-type Ca^{2+} channels and CaMKII may be an essential link between nucleus accumbens dopamine and glutamate systems involved in the neuronal plasticity underlying cocaine carving and relapse.[23] With the importance of L-type Ca^{2+} channels in cocaine-induced behavioral and neuronal plasticity, it is likely that these receptors mediate glutamate transmission and cocaine seeking. Blocking L-type Ca^{2+} channels decreases glutamate-mediated burst firing of accumbal neurons,[330] a physiological effect that would block cocaine priming–induced reinstatement of drug seeking by inhibiting increased glutamate signaling in the accumbens after a priming injection of cocaine.[108] Thus, L-type Ca^{2+} channel antagonists may represent a potential class of pharmacotherapies for cocaine craving and addiction.

Acamprosate

Acamprosate is a derivative of homotaurine (a nonspecific GABA receptor agonist) that was originally developed to treat alcohol dependency and relapse.[478–481] Despite structural similarities to the neurotransmitter GABA, there is no direct evidence indicating that acamprosate binds to recombinant $GABA_A$ receptors or enhances $GABA_A$ receptor function.[482–484] However, acamprosate may indirectly affect $GABA_A$ receptor–mediated signaling by blocking presynaptic $GABA_B$ autoreceptors[483] and/or increasing extracellular levels of taurine, an endogenous amino acid that potentiates $GABA_A$ receptor responses.[485] Acamprosate also modulates glutamate transmission, specifically through NMDA receptor– and mGluR5–mediated mechanisms.[484,486] Overall, acamprosate may function, in part, to restore homeostasis between excitatory and inhibitory neurotransmitter systems by attenuating withdrawal-induced hyperglutamatergic tone in brains exposed to chronic alcohol.[484]

Recent preclinical studies indicate that acamprosate may be beneficial in treating cocaine craving and relapse. In mice, acamprosate administration attenuates cocaine-induced CPP and cocaine

priming–induced reinstatement of psychostimulant CPP.[487,488] In rats trained to self-administer cocaine, acamprosate pretreatment attenuates both cocaine- and cue-induced reinstatement of drug seeking.[489] Taken together, these results indicate that acamprosate may prevent relapse in human cocaine addicts. A phase II clinical trial examining the efficacy of acamprosate on cocaine use and craving in human is currently under way.[30]

Group I metabotropic glutamate receptor (mGluR1/5) antagonists: MPEP, MTEP, and EMQMCM

Recent preclinical studies have demonstrated that mGluR5 antagonists may have potential as pharmacotherapies for treating cocaine craving and relapse. The mGluR5 antagonists MPEP and MTEP were originally developed to study mGluR5 distribution and pharmacological properties in the brain.[490] In addition to negatively modulating mGluR5s, MPEP is also an antagonist of NMDA receptors and it inhibits monoamine oxidase A activity.[491] In contrast to MPEP, MTEP is a more selective mGluR5 antagonist with better pharmacological properties, including higher *in vivo* potency.[490–492] As mentioned previously, constitutive mGluR5–knockout mice do not acquire cocaine self-administration behavior or exhibit cocaine-induced hyperlocomotor activity.[292] Consistent with these results, MPEP pretreatment reduces the locomotor-stimulant properties of cocaine[493] cocaine-induced CPP[494] (however, see Ref. 495), as well as cocaine self-administration behavior in wild-type mice,[292] rats,[294,496,497] and nonhuman primates.[295,498] Systemic administration of MPEP also attenuates cocaine- and cue-induced reinstatement of drug-seeking behavior in nonhuman primates[295] and rats.[298,299] Similar to the behavioral effects of MPEP, MTEP administration inhibits cocaine- and cue-induced reinstatement of cocaine seeking.[297,299] Interestingly, systemic administration of the mGluR1–selective antagonist EMQMCM, but not the mGluR5–selective antagonist MTEP, blocked cocaine-induced behavioral sensitization, which suggests that subtypes of the group I family of mGluRs (mGluR1 and mGluR5) have distinct functional roles in cocaine-mediated behaviors.[499] Collectively, these findings suggest that mGluR1/5s play critical roles in regulating cocaine-mediated behaviors. Results from reinstatement studies are promising in that mGluR5 antagonists may be useful pharmacotherapies for treating cocaine craving and relapse.

Group II metabotropic glutamate receptor (mGluR2/3) agonists: LY379268

LY379268 is a potent and selective agonist of presynaptic mGluR2/3s that has been shown to have anxiolytic- and antipsychotic-like behavioral effects in animal models.[500,501] Administration of LY379268 increases extracellular dopamine levels in the mPFC, nucleus accumbens, and dorsal striatum.[502,503] Furthermore, administration of LY379268 directly into the nucleus accumbens shell, but not core, reduces extracellular dopamine levels, indicating a different neurochemical effect within the accumbens subregions.[504] Repeated amphetamine injections increase extracellular levels of dopamine and glutamate in the nucleus accumbens, and these effects are blocked by systemic administration of LY379268.[505] Taken together, these results suggest that one neurochemical mechanism whereby LY379268 may block drug-seeking behavior is by modulating dopamine and glutamate transmission in the nucleus accumbens.

A growing body of evidence suggests that inhibiting cocaine-induced extracellular glutamate release with mGluR2/3 agonists may block the reinstatement of drug seeking.[506] Whereas moderate doses of LY379268 administered systemically or directly into the nucleus accumbens core selectively attenuate the reinstatement of cocaine-seeking behavior,[300,301] administration of high doses of LY379268 blocks food-seeking behavior.[301] Similarly, systemic and intra-amygdala injections of LY379268 block incubation of cocaine and food seeking, suggesting that activation of mGluR2/3s has nonspecific effects on responding for drugs of abuse and natural rewards.[507,508] However, the aforementioned studies did not examine the role of nucleus accumbens shell mGluR2/3s in the reinstatement of cocaine seeking. Recent findings suggest that LY379268 decreases the propensity to reinstate drug-seeking behavior in rodents through anxiolytic-like behavioral effects that reduce the saliency of stressful stimuli. Clinical studies of LY379268 in cocaine-dependent addicts are required to determine its efficacy in treating cocaine craving and relapse.

Conclusions

The results summarized in this review indicate that repeated exposure to cocaine produces profound changes in glutamate transmission in limbic nuclei, particularly the nucleus accumbens. Indeed, cocaine administration appears to influence virtually every aspect of glutamate transmission, including release, reuptake, receptor expression, receptor trafficking, and intracellular signaling. Thus, preclinical studies have identified many potential targets for the development of therapeutics for cocaine addiction. The ubiquity of glutamate systems in the nervous system, and particularly the important role glutamate plays in various forms of learning and memory, represents a substantial challenge to identifying effective therapeutic glutamate modulators with few serious side effects. Nonetheless, several modulators of glutamate transmission are being tested clinically as antiaddiction therapies, with some success. Ongoing and future preclinical studies will lead to a greater refinement of the cellular and molecular mechanisms that mediate cocaine-induced changes in synaptic plasticity, metaplasticity, and glutamate-mediated signal transduction, which will provide further insight into the pathology of addiction and identify novel therapeutic targets for cocaine addiction.

Acknowledgments

Conflicts of interest

The authors declare no conflicts of interest.

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