Published in final edited form as:

Mol Neurobiol. 2014 October ; 50(2): 494–506. doi:10.1007/s12035-014-8636-6.

Cocaine-induced changes in NMDA receptor signaling

Pavel I. Ortinski

Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania

Department of Pharmacology, Physiology, and Neuroscience, University of South Carolina
School of Medicine

Abstract

Addictive states are often thought to rely on lasting modification of signaling at relevant synapses. A long-standing theory posits that activity at N-methyl-D-aspartate receptors (NMDARs) is a critical component of long-term synaptic plasticity in many brain areas. Indeed, NMDAR signaling has been found to play a role in the etiology of addictive states, in particular following cocaine exposure. However, no consensus is apparent with respect to the specific effects of cocaine exposure on NMDARs. Part of the difficulty lies in the fact that NMDARs interact extensively with multiple membrane proteins and intracellular signaling cascades. This allows for highly heterogeneous patterns of NMDAR regulation by cocaine in distinct brain regions and at distinct synapses. The picture is further complicated by findings that cocaine effects on NMDARs are sensitive to the behavioral history of cocaine exposure, such as the mode of cocaine administration. This review provides a summary of evidence for cocaine-induced changes in NMDAR expression, cocaine-induced alterations in NMDAR function and cocaine effects on NMDAR control of intracellular signaling cascades.

Introduction

Ionotropic glutamate receptors are a primary mediator of fast excitatory activity in the mammalian brain. A prominent member of this family are NMDARs which are expressed widely throughout the brain and are known to be involved in a broad range of cellular responses and functions (Traynelis et al., 2010). NMDARs are assembled as a tetramer of subunits which include GluN1, GluN2A-D, and GluN3A-B. Two GluN1 subunits are obligatory for a functional protein and form a dimer of dimers with two GluN2 or GluN3 subunits (Traynelis et al., 2010). Such di-heteromeric channels are thought to comprise the majority of NMDARs in the central nervous system although recent studies indicate a significant role for the tri-heteromeric subunits assemblies, including GluN1/GluN2B/GluN3 (Tong et al., 2008; Schuler et al., 2008), GluN1/GluN2A/GluN2B (Sheng et al., 1994; Tovar and Westbrook, 1999; Dunah and Standaert, 2003; Al-Hallaq et al., 2007; Tovar et al., 2013), and GluN1/GluN2B/GluN2D (Logan et al., 2007; Brothwell et al., 2008). The assembled NMDARs are stabilized at the membrane via their interactions with the membrane-associated guanylate kinase (MAGUK) family of proteins which includes

such widely-studied members as PSD-95, SAP97, and CASK (Oliva et al., 2012). NMDA receptor expression and activity can be regulated by phosphorylation at more than a dozen sites located largely at GluN2 subunits (Chen and Roche, 2007).

NMDARs are unique among other ligand-gated ionotropic channels in that their activation depends on a number of coincident events. In addition to binding of the endogenous ligand, glutamate, activation of the NMDA channel requires depolarization of the cell membrane which relieves the voltage-dependent block of the channel pore by Mg^{2+} , and the presence of extracellular glycine or D-serine, which act as co-agonists at the glycine/D-serine binding site (Traynelis et al., 2010). NMDAR signaling thus involves simultaneous detection of pre-synaptic release of glutamate, post-synaptic membrane depolarization and a supply of glycine/d-serine. NMDARs are highly permeable to Ca^{2+} in addition to the monovalent cations, Na^{+} and K^{+} , and are in a position to affect a broad range of Ca^{2+} -dependent cellular events.

NMDARs are involved in the pathophysiology of cocaine overdose (Brackett et al., 2000) and multiple studies demonstrate that modulating NMDAR function either pharmacologically or by mutagenesis interferes with various aspects of cocaine-associated behaviors. For example, administration of NMDAR antagonists has been shown to reduce cocaine-induced hyperlocomotion (Pulvirenti et al., 1991; Witkin, 1993; Pulvirenti et al., 1994; Uzbay et al., 2000), reduce sensitization to locomotor effects of cocaine (Karler et al., 1989; Wolf and Jeziorski, 1993; Li et al., 1999) and attenuate self-administration of cocaine (Pierce et al., 1997; Pulvirenti et al., 1997; Hyytia et al., 1999). Others have reported, however, that administration of NMDAR antagonists facilitates cocaine-induced hyperlocomotion (Rodríguez-Borrero et al., 2006), induces locomotor sensitization in the absence of cocaine (Wolf and Khansa, 1991; Wolf and Jeziorski, 1993; Criswell et al., 1993; Carey et al., 1995), and increases cocaine self-administration (Ranaldi et al., 1996; Allen, 2014). Disruption of NMDAR activity selectively in dopaminergic cells attenuates locomotor-activating effects of cocaine, decreases cocaine preference, and prevents reinstatement of cocaine-seeking (Heusner and Palmiter, 2005; Zweifel et al., 2008; Engblom et al., 2008). Others show, however, that development of locomotor-activating effects of cocaine recruits exclusively those NMDAR expressed by non-dopaminergic cells (Luo et al., 2010) and that agonists (Cornish et al., 1999) as well as antagonists (Park et al., 2002; Famous et al., 2007) of NMDARs promote reinstatement of cocaine seeking. Beyond methodological differences, various explanations for such discrepant roles of NMDARs in behavioral correlates of cocaine exposure have been proposed (Wolf, 1998; Carr and Kalivas, 2008; Schmidt and Pierce, 2010) and include: asymptotic dependence of behavioral performance on the dose of an NMDA agonist or antagonist, pharmacological differences between drugs targeting the NMDARs, dynamic interactions between NMDARs in multiple circuits subserving the behavioral response, and interactions between NMDAR and other neurotransmitter systems. An exhaustive treatment of the effects of cocaine on the gamut of systems that could be affected by NMDAR signaling is beyond the scope of this review. Instead, this review focuses on three aspects of cocaine/NMDAR interaction: the effects of cocaine exposure on NMDAR expression levels, cocaine regulation of NMDAR function, and recruitment of NMDAR-dependent intracellular signaling cascades following cocaine presentation.

Cocaine effects on NMDAR expression

Nucleus accumbens and the ventral tegmental area

Table 1 provides an overview of findings on NMDA receptor expression following cocaine exposure at principal nodes of the mesolimbic dopamine reward circuit thought to mediate the behavioral effects of cocaine (Pierce and Kumaresan, 2006). Cocaine-induced changes in NMDAR expression differ between brain areas, but are also highly sensitive to the choice of cocaine administration paradigm and the history of cocaine exposure. This is particularly evident in the nucleus accumbens (NAc), where short withdrawal (3 days or less) from experimenter-administered (non-contingent) cocaine is reported to decrease the NMDAR subunit levels or leave them unchanged (Yamaguchi et al., 2002; Yamamoto and Zahniser, 2012), whereas longer periods of withdrawal from non-contingent cocaine is associated with an increase in NMDAR subunit expression (Ghasemzadeh et al., 2009a, Schumann and Yaka, 2009; Zhang et al., 2007). This pattern of decreased to increased expression of NMDARs with abstinence from non-contingent cocaine is different for animals that are trained to self-administer cocaine. Short withdrawal from self-administered cocaine is associated with no change or an increase in NMDAR expression (Lu et al., 2003; Ortinski et al., 2013), although evidence for longer periods of withdrawal is mixed (Lu et al., 2003; Self et al., 2004).

In the VTA, a principal source of dopaminergic afferents to the NAc, short and long withdrawal periods from both experimenter and self-administered cocaine are associated with up-regulation of GluN1 (Loftis and Janowsky, 2000; Fitzgerald et al., 1996; Lu et al., 2003) with some studies reporting no effect of cocaine on NMDAR expression (Churchill, 1999; Yamamoto and Zahniser, 2012). Although these reports suggest some common themes in regulation of NMDAR subunit expression in the NAc and the VTA, they may not reflect changes in levels of functional NMDARs. Indeed, a radioligand binding study has indicated no differences in binding of ^3H -MK801, a non-competitive NMDA channel blocker, to the NMDARs in the NAc and the VTA following short and long periods of withdrawal from self-administered cocaine (Ben-Shahar et al. 2007). Overall, among the most consistent findings in the NAc are increases in NMDAR expression following either short withdrawal from cocaine self-administration or long-withdrawal from non-contingently administered cocaine. In the VTA, increases in GluN1 expression have been observed following a variety of cocaine exposure paradigms, most consistently following short withdrawal from non-contingent cocaine.

Dorsal striatum

Outside of the NAc and the VTA, the evidence for regulation of NMDAR levels by cocaine is often contradictory. Where some studies demonstrate an increase in the NMDAR expression, others find NMDAR levels to decrease following similar paradigms of cocaine exposure. In the striatum, after short periods of withdrawal, lack of changes and decreases in NMDAR subunit expression have been reported (Yamamoto and Zahniser, 2012; Yamaguchi et al., 2002). However, one binding study indicates an increase in binding of a competitive high affinity NMDAR antagonist, ^3H -CGP39653, to the NMDARs (Itzhak and Martin 2000). After longer periods of withdrawal from non-contingent cocaine, the pattern

of reported changes is further complicated by subunit-specific differences. Thus, GluN1 and GluN2A levels have been reported to decrease (Loftis and Janowsky, 2000; Loftis and Janowsky, 2002; Izawa et al., 2006), while GluN2B levels increase (Loftis and Janowsky, 2000; Loftis and Janowsky, 2002). Results of the binding studies are similarly contradictory: In one report, ^3H -CGP39653 binding increases after 3 days of non-contingent cocaine and 10 days of withdrawal, but does not change after 10 days of non-contingent cocaine and 10 days of withdrawal (Itzhak and Martin, 2000). ^3H -MK801 binding to the NMD ARs does not change after 5 days of non-contingent cocaine and 14 days of withdrawal (Szumlinski et al., 2000). Only a handful of reports examine the effects of self-administered cocaine on NMDAR expression in dorsal striatum with one finding no effects of self-administration on ^3H -MK801 binding (Ben-Shahar et al., 2007) and one reporting an increase in GluN1 expression immediately following 21 days of cocaine self-administration (Crespo et al., 2002). In summary, cocaine has been most frequently reported to lack an effect on NMDAR subunit expression and radioligand binding in dorsal striatum, although both decreases and increases in these metrics of NMDAR content have also been observed in this area.

Prefrontal cortex

In the prefrontal cortex (PFC), short periods of withdrawal from non-contingently administered cocaine have been reported to lead to both decreases (Yamaguchi et al., 2002; Ghasemzadeh et al., 2009; Bhargava and Kumar, 1999) and increases (Loftis and Janowsky, 2000; Itzhak and Stein, 1992) in NMDAR subunit expression and NMDAR binding of radioactive ligands. A few studies report no changes in subunit expression and NMDAR binding under similar experimental conditions (Crespo et al., 2002; Itzhak and Martin, 2000). After longer periods of withdrawal, some evidence appears to suggest an increase in NMDAR expression (Loftis and Janowsky, 2000; Ghasemzadeh et al., 2009), although others fail to find significant differences in either the NMDAR subunit expression or NMDAR binding of radioactive ligands (Ortiz et al., 2006; Scheggi et al., 2002; Itzhak and Martin 2000). Evidence for the effects of self-administered cocaine in the PFC is scarce and mixed. One study reports that self-administered cocaine increases GluN1 expression (Crespo et al., 2002) while another finds a decrease in ^3H -MK801 binding to NMDARs, but only in animals that have been trained to self-administer cocaine in one-hour daily sessions; extending the session duration to six hours results in no changes in ^3H -MK801 binding (Ben-Shahar et al., 2007). The overall picture appears inconclusive in the PFC. Among the least contradictory findings are the lack of changes in NMDAR expression following long withdrawal from non-contingent and self-administered cocaine.

Hippocampus

Studies of NMDAR expression and binding that have been performed in the hippocampus do not agree on a common pattern of receptor regulation by cocaine. Short periods of withdrawal from non-contingent cocaine have been found to decrease (Turchan et al., 2003) GluN1 subunit expression or leave it unaffected (Fitzgerald et al., 1996; Loftis and Janowsky, 2000). Meanwhile, ^3H -CGP39653 binding has been reported to increase after both short and long periods of withdrawal from non-contingent cocaine (Itzhak and Martin, 2000). However, the increase in binding at longer intervals of withdrawal was only observed in rats exposed to cocaine for 10, but not 3 days. One study presents evidence for subunit

specific differences, finding an increase in GluN2B, but no difference in GluN1 levels following 17 days of withdrawal from experimenter-administered cocaine (Scheggi et al., 2002). These NMDAR binding and NMDAR subunit expression experiments do not differentiate between hippocampal subfields. However, a substantive literature now suggests that hippocampal subregions play distinct roles in regulating a variety of cognitive processes including those underlying cocaine-seeking behaviors (Fanselow and Dong, 2010; Lasseter et al., 2010; Sun and Rebec, 2003). A detailed look at NMDAR expression particularly within dorsal and ventral hippocampal fields may reveal a more consistent pattern of NMDAR regulation by cocaine. In the meantime, the few studies that did examine hippocampal levels of NMDARs following cocaine exposure do not present a consistent pattern of results.

Amygdala

Different amygdalar nuclei have also been argued to play distinct roles in motivated behaviors (Phillips et al., 2003). One report examined the expression of GluN1, GluN2A, and GluN2B subunits in the amygdala following one or 30 days of withdrawal from cocaine self-administration (Lu et al., 2005). In basolateral amygdala, GluN2A levels were found to increase with no change in levels of other subunits following one day of withdrawal from cocaine. However, at 30 days of withdrawal, a decrease in GluN2B expression was observed in basolateral amygdala with no change in the expression of other subunits. In central amygdala, an increase in GluN1 levels was observed at 30 days of withdrawal from self-administered cocaine. Other studies that did not differentiate between the amygdalar nuclei have found that cocaine exposure increases the expression of GluN1 and GluN2B subunits and increases ³H-CGP39653 binding following both short and long intervals of withdrawal from non-contingently administered cocaine (Turchan et al., 2003; Itzhak and Martin, 2000). As in the hippocampus, such a limited number studies utilizing different exposure paradigms does not allow for a conclusive picture of cocaine effects on NMDAR expression. However, unlike in the hippocampus where the results are mixed, analyses in the amygdala generally observe an increase in NMDAR subunit expression and radioligand binding except following long withdrawal from cocaine self-administration, where the picture is complicated by differences in regulation of distinct NMDAR subunits.

In summary, these studies indicate that cocaine exposure does not affect NMDAR expression solely through its pharmacological effects in various structures of the mesolimbic pathway. The effects of cocaine exposure are sensitive to cocaine history that includes the mode of cocaine administration as well as duration of withdrawal from cocaine. Other aspects of cocaine exposure, such as whether or not extinction training instead of passive withdrawal from cocaine is present, have also been shown to influence NMDAR expression (Crespo et al., 2002; Ghasemzadeh et al., 2011). Overall, the most consistent, albeit not unequivocal, reports of the pattern of NMDAR changes following cocaine have been in the NAc and the VTA. Notably, the increase of GluN1 expression reported by multiple laboratories to occur in the VTA mirrors the findings in post-mortem tissue from human cocaine addicts (Tang et al., 2003). Unfortunately, robust conclusions of the cocaine effects on NMDAR expression in mesolimbic structures other than the NAc and the VTA are more difficult to make.

Cocaine effects on NMDAR function

Contribution of NMDARs to excitatory synaptic efficacy

Sensitivity of synaptic responses to behavioral history of cocaine exposure has been demonstrated by a number of studies. For example, the AMPA/NMDA receptor-mediated current ratio, a measure of relative synaptic strength, has been reported to increase in the VTA and in the bed nucleus of stria terminalis following self-administered, but not experimenter-administered cocaine (Chen et al., 2008; Dumont et al., 2005). The increase in the VTA was observed 7 days after the last cocaine self-administration session (Chen et al., 2008) and in the bed nucleus of stria terminalis – one day after the last session (Dumont et al., 2005). Interestingly, the AMPA/NMDA ratio remained elevated in the VTA for up to 90 days of withdrawal from cocaine self-administration (Chen et al., 2008). The increase in the AMPA/NMDA ratio has also been observed in the NAc following short withdrawal from experimenter-administered (Kourrich et al., 2007; Dobi et al., 2011) and long withdrawal from self-administered (Ortinski et al., 2012; Otaka et al., 2013) cocaine. Some of these studies provide evidence that duration of withdrawal from cocaine is a critical determinant of changes in the AMPA/NMDA ratio (Kourrich et al., 2007; Ortinski et al., 2012). In the VTA, antagonists at GluN2A- and GluN2B-containing NMDARs have been shown to block the increase in the AMPA/NMDA ratio by cocaine (Schumann et al., 2009). However, in both the VTA and the NAc, the expression of the AMPA/NMDA ratio increase is driven by the AMPA receptor-mediated rather than the NMDAR-mediated component (Thomas et al., 2001; Borgland et al., 2004; Kourrich et al., 2007). Indeed, the NMDA-induced firing (Zhang et al., 1997) and whole-cell NMDAR-mediated currents are not different following cocaine treatment (Thomas et al., 2001; Borgland et al., 2004; Ferrario et al., 2012; Ortinski et al., 2013). The lack of changes in whole-cell NMDAR-mediated currents suggests that the number of functional NMDARs at the cell membrane is not affected by cocaine exposure. These findings lend support to the lack of effect of cocaine treatment on ³H-MK801 binding (Ben-Shahar et al., 2007), a technique that also relies on the presence of functional NMDAR at the cell surface.

NMDAR subunit composition

There is some electrophysiological evidence that cocaine precipitates changes in NMDAR subunit composition, rather than affecting the overall number of NMDARs. Thus, Britt et al., (2012) found that exposure to non-contingently administered cocaine followed by 10–14 days of withdrawal alters the current-voltage relationship of NMDAR-mediated responses specifically at hippocampal afferents to the medium spiny neurons of the NAc. The shape of the current-voltage relationship prior to the cocaine treatment suggested the presence of NMDAR subunits relatively less sensitive to Mg²⁺ blockade. These receptors were no longer observed following the cocaine treatment. Low Mg²⁺-ion sensitivity is a feature of GluN2C-, GluN2D- and GluN3- containing NMDARs (Monyer et al., 1994; Sucher et al., 1995; Tong et al., 2008). The expression of GluN2C and GluN2D subunits has not been detected in the medium spiny neurons of the NAc although a population of larger, presumably cholinergic, neurons throughout the striatum are strongly immunoreactive for the GluN2D subunit (Bloomfield et al., 2007). GluN3B is, however, ubiquitously expressed in the NAc (Wee et al., 2008) and could be the subunit targeted for removal from

hippocampal synapses onto NAc neurons following cocaine exposure. Interestingly, an interaction between cocaine and GluN3-containing NMDARs has been recently highlighted at dopaminergic cells of the VTA (Yuan et al., 2013). This study found that a single injection of cocaine increases synaptic incorporation of GluN3A. In addition to low sensitivity to Mg^{2+} , GluN3A-containing NMDARs have been shown to display reduced Ca^{2+} permeability (Tong et al., 2008). However, Yuan et al. (2013) found that the amplitude of synaptic Ca^{2+} transients remains intact following cocaine treatment, despite up-regulation of GluN3A. The study implied that this effect may be due to increased signaling via the Ca^{2+} -permeable AMPA receptors. Such homeostatic regulation of synaptic Ca^{2+} flux may explain why down-regulating the VTA levels of GluN3A in this study did not affect cocaine-induced locomotion or cocaine-conditioned place preference. Together, the results of these reports suggest that cocaine experience induces an input-specific down-regulation of Mg^{2+} -insensitive NMDARs of undefined subunit composition in the NAc cells and a broader, presumably input-independent, up-regulation of Mg^{2+} -insensitive GluN3A-containing NMDARs in dopaminergic neurons of the VTA.

Some electrophysiological studies have suggested that non-contingent cocaine treatment up-regulates levels of GluN2B-containing NMDAR in the NAc, 24–48 hours following the last cocaine injection (Huang et al., 2009; Brown et al., 2011). Increase in GluN2B-containing NMDARs has been inferred from increased sensitivity to the GluN2B antagonists and longer decay kinetics of the NMDAR-mediated currents. Such an increase has been argued to occur selectively at the so-called “silent synapses”, synapses newly generated in response to cocaine and containing NMDARs, but not AMPA receptors (Huang et al., 2009; Brown et al., 2011). Silent synapses have been proposed to represent a critical site for synaptic plasticity events presumed to encode environmental information (Isaac, 2003; Groc et al., 2006). Cocaine-induced increase of GluN2B at these synapses may identify sites that are unique to the cocaine experience and it can be speculated that targeting such sites will disrupt the molecular “memory” of cocaine experience with single-synapse specificity. However, in animals trained to self-administer cocaine, we have failed to see an increase in silent synapses in the NAc at 24 hours following the last self-administration session (unpublished data). Furthermore, despite an increase in expression of GluN2B protein following self-administration training, the sensitivity of NMDAR-mediated currents to GluN2B antagonist, Ro 25-6981, was equivalent between control and cocaine-experienced animals (Ortinski et al., 2013). Although we did observe an increase in decay kinetics of NMDAR-mediated spontaneous synaptic currents, this was seen following blockade of glutamate reuptake transporters which facilitates the diffusion of released glutamate to extrasynaptic sites (Ortinski et al., 2013). We proposed that cocaine self-administration followed by a 24 hour withdrawal period may trigger redistribution of synaptic NMDARs to extrasynaptic sites without changes in NMDAR subunit composition.

NMDAR coupling to dopamine receptor signaling

Since inhibition of dopamine re-uptake and the resultant increase in dopaminergic transmission are considered critical for the etiology of an addicted state (Kalivas and Volkow, 2005) the link between cocaine addiction and NMDAR function must be considered in the context of dopamine receptor activation. Acute application of the

dopamine D1 receptor (D1DR), but not dopamine D2 receptor (D2DR) agonists potentiates NMDAR-mediated currents in striatal and NAc neurons (Cepeda et al., 1993; Harvey and Lacey, 1997; Cepeda and Levine, 1998; Chergui and Lacey, 1999; Flores-Hernández et al., 2002; but see Beurrier and Malenka, 2002). This effect of D1DR agonists has been reported to involve Ca^{2+} -channels based on the finding that application of L-type Ca^{2+} -channel antagonists strongly attenuates D1DR modulation of NMDAR currents (Cepeda et al., 1998). In addition to such acute effects of D1DR agonists, D1DR stimulation appears to elicit a delayed effect on NMDARs function. Thus, in the VTA, NMDAR-mediated currents are potentiated 10–20 minutes following, but not during, D1DR activation in a PKA-dependent manner (Shilström et al., 2006). A similar effect of cocaine has recently been reported to require a downregulation in D2DR signaling (Madhavan et al., 2013). A delayed onset enhancement of NMDAR-currents by D1DRs has also been observed in the CA1 pyramidal cells of the hippocampus and was found to rely on NMDAR-independent increase in intracellular Ca^{2+} (Yang, 2000). Interestingly, in the NAc, synaptic and whole-cell NMDAR responses, while facilitated during the D1DR stimulation, are suppressed 1–2 hours following the stimulation (Ortinski et al., 2013). These results suggest that D1DRs dynamically regulate NMDAR function and that the manner of regulation may depend on the brain area examined and on duration of exposure to a D1DR agonist.

To summarize, cocaine exposure affects NMDAR function via a complex network of effects. Cocaine alters the subunit composition of NMDARs at the cell surface, regulates synaptic targeting of NMDAR, and modulates the cross-talk between the NMDARs and the D1DRs. The concluding section examines the NMDAR interaction with D1DRs from the perspective of intracellular targets engaged by co-activation of these receptors.

Intracellular targets of NMDAR/D1DR co-activation

Synergistic effects of NMDAR/D1DR signaling on MAPK/ERK cascade

Dopamine receptor signaling following cocaine exposure has been extensively studied with a broad consensus on the importance of D1DR-activated intracellular cascades in various phases of cocaine addiction (Kalivas and O'Brien 2008; Lobo and Nestler, 2011; Berke and Hyman 2000). D1DRs activation leads to stimulation of adenylyl cyclase activity, prototypic of G_s -protein-coupled receptors, production of cyclic AMP (cAMP) and activation of the cAMP-dependent protein kinase (PKA) (Missale, 1998). PKA acts on two major intracellular pathways: DARPP-32 and the MAPK/ERK cascades. Disruption of either the DARPP-32 or the MAPK/ERK signaling has been shown to interfere with behavioral effects of cocaine exposure (Zhang et al., 2006; Zachariou et al., 2006; Pierce et al., 1999; Valjent et al., 2000; Mattson et al., 2005). The DARPP-32 cascade has been implicated in mediating the enhancement of NMDAR currents by D1DR agonists (Flores-Hernandez, 2002), although some have attributed this effect to PKC signaling (Chergui and Lacey, 1999; Li et al., 2010). Interestingly, Sarantis et al. (2009) show that although NMDA and D1 receptor agonists each increase the phosphorylation of DARPP-32 in striatal slices, co-activation of NMDARs and D1DRs does not lead to a further increase in DARPP-32 phosphorylation. Co-activation of NMDARs and D1DRs does, however, increase the levels of phosphorylated ERK1/2 beyond the levels achieved by NMDAR or D1DR stimulation alone.

Synergistic effects of D1DR and NMDAR activation, thus, appear to involve the MAPK/ERK pathway, and not the DARPP-32 pathway. The intracellular mechanisms leading to such a synergistic effect may require phosphorylation of the GluN2B subunit by a Src family kinase and involve activation of protein phosphatase 2B (calcineurin) by NMDAR-derived Ca^{2+} (Pascoli et al., 2011; Nishi et al., 2011). Calcineurin has been shown to dephosphorylate DARPP-32, terminating the D1/PKA/DARPP-32 signaling and potentially biasing the D1DR signaling toward the MAPK/ERK-mediated effects (Nairn et al., 2004; Halpain et al., 1990; Nishi et al., 1999). The cascade of intracellular events triggered by D1DR/NMDAR co-activation is summarized in Figure 1.

Activation of ERK by cocaine

Cocaine exposure is known to increase ERK phosphorylation, an effect that requires activation of both the NMDAR and D1DRs (Valjent et al., 2000; Jenab et al., 2005; Sun et al., 2008; Jiao et al., 2007; Sarantis et al., 2009; Lu et al., 2006). Blockade of D2DR signaling does not interfere with cocaine activation of ERK (Valjent et al., 2000) while disruption of D3 receptor signaling in a D3 knock-out mouse has been shown to potentiate cocaine-induced phosphorylation of ERK (Jiao et al., 2007). The latter suggests that D3 receptor signaling plays an inhibitory role with respect to ERK activation by cocaine. Given that discrete populations of striatal neuron subtypes are enriched in D1 (striatonigral neurons) and D2 (striatopallidal neurons) dopamine receptor subtypes, it is of further import, that ERK phosphorylation in response to cocaine has been observed to occur in a cell-type specific manner. Multiple studies now report that exposure to cocaine increases ERK phosphorylation selectively in D1DRs of the dorsal striatum and nucleus accumbens (Gangarossa et al. 2013; Bertran-Gonzalez et al., 2008; Gerfen et al., 2008).

Transcriptional consequences of ERK activation

The MAPK/ERK cascade leads to activation of CREB and a number of other gene transcription pathways prominently implicated in learning and memory (Cestari et al., 2013). Activation of the ERK pathway by synergistic action of NMDARs and D1DRs may critically contribute to neuroadaptations precipitated by exposure to cocaine. Thus, transcription of the immediate early gene *c-fos*, that has been suggested to identify neuronal pools selectively activated by cocaine exposure (Berretta et al., 1992; Koya et al., 2012) may be dependent on ERK signaling and may be attenuated by D1DR and NMDAR blockade (Torres and Rivier, 1993; Jenab et al., 2003; Sun et al., 2008). Activation of the MAPK/ERK pathway has also been found to influence NMDAR subunit composition (Suzuki et al., 2005; Yuen et al., 2005; Rani et al., 2005). Moreover, a number of reports point to a link between the MAPK/ERK pathway activation and synaptic location of activated NMDARs. Synaptic NMDARs facilitate the induction of MAPK/ERK signaling while activation of extrasynaptic NMDARs opposes such induction (Ivanov et al., 2006; Léveillé et al., 2008; Karpova et al., 2013; Gladding and Raymond, 2011). Interestingly, an increase in activity of glutamate re-uptake transporters observed following cocaine self-administration (Ortinski et al., 2013) may promote MAPK/ERK activation by restricting glutamate signaling to synaptically located NMDARs (Léveillé et al., 2008).

Conclusions

NMDAR response to cocaine is characterized by alterations in NMDAR subunit composition, synaptic re-distribution of the assembled protein, differences in protein expression levels, and altered coupling of NMDARs to D1DR-mediated signals. These effects appear to be strongly regulated by the behavioral history of cocaine exposure including the mode and duration of cocaine administration and duration and nature of the withdrawal period (i.e. passive withdrawal or extinction). In addition, cocaine promotes NMDAR-dependent activation of transcriptional cascades that may, among other effects, provide feedback control over NMDAR expression and function. The heterogeneity of NMDAR responses may underpin the triggers for a broad spectrum of neuroadaptations associated with cocaine exposure. Unraveling the relative importance of these neuroadaptations and the precise mechanisms by which the NMDAR contribute to their development may yield unprecedented control over cocaine-induced neuroplasticity and ultimately addictive behavior.

Acknowledgments

This work was funded by NIH grant K01DA031747 to PIO.

References

1. Al-Hallaq RA, Conrads TP, Veenstra TD, Wenthold RJ. NMDA di-heteromeric receptor populations and associated proteins in rat hippocampus. *J Neurosci.* 2007; 27(31):8334–8343. [PubMed: 17670980]
2. Allen RM. Continuous exposure to dizocilpine facilitates escalation of cocaine consumption in male Sprague-Dawley rats. *Drug Alcohol Depend.* 2014; 134:38–43. [PubMed: 24103127]
3. Ben-Shahar O, Keeley P, Cook M, Brake W, Joyce M, Nyffeler M, Heston R, Ettenberg A. Changes in levels of D1, D2, or NMDA receptors during withdrawal from brief or extended daily access to IV cocaine. *Brain Research.* 2007; 1131:220–228. [PubMed: 17161392]
4. Berhow MT, Hiroi N, Nestler EJ. Regulation of ERK (extracellular signal regulated kinase), part of the neurotrophin signal transduction cascade, in the rat mesolimbic dopamine system by chronic exposure to morphine or cocaine. *J Neurosci.* 1996; 16(15):4707–4715. [PubMed: 8764658]
5. Berke JD, Hyman SE. Addiction, dopamine, and the molecular mechanisms of memory. *Neuron.* 2000; 25(3):515–532. [PubMed: 10774721]
6. Berretta S, Robertson HA, Graybiel AM. Dopamine and glutamate agonists stimulate neuron-specific expression of Fos-like protein in the striatum. *J Neurophysiol.* 1992; 68(3):767–777. [PubMed: 1359024]
7. Bertran-Gonzalez J, Bosch C, Maroteaux M, Matamalas M, Herve D, Valjent E, Girault JA. Opposing patterns of signaling activation in dopamine D1 and D2 receptor-expressing striatal neurons in response to cocaine and haloperidol. *Journal of Neuroscience.* 2008; 28(22):5671–5685. [PubMed: 18509028]
8. Beurrier C, Malenka RC. Enhanced inhibition of synaptic transmission by dopamine in the nucleus accumbens during behavioral sensitization to cocaine. *J Neurosci.* 2002; 22(14):5817–5822. [PubMed: 12122043]
9. Bhargava HN, Kumar S. Sensitization to the locomotor stimulant effect of cocaine modifies the binding of [3H]MK-801 to brain regions and spinal cord of the mouse. *Gen Pharmacol.* 1999; 32(3):359–363. [PubMed: 10211592]
10. Bloomfield C, O'Donnell P, French SJ, Totterdell S. Cholinergic neurons of the adult rat striatum are immunoreactive for glutamatergic N-methyl-d-aspartate 2D but not N-methyl-d-aspartate 2C receptor subunits. *Neuroscience.* 2007; 150(3):639–646. [PubMed: 17961930]

11. Borgland SL. Acute and Chronic Cocaine-Induced Potentiation of Synaptic Strength in the Ventral Tegmental Area: Electrophysiological and Behavioral Correlates in Individual Rats. *Journal of Neuroscience*. 2004; 24(34):7482–7490. [PubMed: 15329395]
12. Brackett RL, Pouw B, Blyden JF, Nour M, Matsumoto RR. Prevention of cocaine-induced convulsions and lethality in mice: effectiveness of targeting different sites on the NMDA receptor complex. *Neuropharmacology*. 2000; 39(3):407–418. [PubMed: 10698007]
13. Britt JP, Benaliouad F, McDevitt RA, Stuber GD, Wise RA, Bonci A. Synaptic and behavioral profile of multiple glutamatergic inputs to the nucleus accumbens. *Neuron*. 2012; 76(4):790–803. [PubMed: 23177963]
14. Brothwell SL, Barber JL, Monaghan DT, Jane DE, Gibb AJ, Jones S. NR2B- and NR2D-containing synaptic NMDA receptors in developing rat substantia nigra pars compacta dopaminergic neurones. *J Physiol*. 2008; 586(3):739–750. [PubMed: 18033813]
15. Brown TE, Lee BR, Mu P, Ferguson D, Dietz D, Ohnishi YN, Lin Y, Suska A, Ishikawa M, Huang YH, Shen H, Kalivas PW, Sorg BA, Zukin RS, Nestler EJ, Dong Y, Schluter OM. A silent synapse-based mechanism for cocaine-induced locomotor sensitization. *Journal of Neuroscience*. 2011; 31(22):8163–8174. [PubMed: 21632938]
16. Carey RJ, Dai H, Krost M, Huston JP. The NMDA receptor and cocaine: evidence that MK-801 can induce behavioral sensitization effects. *Pharmacol Biochem Behav*. 1995; 51(4):901–908. [PubMed: 7675875]
17. Carr DB, Kalivas PW. Confused about NMDA and addiction? Targeted knockouts provide answers and new questions. *Neuron*. 2008; 59(3):353–355. [PubMed: 18701061]
18. Cepeda C, Buchwald NA, Levine MS. Neuromodulatory actions of dopamine in the neostriatum are dependent upon the excitatory amino acid receptor subtypes activated. *Proc Natl Acad Sci U S A*. 1993; 90(20):9576–9580. [PubMed: 7692449]
19. Cepeda C, Levine MS. Dopamine and N-methyl-D-aspartate receptor interactions in the neostriatum. *Dev Neurosci*. 1998; 20(1):1–18. [PubMed: 9600386]
20. Cestari V, Rossi-Arnaud C, Saraulli D, Costanzi M. The MAP(K) of fear: From memory consolidation to memory extinction. *Brain Res Bull*. 2013 E-pub ahead of print.
21. Chen B-S, Roche KW. Regulation of NMDA receptors by phosphorylation. *Neuropharmacology*. 2007; 53(3):362–368. [PubMed: 17644144]
22. Chen BT, Bowers MS, Martin M, Hopf FW, Guillory AM, Carelli RM, Chou JK, Bonci A. Cocaine but not natural reward self-administration nor passive cocaine infusion produces persistent LTP in the VTA. *Neuron*. 2008; 59(2):288–297. [PubMed: 18667156]
23. Chergui K, Lacey MG. Modulation by dopamine D1-like receptors of synaptic transmission and NMDA receptors in rat nucleus accumbens is attenuated by the protein kinase C inhibitor Ro 32-0432. *Neuropharmacology*. 1999; 38(2):223–231. [PubMed: 10218863]
24. Churchill L, Swanson CJ, Urbina M, Kalivas PW. Repeated cocaine alters glutamate receptor subunit levels in the nucleus accumbens and ventral tegmental area of rats that develop behavioral sensitization. *J Neurochem*. 1999; 72(6):2397–2403. [PubMed: 10349849]
25. Cornish JL, Duffy P, Kalivas PW. A role for nucleus accumbens glutamate transmission in the relapse to cocaine-seeking behavior. *Neuroscience*. 1999; 93(4):1359–1367. [PubMed: 10501460]
26. Crespo JA, Oliva JM, Ghasemzadeh MB, Kalivas PW, Ambrosio E. Neuroadaptive changes in NMDAR1 gene expression after extinction of cocaine self-administration. *Ann N Y Acad Sci*. 2002; 965:78–91. [PubMed: 12105087]
27. Criswell HE, Johnson KB, Mueller RA, Breese GR. Evidence for involvement of brain dopamine and other mechanisms in the behavioral action of the N-methyl-D-aspartic acid antagonist MK-801 in control and 6-hydroxydopamine-lesioned rats. *J Pharmacol Exp Ther*. 1993; 265(2):1001–1010. [PubMed: 8098756]
28. Dobi A, Seabold GK, Christensen CH, Bock R, Alvarez VA. Cocaine-induced plasticity in the nucleus accumbens is cell specific and develops without prolonged withdrawal. *J Neurosci*. 2011; 31(5):1895–1904. [PubMed: 21289199]
29. Dumont EC, Mark GP, Mader S, Williams JT. Self-administration enhances excitatory synaptic transmission in the bed nucleus of the stria terminalis. *Nat Neurosci*. 2005; 8(4):413–414. [PubMed: 15735642]

30. Dunah AW, Standaert DG. Subcellular segregation of distinct heteromeric NMDA glutamate receptors in the striatum. *J Neurochem*. 2003; 85(4):935–943. [PubMed: 12716425]
31. Edwards S, Graham DL, Bachtell RK, Self DW. Region-specific tolerance to cocaine-regulated cAMP-dependent protein phosphorylation following chronic self-administration. *Eur J Neurosci*. 2007; 25(7):2201–2213. [PubMed: 17439498]
32. Engblom D, Bilbao A, Sanchis-Segura C, Dahan L, Perreau-Lenz S, Balland B, Parkitna JR, Luján R, Halbout B, Mameli M. Glutamate receptors on dopamine neurons control the persistence of cocaine seeking. *Neuron*. 2008; 59(3):497–508. [PubMed: 18701074]
33. Famous KR, Schmidt HD, Pierce RC. When administered into the nucleus accumbens core or shell, the NMDA receptor antagonist AP-5 reinstates cocaine-seeking behavior in the rat. *Neurosci Lett*. 2007; 420(2):169–173. [PubMed: 17513051]
34. Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron*. 2010; 65(1):7–19. [PubMed: 20152109]
35. Ferrario CR, Goussakov I, Stutzmann GE, Wolf ME. Withdrawal from cocaine self-administration alters NMDA receptor-mediated Ca²⁺ entry in nucleus accumbens dendritic spines. *PLoS ONE*. 2012; 7(8):e40898. [PubMed: 22870207]
36. Ferrario CR, Li X, Wang X, Reimers JM, Uejima JL, Wolf ME. The role of glutamate receptor redistribution in locomotor sensitization to cocaine. *Neuropsychopharmacology*. 2010; 35(3):818–833. [PubMed: 19924109]
37. Fitzgerald LW, Ortiz J, Hamedani AG, Nestler EJ. Drugs of abuse and stress increase the expression of GluR1 and NMDAR1 glutamate receptor subunits in the rat ventral tegmental area: common adaptations among cross-sensitizing agents. *J Neurosci*. 1996; 16(1):274–282. [PubMed: 8613793]
38. Flores-Hernández J, Cepeda C, Hernández-Echeagaray E, Calvert C, Jokel E, Fienberg A, Greengard P, Levine M. Dopamine enhancement of NMDA currents in dissociated medium-sized striatal neurons: role of D1 receptors and DARPP-32. *Journal of Neurophysiology*. 2002; 88(6):3010–3020. [PubMed: 12466426]
39. Gangarossa G, Espallergues J, de Kerchove d'Exaerde A, El Mestikawy S, Gerfen CR, Herve D, Girault JA, Valjent E. Distribution and compartmental organization of GABAergic medium-sized spiny neurons in the mouse nucleus accumbens. *Front Neural Circuits*. 2013; 7:22. [PubMed: 23423476]
40. Gerfen CR, Paletzki R, Worley P. Differences between dorsal and ventral striatum in Drd1a dopamine receptor coupling of dopamine- and cAMP-regulated phosphoprotein-32 to activation of extracellular signal-regulated kinase. *J Neurosci*. 2008; 28(28):7113–7120. [PubMed: 18614680]
41. Ghasemzadeh MB, Mueller C, Vasudevan P. Behavioral sensitization to cocaine is associated with increased glutamate receptor trafficking to the postsynaptic density after extended withdrawal period. *Neuroscience*. 2009; 159(1):414–426. [PubMed: 19105975]
42. Ghasemzadeh MB, Vasudevan P, Giles C, Purgianto A, Seubert C, Mantsch JR. Glutamatergic plasticity in medial prefrontal cortex and ventral tegmental area following extended-access cocaine self-administration. *Brain Res*. 2011; 1413:60–71. [PubMed: 21855055]
43. Ghasemzadeh MB, Vasudevan P, Mueller C. Locomotor sensitization to cocaine is associated with distinct pattern of glutamate receptor trafficking to the postsynaptic density in prefrontal cortex: early versus late withdrawal effects. *Pharmacol Biochem Behav*. 2009; 92(3):383–392. [PubMed: 19135470]
44. Groc L, Heine M, Cousins SL, Stephenson FA, Lounis B, Cognet L, Choquet D. NMDA receptor surface mobility depends on NR2A-2B subunits. *Proc Natl Acad Sci U S A*. 2006; 103(49):18769–18774. [PubMed: 17124177]
45. Halpain S, Girault JA, Greengard P. Activation of NMDA receptors induces dephosphorylation of DARPP-32 in rat striatal slices. *Nature*. 1990; 343(6256):369–372. [PubMed: 2153935]
46. Harvey J, Lacey MG. A postsynaptic interaction between dopamine D1 and NMDA receptors promotes presynaptic inhibition in the rat nucleus accumbens via adenosine release. *J Neurosci*. 1997; 17(14):5271–5280. [PubMed: 9204911]

47. Hemby SE, Tang W, Muly EC, Kuhar MJ, Howell L, Mash DC. Cocaine-induced alterations in nucleus accumbens ionotropic glutamate receptor subunits in human and non-human primates. *Journal of Neurochemistry*. 2005; 95(6):1785–1793. [PubMed: 16363995]
48. Heusner C, Palmiter R. Expression of mutant NMDA receptors in dopamine D1 receptor-containing cells prevents cocaine sensitization and decreases cocaine preference. *Journal of Neuroscience*. 2005; 25(28):6651–6657. [PubMed: 16014726]
49. Huang YH, Lin Y, Mu P, Lee BR, Brown TE, Wayman G, Marie H, Liu W, Yan Z, Sorg BA. In vivo cocaine experience generates silent synapses. *Neuron*. 2009; 63(1):40–47. [PubMed: 19607791]
50. Hyttia P, Backstrom P, Liljequist S. Site-specific NMDA receptor antagonists produce differential effects on cocaine self-administration in rats. *Eur J Pharmacol*. 1999; 378(1):9–16. [PubMed: 10478559]
51. Isaac JT. Postsynaptic silent synapses: evidence and mechanisms. *Neuropharmacology*. 2003; 45(4):450–460. [PubMed: 12907306]
52. Itzhak Y. Modulation of the PCP/NMDA receptor complex and sigma binding sites by psychostimulants. *Neurotoxicol Teratol*. 1994; 16(4):363–368. [PubMed: 7526145]
53. Itzhak Y, Martin JL. Cocaine-induced kindling is associated with elevated NMDA receptor binding in discrete mouse brain regions. *Neuropharmacology*. 2000; 39(1):32–39. [PubMed: 10665817]
54. Itzhak Y, Stein I. Sensitization to the toxic effects of cocaine in mice is associated with the regulation of N-methyl-D-aspartate receptors in the cortex. *J Pharmacol Exp Ther*. 1992; 262(2):464–470. [PubMed: 1386882]
55. Ivanov A, Pellegrino C, Rama S, Dumalska I, Salyha Y, Ben-Ari Y, Medina I. Opposing role of synaptic and extrasynaptic NMDA receptors in regulation of the extracellular signal-regulated kinases (ERK) activity in cultured rat hippocampal neurons. *J Physiol*. 2006; 572(Pt 3):789–798. [PubMed: 16513670]
56. Izawa R, Jaber M, Deroche-Gamonet V, Sillaber I, Kellendonk C, Le Moal M, Tronche F, Piazza PV. Gene expression regulation following behavioral sensitization to cocaine in transgenic mice lacking the glucocorticoid receptor in the brain. *Neuroscience*. 2006; 137(3):915–924. [PubMed: 16326019]
57. Jenab S, Festa ED, Nazarian A, Wu HB, Sun WL, Hazim R, Russo SJ, Quinones-Jenab V. Cocaine induction of ERK proteins in dorsal striatum of Fischer rats. *Brain Res Mol Brain Res*. 2005; 142(2):134–138. [PubMed: 16271798]
58. Jiao H, Zhang L, Gao F, Lou D, Zhang J, Xu M. Dopamine D(1) and D(3) receptors oppositely regulate NMDA- and cocaine-induced MAPK signaling via NMDA receptor phosphorylation. *J Neurochem*. 2007; 103(2):840–848. [PubMed: 17897358]
59. Kalivas PW, O'Brien C. Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology*. 2008; 33(1):166–180. [PubMed: 17805308]
60. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry*. 2005; 162(8):1403–1413. [PubMed: 16055761]
61. Karler R, Calder LD, Chaudhry IA, Turkanis SA. Blockade of "reverse tolerance" to cocaine and amphetamine by MK-801. *Life Sci*. 1989; 45(7):599–606. [PubMed: 2671566]
62. Karpova A, Mikhaylova M, Bera S, Bar J, Reddy PP, Behnisch T, Rankovic V, Spilker C, Bethge P, Sahin J, Kaushik R, Zuschratter W, Kahne T, Naumann M, Gundelfinger ED, Kreutz MR. Encoding and transducing the synaptic or extrasynaptic origin of NMDA receptor signals to the nucleus. *Cell*. 2013; 152(5):1119–1133. [PubMed: 23452857]
63. Kourrich S, Rothwell PE, Klug JR, Thomas MJ. Cocaine experience controls bidirectional synaptic plasticity in the nucleus accumbens. *Journal of Neuroscience*. 2007; 27(30):7921–7928. [PubMed: 17652583]
64. Koya E, Cruz FC, Ator R, Golden SA, Hoffman AF, Lupica CR, Hope BT. Silent synapses in selectively activated nucleus accumbens neurons following cocaine sensitization. *Nat Neurosci*. 2012; 15(11):1556–1562. [PubMed: 23023294]
65. Lasseter HC, Xie X, Ramirez DR, Fuchs RA. Sub-region specific contribution of the ventral hippocampus to drug context-induced reinstatement of cocaine-seeking behavior in rats. *Neuroscience*. 2010; 171(3):830–839. [PubMed: 20870011]

66. Le Greves P, Zhou Q, Huang W, Nyberg F. Effect of combined treatment with nandrolone and cocaine on the NMDA receptor gene expression in the rat nucleus accumbens and periaqueductal gray. *Acta Psychiatr Scand Suppl.* 2002; (412):129–132. [PubMed: 12072144]
67. Léveillé F, El Gaamouch F, Goux E, Lecocq M, Lobner D, Nicole O, Buisson A. Neuronal viability is controlled by a functional relation between synaptic and extrasynaptic NMDA receptors. *FASEB J.* 2008; 22(12):4258–4271. [PubMed: 18711223]
68. Li Y, Hu XT, Berney TG, Vartanian AJ, Stine CD, Wolf ME, White FJ. Both glutamate receptor antagonists and prefrontal cortex lesions prevent induction of cocaine sensitization and associated neuroadaptations. *Synapse.* 1999; 34(3):169–180. [PubMed: 10523754]
69. Li Y-C, Liu G, Hu J-L, Gao W-J, Huang Y-Q. Dopamine D1 receptor-mediated enhancement of NMDA receptor trafficking requires rapid PKC-dependent synaptic insertion in the prefrontal neurons. *Journal of Neurochemistry*:no-no. 2010
70. Lobo MK, Nestler EJ. The striatal balancing act in drug addiction: distinct roles of direct and indirect pathway medium spiny neurons. *Front Neuroanat.* 2011; 5:41. [PubMed: 21811439]
71. Loftis JM, Janowsky A. Regulation of NMDA receptor subunits and nitric oxide synthase expression during cocaine withdrawal. *J Neurochem.* 2000; 75(5):2040–2050. [PubMed: 11032893]
72. Loftis JM, Janowsky A. Cocaine treatment- and withdrawal-induced alterations in the expression and serine phosphorylation of the NR1 NMDA receptor subunit. *Psychopharmacology (Berl).* 2002; 164(4):349–359. [PubMed: 12457264]
73. Logan SM, Partridge JG, Matta JA, Buonanno A, Vicini S. Long-lasting NMDA receptor-mediated EPSCs in mouse striatal medium spiny neurons. *J Neurophysiol.* 2007; 98(5):2693–2704. [PubMed: 17804581]
74. Lu L, Dempsey J, Shaham Y, Hope BT. Differential long-term neuroadaptations of glutamate receptors in the basolateral and central amygdala after withdrawal from cocaine self-administration in rats. *J Neurochem.* 2005; 94(1):161–168. [PubMed: 15953359]
75. Lu L, Grimm JW, Shaham Y, Hope BT. Molecular neuroadaptations in the accumbens and ventral tegmental area during the first 90 days of forced abstinence from cocaine self-administration in rats. *Journal of Neurochemistry.* 2003; 85(6):1604–1613. [PubMed: 12787079]
76. Lu L, Koya E, Zhai H, Hope BT, Shaham Y. Role of ERK in cocaine addiction. *Trends Neurosci.* 2006; 29(12):695–703. [PubMed: 17084911]
77. Luo Y, Good CH, Diaz-Ruiz O, Zhang Y, Hoffman AF, Shan L, Kuang SY, Malik N, Chefer VI, Tomac AC, Lupica CR, Backman CM. NMDA receptors on non-dopaminergic neurons in the VTA support cocaine sensitization. *PLoS ONE.* 2010; 5(8):e12141. [PubMed: 20808436]
78. Madhavan A, Argilli E, Bonci A, Whistler JL. Loss of D2 dopamine receptor function modulates cocaine-induced glutamatergic synaptic potentiation in the ventral tegmental area. *J Neurosci.* 2013; 33(30):12329–12336. [PubMed: 23884939]
79. Mattson BJ, Bossert JM, Simmons DE, Nozaki N, Nagarkar D, Kreuter JD, Hope BT. Cocaine-induced CREB phosphorylation in nucleus accumbens of cocaine-sensitized rats is enabled by enhanced activation of extracellular signal-related kinase, but not protein kinase A. *J Neurochem.* 2005; 95(5):1481–1494. [PubMed: 16219028]
80. Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. Dopamine receptors: from structure to function. *Physiol Rev.* 1998; 78(1):189–225. [PubMed: 9457173]
81. Monyer H, Burnashev N, Laurie DJ, Sakmann B, Seeburg PH. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. *Neuron.* 1994; 12(3):529–540. [PubMed: 7512349]
82. Nairn AC, Svenningsson P, Nishi A, Fisone G, Girault JA, Greengard P. The role of DARPP-32 in the actions of drugs of abuse. *Neuropharmacology.* 2004; 47(Suppl 1):14–23. [PubMed: 15464122]
83. Nishi A, Kuroiwa M, Shuto T. Mechanisms for the modulation of dopamine d(1) receptor signaling in striatal neurons. *Front Neuroanat.* 2011; 5:43. [PubMed: 21811441]
84. Nishi A, Snyder GL, Nairn AC, Greengard P. Role of calcineurin and protein phosphatase-2A in the regulation of DARPP-32 dephosphorylation in neostriatal neurons. *J Neurochem.* 1999; 72(5):2015–2021. [PubMed: 10217279]

85. Oliva C, Escobedo P, Astorga C, Molina C, Sierralta J. Role of the MAGUK protein family in synapse formation and function. *Dev Neurobiol.* 2012; 72(1):57–72. [PubMed: 21739617]
86. Ortinski PI, Turner JR, Pierce RC. Extrasynaptic targeting of NMDA receptors following D1 dopamine receptor activation and cocaine self-administration. *J Neurosci.* 2013; 33(22):9451–9461. [PubMed: 23719812]
87. Ortinski PI, Vassoler FM, Carlson GC, Pierce RC. Temporally dependent changes in cocaine-induced synaptic plasticity in the nucleus accumbens shell are reversed by D1-like dopamine receptor stimulation. *Neuropsychopharmacology.* 2012; 37(7):1671–1682. [PubMed: 22414814]
88. Ortiz JG, Gonzalez-Cabrera S, Rubio-Davila M, Tirado-Costacamps A, Vazquez-Torres R, Berrios-Cartagena N, Silva WI, Jimenez-Rivera CA. AMPA and NMDA receptors in P2 fractions of cocaine and cocaine-prazosin-treated rats. *Ann N Y Acad Sci.* 2006; 1074:403–410. [PubMed: 17105938]
89. Otaka M, Ishikawa M, Lee BR, Liu L, Neumann PA, Cui R, Huang YH, Schluter OM, Dong Y. Exposure to cocaine regulates inhibitory synaptic transmission in the nucleus accumbens. *J Neurosci.* 2013; 33(16):6753–6758. [PubMed: 23595733]
90. Park WK, Bari AA, Jey AR, Anderson SM, Spealman RD, Rowlett JK, Pierce RC. Cocaine administered into the medial prefrontal cortex reinstates cocaine-seeking behavior by increasing AMPA receptor-mediated glutamate transmission in the nucleus accumbens. *J Neurosci.* 2002; 22(7):2916–2925. [PubMed: 11923456]
91. Pascoli V, Besnard A, Herve D, Pages C, Heck N, Girault JA, Caboche J, Vanhoutte P. Cyclic adenosine monophosphate-independent tyrosine phosphorylation of NR2B mediates cocaine-induced extracellular signal-regulated kinase activation. *Biol Psychiatry.* 2011; 69(3):218–227. [PubMed: 21055728]
92. Phillips AG, Ahn S, Howland JG. Amygdalar control of the mesocorticolimbic dopamine system: parallel pathways to motivated behavior. *Neurosci Biobehav Rev.* 2003; 27(6):543–554. [PubMed: 14599435]
93. Pierce RC, Kumaresan V. The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? *Neurosci Biobehav Rev.* 2006; 30(2):215–238. [PubMed: 16099045]
94. Pierce RC, Meil WM, Kalivas PW. The NMDA antagonist, dizocilpine, enhances cocaine reinforcement without influencing mesoaccumbens dopamine transmission. *Psychopharmacology (Berl).* 1997; 133(2):188–195. [PubMed: 9342786]
95. Pierce RC, Pierce-Bancroft AF, Prasad BM. Neurotrophin-3 contributes to the initiation of behavioral sensitization to cocaine by activating the Ras/Mitogen-activated protein kinase signal transduction cascade. *J Neurosci.* 1999; 19(19):8685–8695. [PubMed: 10493769]
96. Pulvirenti L, Balducci C, Koob GF. Dextromethorphan reduces intravenous cocaine self-administration in the rat. *Eur J Pharmacol.* 1997; 321(3):279–283. [PubMed: 9085038]
97. Pulvirenti L, Berrier R, Kreifeldt M, Koob GF. Modulation of locomotor activity by NMDA receptors in the nucleus accumbens core and shell regions of the rat. *Brain Res.* 1994; 664(1–2): 231–236. [PubMed: 7895034]
98. Pulvirenti L, Swerdlow NR, Koob GF. Nucleus accumbens NMDA antagonist decreases locomotor activity produced by cocaine, heroin or accumbens dopamine, but not caffeine. *Pharmacol Biochem Behav.* 1991; 40(4):841–845. [PubMed: 1687766]
99. Ranaldi R, French E, Roberts DC. Systemic pretreatment with MK-801 (dizocilpine) increases breaking points for self-administration of cocaine on a progressive-ratio schedule in rats. *Psychopharmacology (Berl).* 1996; 128(1):83–88. [PubMed: 8944410]
100. Rani CS, Qiang M, Ticku MK. Potential role of cAMP response element-binding protein in ethanol-induced N-methyl-D-aspartate receptor 2B subunit gene transcription in fetal mouse cortical cells. *Mol Pharmacol.* 2005; 67(6):2126–2136. [PubMed: 15774772]
101. Rodriguez-Borrero E, Bernardo Colon A, Burgos-Martir MA, Alvarez Carillo JE, del Campo YE, Abella-Ramirez C, Maldonado-Vlaar CS. NMDA antagonist AP-5 increase environmentally induced cocaine-conditioned locomotion within the nucleus accumbens. *Pharmacol Biochem Behav.* 2006; 85(1):178–184. [PubMed: 16963113]

102. Sarantis K, Matsokis N, Angelatou F. Synergistic interactions of dopamine D1 and glutamate NMDA receptors in rat hippocampus and prefrontal cortex: Involvement of ERK1/2 signaling. *Neuroscience*. 2009; 163(4):1135–1145. [PubMed: 19647050]
103. Scheggi S, Mangiavacchi S, Masi F, Gambarana C, Tagliamonte A, De Montis MG. Dizocilpine infusion has a different effect in the development of morphine and cocaine sensitization: behavioral and neurochemical aspects. *Neuroscience*. 2002; 109(2):267–274. [PubMed: 11801363]
104. Schilström B, Yaka R, Argilli E, Suvarna N, Schumann J, Chen B, Carman M, Singh V, Mailliard W, Ron D, Bonci A. Cocaine enhances NMDA receptor-mediated currents in ventral tegmental area cells via dopamine D5 receptor-dependent redistribution of NMDA receptors. *J Neurosci*. 2006; 26(33):8549–8558. [PubMed: 16914681]
105. Schmidt HD, Pierce RC. Cocaine-induced neuroadaptations in glutamate transmission. *Annals of the New York Academy of Sciences*. 2010; 1187(1):35–75. [PubMed: 20201846]
106. Schuler T, Mesic I, Madry C, Bartholomäus I, Laube B. Formation of NR1/NR2 and NR1/NR3 heterodimers constitutes the initial step in N-methyl-D-aspartate receptor assembly. *J Biol Chem*. 2008; 283(1):37–46. [PubMed: 17959602]
107. Schumann J, Matzner H, Michaeli A, Yaka R. NR2A/B-containing NMDA receptors mediate cocaine-induced synaptic plasticity in the VTA and cocaine psychomotor sensitization. *Neurosci Lett*. 2009; 461(2):159–162. [PubMed: 19524640]
108. Schumann J, Yaka R. Prolonged withdrawal from repeated noncontingent cocaine exposure increases NMDA receptor expression and ERK activity in the nucleus accumbens. *J Neurosci*. 2009; 29(21):6955–6963. [PubMed: 19474322]
109. Self D, Choi K, Simmons D, Walker J, CS S. Extinction Training Regulates Neuroadaptive Responses to Withdrawal from Chronic Cocaine Self-Administration. *Learning & Memory*. 2004; 11(5):648–657. [PubMed: 15466321]
110. Sheng M, Cummings J, Roldan LA, Jan YN, Jan LY. Changing subunit composition of heteromeric NMDA receptors during development of rat cortex. *Nature*. 1994; 368(6467):144–147. [PubMed: 8139656]
111. Sucher NJ, Akbarian S, Chi CL, Leclerc CL, Awobuluyi M, Deitcher DL, Wu MK, Yuan JP, Jones EG, Lipton SA. Developmental and regional expression pattern of a novel NMDA receptor-like subunit (NMDAR-L) in the rodent brain. *J Neurosci*. 1995; 15(10):6509–6520. [PubMed: 7472413]
112. Sun W, Rebec GV. Lidocaine inactivation of ventral subiculum attenuates cocaine-seeking behavior in rats. *J Neurosci*. 2003; 23(32):10258–10264. [PubMed: 14614084]
113. Sun WL, Zhou L, Hazim R, Quinones-Jenab V, Jenab S. Effects of dopamine and NMDA receptors on cocaine-induced Fos expression in the striatum of Fischer rats. *Brain Res*. 2008; 1243:1–9. [PubMed: 18822274]
114. Suzuki K, Sato M, Morishima Y, Nakanishi S. Neuronal depolarization controls brain-derived neurotrophic factor-induced upregulation of NR2C NMDA receptor via calcineurin signaling. *J Neurosci*. 2005; 25(41):9535–9543. [PubMed: 16221864]
115. Szumlinski KK, Herrick-Davis K, Teitler M, Maisonneuve IM, Glick SD. Behavioural sensitization to cocaine is dissociated from changes in striatal NMDA receptor levels. *Neuroreport*. 2000; 11(12):2785–2788. [PubMed: 10976963]
116. Tang WX, Fasulo WH, Mash DC, Hemby SE. Molecular profiling of midbrain dopamine regions in cocaine overdose victims. *J Neurochem*. 2003; 85(4):911–924. [PubMed: 12716423]
117. Thomas MJ, Beurrier C, Bonci A, Malenka RC. Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine. *Nature Neuroscience*. 2001; 4(12):1217–1223.
118. Tong G, Takahashi H, Tu S, Shin Y, Talantova M, Zago W, Xia P, Nie Z, Goetz T, Zhang D, Lipton SA, Nakanishi N. Modulation of NMDA receptor properties and synaptic transmission by the NR3A subunit in mouse hippocampal and cerebrocortical neurons. *J Neurophysiol*. 2008; 99(1):122–132. [PubMed: 18003876]

119. Tong H, Gibb AJ. Dopamine D1 receptor inhibition of NMDA receptor currents mediated by tyrosine kinase-dependent receptor trafficking in neonatal rat striatum. *The Journal of Physiology*. 2008; 586(19):4693–4707. [PubMed: 18703578]
120. Torres G, Rivier C. Cocaine-induced expression of striatal c-fos in the rat is inhibited by NMDA receptor antagonists. *Brain Res Bull*. 1993; 30(1–2):173–176. [PubMed: 8420627]
121. Tovar KR, McGinley MJ, Westbrook GL. Triheteromeric NMDA receptors at hippocampal synapses. *J Neurosci*. 2013; 33(21):9150–9160. [PubMed: 23699525]
122. Tovar KR, Westbrook GL. The incorporation of NMDA receptors with a distinct subunit composition at nascent hippocampal synapses in vitro. *J Neurosci*. 1999; 19(10):4180–4188. [PubMed: 10234045]
123. Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, Hansen KB, Yuan H, Myers SJ, Dingledine R. Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol Rev*. 2010; 62(3):405–496. [PubMed: 20716669]
124. Turchan J, Maj M, Przewlocka B. The effect of drugs of abuse on NMDAR1 receptor expression in the rat limbic system. *Drug Alcohol Depend*. 2003; 72(2):193–196. [PubMed: 14636974]
125. Uzbay IT, Wallis CJ, Lal H, Forster MJ. Effects of NMDA receptor blockers on cocaine-stimulated locomotor activity in mice. *Behav Brain Res*. 2000; 108(1):57–61. [PubMed: 10680757]
126. Valjent E, Corvol JC, Pages C, Besson MJ, Maldonado R, Caboche J. Involvement of the extracellular signal-regulated kinase cascade for cocaine-rewarding properties. *J Neurosci*. 2000; 20(23):8701–8709. [PubMed: 11102476]
127. Wee KS, Zhang Y, Khanna S, Low CM. Immunolocalization of NMDA receptor subunit NR3B in selected structures in the rat forebrain, cerebellum, and lumbar spinal cord. *J Comp Neurol*. 2008; 509(1):118–135. [PubMed: 18425811]
128. Witkin JM. Blockade of the locomotor stimulant effects of cocaine and methamphetamine by glutamate antagonists. *Life Sci*. 1993; 53(24):PL405–PL410. [PubMed: 7902523]
129. Wolf ME. The role of excitatory amino acids in behavioral sensitization to psychomotor stimulants. *Prog Neurobiol*. 1998; 54(6):679–720. [PubMed: 9560846]
130. Wolf ME, Jeziorski M. Coadministration of MK-801 with amphetamine, cocaine or morphine prevents rather than transiently masks the development of behavioral sensitization. *Brain Res*. 1993; 613(2):291–294. [PubMed: 8186979]
131. Wolf ME, Khansa MR. Repeated administration of MK-801 produces sensitization to its own locomotor stimulant effects but blocks sensitization to amphetamine. *Brain Res*. 1991; 562(1):164–168. [PubMed: 1839240]
132. Yamaguchi M, Suzuki T, Abe S, Hori T, Kurita H, Asada T, Okado N, Arai H. Repeated cocaine administration differentially affects NMDA receptor subunit (NR1, NR2A-C) mRNAs in rat brain. *Synapse*. 2002; 46(3):157–169. [PubMed: 12325043]
143. Yamamoto DJ, Zahniser NR. Differences in rat dorsal striatal NMDA and AMPA receptors following acute and repeated cocaine-induced locomotor activation. *PLoS One*. 2012; 7(5):e37673. [PubMed: 22655064]
144. Yang SN. Sustained enhancement of AMPA receptor- and NMDA receptor-mediated currents induced by dopamine D1/D5 receptor activation in the hippocampus: an essential role of postsynaptic Ca²⁺. *Hippocampus*. 2000; 10(1):57–63. [PubMed: 10706217]
145. Yuan T, Mameli M, EC OC, Dey PN, Verpelli C, Sala C, Perez-Otano I, Luscher C, Bellone C. Expression of cocaine-evoked synaptic plasticity by GluN3A-containing NMDA receptors. *Neuron*. 2013; 80(4):1025–1038. [PubMed: 24183704]
146. Yuen EY, Jiang Q, Chen P, Gu Z, Feng J, Yan Z. Serotonin 5-HT_{1A} receptors regulate NMDA receptor channels through a microtubule-dependent mechanism. *J Neurosci*. 2005; 25(23):5488–5501. [PubMed: 15944377]
147. Zachariou V, Sgambato-Faure V, Sasaki T, Svenningsson P, Berton O, Fienberg AA, Nairn AC, Greengard P, Nestler EJ. Phosphorylation of DARPP-32 at Threonine-34 is required for cocaine action. *Neuropsychopharmacology*. 2006; 31(3):555–562. [PubMed: 16123776]

148. Zhang L, Lou D, Jiao H, Zhang D, Wang X, Xia Y, Zhang J, Xu M. Cocaine-induced intracellular signaling and gene expression are oppositely regulated by the dopamine D1 and D3 receptors. *J Neurosci*. 2004; 24(13):3344–3354. [PubMed: 15056714]
149. Zhang X, Lee TH, Davidson C, Lazarus C, Wetsel WC, Ellinwood EH. Reversal of cocaine-induced behavioral sensitization and associated phosphorylation of the NR2B and GluR1 subunits of the NMDA and AMPA receptors. *Neuropsychopharmacology*. 2007; 32(2):377–387. [PubMed: 16794574]
150. Zhang XF, Hu XT, White FJ, Wolf ME. Increased responsiveness of ventral tegmental area dopamine neurons to glutamate after repeated administration of cocaine or amphetamine is transient and selectively involves AMPA receptors. *J Pharmacol Exp Ther*. 1997; 281(2):699–706. [PubMed: 9152375]
151. Zhang Y, Svenningsson P, Picetti R, Schlussman SD, Nairn AC, Ho A, Greengard P, Kreek MJ. Cocaine self-administration in mice is inversely related to phosphorylation at Thr34 (protein kinase A site) and Ser130 (kinase CK1 site) of DARPP-32. *J Neurosci*. 2006; 26(10):2645–2651. [PubMed: 16525043]
152. Zweifel LS, Argilli E, Bonci A, Palmiter RD. Role of NMDA receptors in dopamine neurons for plasticity and addictive behaviors. *Neuron*. 2008; 59(3):486–496. [PubMed: 18701073]

Figure 1.

A summary of intracellular signaling mechanisms involved in the synergistic effects of D1DR and NMDAR activation. Arrows indicates stimulation, squares indicate suppression of activity. Ras-GRF1, Ras-guanine nucleotide-releasing factor 1; G_sβγ, β/γ subunits of the G_s protein; G_sα, α subunit of the G_s protein; AC, adenylyl cyclase; CaMKII, calcium-calmodulin kinase II; Ras, small GTP-ase members of the rat sarcoma superfamily of proteins; cAMP, cyclic adenosine monophosphate; ATP, adenosine triphosphate; Raf, Ras effector protein; MEK, MAPK/ERK kinase; PKA, protein kinase A; DARPP-32, dopamine- and cAMP-regulated phosphoprotein, Mr 32 kDa; MAPK/ERK, mitogen-activated protein

kinase/extracellular signal-regulated kinase; STEP, striatal-enriched protein phosphatase; PP-1, protein-phosphatase 1; MSK/RSK, mitogen- and stress-activated protein kinase/ 90 kDa ribosomal S6 kinase; CREB, cAMP response element-binding protein. Adapted, with permission, from Schmidt and Pierce (2010).

Table 1

A summary of cocaine-induced changes in NMDAR expression and binding of radioactive ligands in areas of the mesolimbic dopamine reward circuit. Tissue levels of NMDAR protein or mRNA were examined unless otherwise indicated. Arrows indicate no change ($\leftrightarrow$), an increase ($\uparrow$) or a decrease ($\downarrow$) in subunit expression or receptor binding. Changes were considered significant when reported with $p < 0.05$. Withdrawal (wd).

Brain Area	Observed change	Species	Cocaine history	References and notes
Nucleus accumbens			Non-contingent, short withdrawal	
	$\leftrightarrow$ GluN1	Rat	14 days/16–18 hr wd	Fitzgerald et al., 1996
	$\downarrow$ GluN1	Rat	14 days/24 hr wd	Yamaguchi et al., 2002, LeGreves et al., 2002
	$\leftrightarrow$ GluN1	Rat	21 days/no wd	Crespo et al., 2002
	$\leftrightarrow$ GluN1, 2A, 2B	Rat	5 days/1 day wd	Ghasemzadeh et al., 2009a; Schumann and Yaka, 2009
	$\leftrightarrow$ GluN1, 2A, 2B	Rat	7 d and acute dose	Yamamoto and Zahniser 2012
	$\downarrow$ GluN2B	Rat	7 days/24 hr wd	Loftis and Janowsky 2000
	$\leftrightarrow$ GluN1	Rat	7 days/1 day wd	Churchill et al., 1999 (cocaine-sensitized rats only)
			Non-contingent, long withdrawal	
	$\uparrow$ GluN1, 2A, 2B	Rat	5 days/21 day wd	Ghasemzadeh et al., 2009a; Schumann and Yaka, 2009
	$\uparrow$ GluN2B	Rat	7 days/14 day wd	Loftis and Janowsky 2000
	$\uparrow$ GluN2B	Rat	4 days/14 days wd then acute dose	Zhang et al., 2007
	$\leftrightarrow$ GluN2B	Rat	8 days/15 days wd	Ferrario et al., 2010 (suggest an increase in GluN2A)
	$\leftrightarrow$ GluN1	Rat	7 days /21 day wd	Churchill et al., 1999 (cocaine-sensitized rats only)
	$\uparrow$ GluN1, $\uparrow$ GluN2B	Rat	14 days/17 day wd	Scheggi et al., 2002
			Self-administered, short withdrawal	
	$\uparrow$ GluN1	Rat	10 days/1 day wd (6 hrs/day)	Lu et al., 2003
	$\uparrow$ GluN1	Rat	21 days/no wd (2 hrs/day)	Crespo et al., 2002
	$\uparrow$ GluN2A, 2B, $\leftrightarrow$ GluN1	Rat	14 days/1 day wd (2 hrs/day)	Ortinski et al., 2013
	$\leftrightarrow$ ^{3} H-MK801	Rat	8 days/20 min wd (1 hr/day or 6 hrs/day)	Ben-Shahar et al. 2007
			Self-administered, long withdrawal	
	$\uparrow$ GluN1	Rat	10 days/90 day wd (6 hrs/day)	Lu et al., 2003
	$\leftrightarrow$ ^{3} H-MK801	Rat	8 days/14 or 60 day wd (1 hr/day or 6 hrs/day)	Ben-Shahar et al. 2007
	$\downarrow$ GluN1	Rat	14 days/1 wk wd (4 hrs/day)	Self et al., 2004 (decrease in core, no difference in shell)

Brain Area	Observed change ↔GluN1, GluN2A, 2B	Species Rat	Cocaine history 10 days/14 day wd (6 hrs/day)	References and notes Ferrario et al., 2012 (post-synaptic density fractions)
Ventral tegmental area				
	↔GluN1, 2A, 2B	Rat	7 d /40 min wd	Yamamoto and Zahniser 2012
	↑GluN1	Rat	7 days/72 hr wd	Loftis and Janowsky 2000
	↑GluN1	Rat	14 days/16–18 hr wd	Fitzgerald et al., 1996
	↑GluN1	Rat	7 days/1 day wd	Churchill et al., 1999 (cocaine-sensitized rats only)
Non-contingent, long withdrawal				
	↑GluN1	Rat	7 days /14 day wd	Loftis and Janowsky 2000
	↔GluN1	Rat	7 days /21 day wd	Churchill et al., 1999 (cocaine-sensitized rats only)
Self-administered, short withdrawal				
	↑GluN1	Rat	10 days/1 day wd (6 hrs/day)	Lu et al., 2003
	↔ ³ H -MK801	Rat	8 days/20 min wd (1 hr/day or 6 hrs/day)	Ben-Shahar et al. 2007
Self-administered, long withdrawal				
	↑GluN1	Rat	10 days/90 day wd (6 hrs/day)	Lu et al., 2003
	↔GluN1	Rat	14 days/10 day wd (6 hrs/day)	Ghasemzadeh et al., 2011 (suggest a decrease in post-synaptic density fractions)
	↔ ³ H -MK801	Rat	8 days/14 or 60 day wd (1 hr/day or 6 hrs/day)	Ben-Shahar et al. 2007
Dorsal Striatum				
	↔GluN1	Rat	21 days/no wd	Crespo et al., 2002
	↔GluN1, 2A, 2B	Rat	7 d/40 min wd	Yamamoto and Zahniser 2012
	↔GluN1	Rat	2 weeks/16–18 hr wd	Fitzgerald et al., 1996
	↑ ³ H-CGP	Mouse	3 or 10 days/ 1 day wd	Itzhak and Martin 2000
	↓GluN1	Rat	14 days/24 hr wd	Yamaguchi et al., 2002
	↔GluN1	Rat	7 days/24 hr wd	Loftis and Janowsky 2002
Non-contingent, long withdrawal				
	↑GluN2B, ↓GluN1	Rat	7 days /14 day wd	Loftis and Janowsky 2000, Loftis and Janowsky 2002
	↓GluN2A, ↔GluN1	Mouse	9 days/30 day wd then acute dose	Izawa et al., 2006 (cocaine administered every other day)
	↑ ³ H-CGP	Mouse	3 days/ 10 day wd	Itzhak and Martin 2000
	↔ ³ H-CGP	Mouse	10 days/ 10 day wd	Itzhak and Martin 2000

Brain Area	Observed change	Species	Cocaine history	References and notes
	↔ ³ H-MK801	Rat	5 days/14 day wd	Szumliński et al., 2000
	↔GluN2B	Rat	8 days/15 days wd	Ferrario et al., 2010
			Self-administered, short withdrawal	
	↑GluN1	Rat	21 days/ no wd (2 hrs/day)	Crespo et al., 2002
	↔ ³ H -MK801	Rat	8 days/20 min wd (1 hr/day or 6 hrs/day)	Ben-Shahar et al. 2007
			Self-administered, long withdrawal	
	↔ ³ H -MK801	Rat	8 days/14 or 60 day wd (1 hr/day or 6 hrs/day)	Ben-Shahar et al. 2007
PFC			Non-contingent, short withdrawal	
	↔GluN1	Rat	21 days/no wd	Crespo et al., 2002
	↑GluN2B, ↔GluN1	Rat	7 days /24 hr wd	Loftis and Janowsky 2000; Loftis and Janowsky 2002
	↑ ³ H-CGP	Mouse	7 days/24 hr wd	Itzhak 1994; Itzhak and Stein 1992
	↔ ³ H-CGP	Mouse	3 days/ 1 day wd	Itzhak and Martin 2000
	↑ ³ H-CGP	Mouse	10 days/ 1 day wd	Itzhak and Martin 2000
	↓ ³ H-MK-801	Mouse	7 days/1 hr or 40 hour wd	Bhargava and Kumar 1999
	↓GluN1	Rat	14 days/24 hr wd	Yamaguchi et al., 2002
	↓GluN1, 2A, 2B	Rat	7 days/1 day wd	Ghasemzadeh et al., 2009b
			Non-contingent, long withdrawal	
	↑GluN2B	Rat	7 days /14 day wd	Loftis and Janowsky 2000
	↔GluN2A	Rat	5 days/14 days wd then acute dose	Ortiz et al., 2006 (synaptic membrane fractions)
	↑GluN1, ↑GluN2A	Rat	7 days/21 day wd	Ghasemzadeh et al., 2009b
	↔ ³ H-CGP	Mouse	3 days/ 10 day wd	Itzhak and Martin 2000
	↔ ³ H-CGP	Mouse	10 days/ 10 day wd	Itzhak and Martin 2000
	↔GluN1, GluN2B	Rat	14 days/17 day wd	Scheggi et al., 2002
			Self-administered, short withdrawal	
	↑GluN1	Rat	21 days/no wd (2 hrs/day)	Crespo et al., 2002
	↓ ³ H-MK801	Rat	8 days/20 min wd (1 hr/day)	Ben-Shahar et al. 2007
	↔ ³ H-MK801	Rat	8 days/20 min wd (6 hrs/day)	Ben-Shahar et al. 2007
			Self-administered, long withdrawal	
	↔GluN1	Rat	14 days/10 day wd (6 hrs/day)	Ghasemzadeh et al., 2011 (also no change in synaptosomal fractions)
	↔ ³ H-MK801	Rat	8 days/14 or 60 day wd (6 hrs/day)	Ben-Shahar et al. 2007
Hippocampus			Non-contingent, short withdrawal	

Brain Area	Observed change	Species	Cocaine history	References and notes
	↔GluN2B	Rat	7 days/24 or 72 hr wd	Loftis and Janowsky 2000
	↔GluN1	Rat	14 days/16–18 hr wd	Fitzgerald et al., 1996
	↓GluN1	Rat	5 days/3 or 48 hr wd	Turchan et al., 2003
	↑ ³ H-CGP	Mouse	3 or 10 days/ 1 day wd	Itzhak and Martin 2000
			Non-contingent, long withdrawal	
	↔ ³ H-CGP binding	Mouse	3 days/ 10 day wd	Itzhak and Martin 2000
	↑ ³ H-CGP	Mouse	10 days/ 10 day wd	Itzhak and Martin 2000
	↑GluN2B, ↔GluN1	Rat	14 days/17 day wd	Scheggi et al., 2002
Amygdala			Non-contingent, short withdrawal	
	↑GluN1	Rat	5 days/3 hr wd	Turchan et al., 2003
	↑ ³ H-CGP	Mouse	3 or 10 days/ 1 day wd	Itzhak and Martin 2000
			Non-contingent, long withdrawal	
	↑ ³ H-CGP	Mouse	3 or 10 days/ 10 day wd	Itzhak and Martin 2000
			Self-administered, short withdrawal	
	↑GluN2A	Rat	10 days/1 hr wd (6 hrs/day)	Lu et al., 2005 (see text for details)
			Self-administered, long withdrawal	
	↓GluN2B, ↑GluN1, ↔GluN2A, 2B	Rat	10 days/ 30 day wd (6 hrs/day)	Lu et al., 2005 (see text for details)