Published in final edited form as:

Ann N Y Acad Sci. 2010 February ; 1187: 129–139. doi:10.1111/j.1749-6632.2009.05154.x.

Synaptic plasticity in the mesolimbic system:

Therapeutic implications for substance abuse

Billy T. Chen^{1,2,3}, F. Woodward Hopf^{1,2,3}, and Antonello Bonci^{1,2,3,4}

¹ Ernest Gallo Clinic and Research Center, University of California, San Francisco, California, USA

² Department of Neurology, University of California, San Francisco, California, USA

³ Wheeler Center for the Neurobiology of Addiction, University of California, San Francisco, California, USA

⁴ Program in Neuroscience, University of California, San Francisco, California, USA

Abstract

In an ever-changing environment, animals must learn new behavioral strategies for the successful procurement of food, sex, and other needs. Synaptic plasticity within the mesolimbic system, a key reward circuit, affords an animal the ability to adapt and perform essential goal-directed behaviors. Ironically, drugs of abuse can also induce synaptic changes within the mesolimbic system, and such changes are hypothesized to promote deleterious drug-seeking behaviors in lieu of healthy, adaptive behaviors. In this review, we will discuss drug-induced neuroadaptations in excitatory transmission in the ventral tegmental area and the nucleus accumbens, two critical regions of the mesolimbic system, and the possible role of dopamine receptors in the development of these neuroadaptations. In particular, we will focus our discussion on recent studies showing changes in AMPA receptor function as a common molecular target of addictive drugs, and the possible behavioral consequences of such neuroadaptations.

Keywords

addiction; ventral tegmental area; nucleus accumbens; synaptic plasticity; dopamine; LTP; LTD

Introduction

The mesolimbic system, formed in part by the ventral tegmental area (VTA) and the nucleus accumbens (NAcb), is an integral part of the brain's reward circuit. Dopamine (DA) neurons in the VTA provide one of the major sources of DA to limbic structures, including the NAcb. DA has been implicated in the encoding of reinforcement and learning,¹ whereas the NAcb is considered a limbic-motor interface to which relevant stimuli are processed to influence initiation of behavior.^{2–7} Together, the VTA and the NAcb, along with other areas, such as the prefrontal cortex, thalamus, and amygdala, are considered to play a critical role in the control of motivated and goal-directed behaviors. A confluence of experimental data has emerged to support the hypothesis that the development and persistent expression of addictive behaviors occurs through the usurpation of natural learning and mechanisms within the limbic system.

Address for correspondence: Antonello Bonci, M.D., Department of Neurology, Ernest Gallo Clinic & Research Center, University of California, San Francisco, CA. Voice: 510 985-3890; fax: 510 985-3101. Antonello.bonci@ucsf.edu.

Conflicts of interest

The authors declare no conflicts of interest.

Through maladaptive learning mechanisms, drugs of abuse can hijack the reward circuit to induce aberrantly long-lasting forms of synaptic plasticity that may serve to drive the persistent drug-seeking behaviors that are observed with addicts.

The VTA and NAc receive extensive glutamatergic inputs from the prefrontal cortex and other brain areas, and these excitatory inputs have been considered critical for establishing and expressing addictive and other motivated behaviors.^{2–7} Increased glutamate function onto VTA DA neurons may alter the generation of firing in VTA DA neurons during goal-directed behaviors and promote repetition of these behaviors. Thus, many studies using glutamate receptor antagonists or GABA receptor agonists suggest that VTA and NAc inactivation prevents the expression of a variety of motivated and goal-directed behaviors^{4,8,9} (but see Refs. ¹⁰ and ¹¹). In addition, DA receptor signaling through D1-type (D1R, D1, or D5) and/or D2-type (D2R, D2, D3, or D4) receptors is required for a wide range of functions of the NAc.^{4,9,12–15} Importantly, because most drugs of abuse cause an increase in extracellular DA in the projection targets of DA neurons,¹⁶ this report will first review our current understanding of how DA might modulate glutamatergic synaptic plasticity in mesolimbic brain regions. This topic will be examined in the context of *in vitro* brain slice experiments and plasticity induction in the anesthetized animal.

We will also address how drug abuse research has progressed, from the consequences of passive (i.e., experimenter administered) versus active (i.e., self-administration) exposure to drugs. Repeated passive exposure to a given drug can enhance or “sensitize” the locomotor-activating effects of that drug, called “behavioral sensitization.” Because locomotor sensitization can be long-lasting and can enhance subsequent drug self-administration, sensitization has been considered a model of enhanced drug seeking during abstinence. Drug-related sensitization has been observed in humans and can contribute to enhancement of psychoses with repeated psychostimulant exposure. However, although pharmacological effects through passive drug exposure can produce enduring plastic changes, human drug intake is typically active and voluntary, and associational learning between drug taking and subsequent “reward” or negative consequences may be a critical component in the development of addiction.

Synaptic plasticity in the mesolimbic system: general concepts

In vitro brain slice modeling has demonstrated that glutamatergic synapses in the VTA and NAc can express plasticity. Indeed, many studies have found that long-term potentiation (LTP) or long-term depression (LTD) of evoked alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPA) currents can be induced in both regions.^{17–19} Not surprisingly, reported results indicate that there is diversity in the underlying mechanisms of LTP and LTD induction. This may depend in part on the frequency of stimulation and other details of the LTP/LTD induction protocol. For example, the use of spike-timing-dependent plasticity²⁰ has increased in recent studies. This may be in part because some experimenters feel that this method is more physiologically relevant. Unlike older induction protocols, which consist of holding the neuron at depolarized potential for a long period, while at the same time stimulating afferents at high or low frequencies, spike-timing-dependent plasticity protocols intersperse stimulating stimuli with rapid cell depolarization, in a manner more resembling normal physiological activity of the neuron. Despite the differences in induction protocol, studies have observed a high-frequency stimulation (HFS)- and *N*-methyl-D-aspartate receptor (NMDAR)-dependent LTP in the VTA and NAc.^{17,21–26} Activation of NMDARs and the subsequent increase in postsynaptic calcium are required for LTP in many nonmesolimbic brain areas, such as the hippocampus,²⁷ indicating that there could be mechanistic similarities between LTP induction mechanisms across brain regions.

The increase or decrease in synaptic strengths observed in LTP and LTD, respectively, can be associated with differential trafficking and cell surface expression of different AMPAR subunits.^{27,28} AMPARs are typically composed of four subunit proteins (GluR1–4), which can form hetero- or homo-meric complexes. In both the VTA and NAcB AMPARs are thought to exist as heteromeric complexes containing both GluR2/3 and GluR1 subunits in the basal state, before any changes in synaptic strength occur. Studies of excitatory synaptic input support the idea that most synaptic AMPARs under control conditions contain the specific AMPAR subunit GluR2, which forms heteromeric receptors with either GluR1 or GluR3 (i.e., GluR1/2 or GluR2/3 receptors). In contrast, there are few GluR2-lacking AMPARs (i.e., GluR1/1 or GluR1/3 AMPARs, which we term “GluR1-type”; e.g., Ref. ²⁹). GluR1-type AMPARs have a greater single-channel conductance than AMPARs containing GluR2 and are permeable to calcium, which may serve to facilitate calcium-dependent signaling events.²⁷ The identification of different AMPAR subunits has been greatly aided by biochemical cross-linking methods that affect only receptors on the cell surface, allowing precise determination of surface expression of particular GluR subunits. In addition, because GluR2-lacking AMPARs are blocked by intracellular polyamines at positive potentials, a characteristic inward rectifying current–voltage relationship can be used to determine the presence or absence of GluR2-lacking AMPARs. Finally, AMPAR subunit–selective peptide antagonists are available to allow delineation of the relative contribution of GluR1- and GluR2-containing AMPARs *in vitro* and *in vivo*. Importantly, an increase in the surface expression of GluR1-type AMPARs lacking GluR2 has been observed after drug administration,^{23,27,30–32} suggesting that differential trafficking of AMPAR subunits may underlie drug-seeking behaviors.

DA and synaptic plasticity in the VTA

Excitatory synapses on VTA DA neurons exhibit both LTP^{17,33} and LTD.^{29,34} VTA LTP requires NM-DARs and postsynaptic calcium,^{17,24,26,33,35–37} similar to LTP in other brain areas.²⁷ Several groups have reported that LTD can be generated in VTA DA neurons, but like LTD in other brain regions²⁷ the mechanisms underlying LTD may differ depending on the induction protocol. LTD can be triggered by activation of voltage-dependent calcium channels and does not require NMDAR activation,^{29,34} but LTD can also be triggered by activation of metabotropic glutamate receptors (mGluRs).^{30,31} Both of these forms of LTD appear to involve a decrease in cell surface GluR1-containing AMPARs.^{30,31,38} Finally, DA receptor inhibition does not block induction of VTA LTD,²⁹ although increased DA signaling through D2Rs suppresses LTD.^{27,29,38} Thus, DA is not necessary for VTA LTD or LTP but can modulate LTD induction.

DA and synaptic plasticity in the NAcB

Several studies have examined the ability of repeated stimulation of glutamatergic afferents to alter functional properties of excitatory synapses on NAcB medium spiny neurons *in vitro*. Multiple forms of LTD and LTP have been identified, and multiple groups agree that NAcB LTD is not modulated by DA receptor activation.^{21,29,39} These findings are in contrast with those from the dorsal striatum, where LTD induction requires DA receptors.^{40,41} In contrast, dorsal striatum and NAcB LTD both require mGluR activation leading to increased postsynaptic calcium levels and production of endocannabinoids (eCBs), although non-eCB mechanisms for mGluR-dependent LTD have been identified.^{41–44}

In general, HFS-induced LTP that is dependent on NMDAR activation and postsynaptic calcium is observed in several brain regions,²⁷ including the NAcB.^{21,45–47} However, studies of DA receptor regulation of NAcB LTP are more mixed, with reports of no regulation by DA receptors,²¹ a requirement for DA receptors,^{25,48} or inhibition of LTP induction by DA receptors.²² In addition, *in vivo* studies in anesthetized, intact animals suggest that there could

be complex and selective modulation of hippocampal and cortical inputs to the NAc by HFS, D1Rs, and D2Rs.⁴⁸ Interestingly, several induction procedures that can produce LTD in the brain slice also produce LTP in the dorsal striatum of the intact animals.^{49,50}

Thus, the basic molecular mechanisms underlying striatal LTD (mGluR, calcium, eCBs) and striatal LTP (NMDAR, calcium) are similar in dorsal striatum and NAc. In contrast, DA modulation of glutamatergic plasticity differs across the striatal subregions, with a role for DA receptors in LTD induction in the dorsal striatum but not the NAc. However, studies of DA modulation of striatal LTP have produced more mixed results. Such discrepancies could be explained by differences in stimulation procedure or by other details, such as age or species of animal studied. In addition, striatal regions contain multiple populations of spiny neurons, and recent studies using green fluorescent protein-labeled D1R- and D2R-type neurons have contrasted the neuromodulator regulation of glutamatergic plasticity in these two cell populations.^{51,52}

Synaptic plasticity in the VTA induced by exposure to drugs of abuse

The ability of drugs of abuse to produce synaptic plasticity in the VTA was first demonstrated using a single experimenter-administered cocaine injection.³⁵ Remarkably, subsequent studies showed that a single injection of a variety of abused drugs (e.g., cocaine, morphine, nicotine) but not nonabused drugs (fluoxetine or carbamazepine) led to potentiation of glutamatergic synapses in VTA DA neurons.³⁶ This potentiation was mediated by an increase in AMPAR-mediated synaptic response.^{19,30,31,35,36,53,54} This LTP-like increase in AMPAR signaling in the VTA was transient, lasting 5 days, but was no longer potentiated 10 days after the cocaine injection.³⁵ Further, this LTP required NMDARs, D1Rs, or orexin receptor activity, because blocking any of these receptors inhibits both the expression of behavioral sensitization and the cocaine-triggered potentiation of AMPARs.^{23,35,36,55,56}

This cocaine-induced potentiation of AMPAR-mediated synaptic response is also shown to occlude further induction of LTP^{23,35,37} (but see Ref. ²⁰). This finding is consistent with the idea that if excitatory synapses in the VTA are already saturated by cocaine exposure, no further plasticity could be induced. Further, cocaine-induced LTP in the VTA is associated with an increase in the proportion of GluR1-containing, GluR2-lacking AMPARs.^{23,30,31} Interestingly, the cocaine-induced increase in GluR1-containing AMPARs can be reversed via an mGluR-dependent mechanism that replaces GluR2-lacking AMPARs with GluR2-containing AMPARs.^{30,31}

The short-lasting LTP in VTA DA neurons induced by cocaine may occur because only one shot was administered. Would LTP last longer if more injections were administered? This supposition was examined in additional studies where rats were given seven shots across 7 consecutive days. Surprisingly, repeated experimenter-administered cocaine injections did not further increase the duration of LTP in VTA DA neurons. Rats receiving seven cocaine injections (once/day for 7 days) exhibited potentiation that lasted only 5 days but returned to naïve state after 10 days of abstinence.⁵⁵ This length of LTP in VTA is similar to the time course that was previously observed after one cocaine exposure.³⁵ Taken together, these data suggest that regardless of the number of drug injections, LTP at VTA DA neurons is transient.

Because associative learning mechanisms may play a vital role in the development of addiction, changes in synaptic plasticity in VTA DA neurons should also be examined using voluntary cocaine self-administration models. In stark contrast to the consequences of passive cocaine administration, cocaine self-administration enhanced AMPAR-mediated responses in VTA DA neurons for at least 3 months of abstinence.⁵⁷ Importantly, self-administration of natural rewards also induced LTP in VTA DA neurons, but this potentiation was transient, lasting for up to 7 days.^{26,57} These findings suggest that learning in relation to natural rewards has much

shorter-lasting effects on VTA function than drug self-administration. Further, these results strongly support the hypothesis that drugs of abuse hijack learning and memory mechanisms normally used for natural rewards. Importantly, Chen *et al.*⁵⁷ also observed that when rats were passively administered intravenous cocaine infusions, in similar temporal patterns and cocaine concentration, potentiation of AMPAR signaling in VTA DA cells was not observed. This finding suggests that the pharmacological effect of cocaine alone is insufficient to induce potentiation of AMPAR function on VTA DA neurons but that associative learning acquired during self-administration is necessary to induce AMPAR LTP in VTA DA neurons.

Of further interest is how this VTA in VTA DA cells is affected when drug-seeking behavior is extinguished. Remarkably, LTP in VTA DA neurons is not depotentiated when drug-seeking behavior is extinguished.⁵⁷ Also, this LTP was not further enhanced after the restoration of the drug-seeking response during a cue-induced reinstatement session. This persistent strengthening of the glutamate transmission supports the hypothesis that extinction training is not “unlearning” of old behavior but rather is a new form of learning that leaves the original memories intact.^{58,59} Further, it shows that neuroadaptations induced by drug self-administration can form a powerful “memory” that remains intact despite the absence of drug-seeking behaviors and may serve to trigger relapses activated by drug-associated cues.

The behavioral consequence of LTP in the VTA is further complicated by the recent findings that individual VTA DA neurons that project to different target regions, such as the prefrontal cortex or NAc,^{60,61} may express different receptors and thus may be differently modulated by drugs of abuse. In addition, subpopulations of DA neurons can also show strong activation by aversive stimuli,⁶² demonstrating that DA neurons do not respond only to reinforcing stimuli. Thus, because most studies that examine the effects of drugs of abuse on VTA neurons have not identified pathway-specific populations of VTA DA neurons, our understanding of the relationship between experience-dependent synaptic plasticity in these cells and their specific projection targets is incomplete. However, even with this caveat, many studies have shown that most VTA DA neurons exhibit a given plastic change (e.g., an increase in AMPAR signaling *in vitro* or *in vivo*^{23,26,35,37}) raising the possibility that both mesolimbic and mesocortical VTA DA neurons undergo experience-dependent plasticity after exposure to drugs of abuse.

Finally, drug exposure can affect other, nonglutamatergic transmission in the VTA, for example, by affecting GABAergic signaling.^{20,63,64} Although a comprehensive discussion of these other forms of synaptic plasticity goes beyond the scope of this review, it is critical to be mindful of other forms of plasticity that can be modulated by drugs of abuse and that all physiological changes induced by drugs must be considered to gain a complete understanding of the role of VTA neurons in modulating addictive behaviors after exposure to drugs of abuse.

Synaptic plasticity in the NAc induced by exposure to drugs of abuse

Changes in the NAc after single or repeated exposure to a drug of abuse are different from those seen in the VTA. In addition, we attempt to provide a comprehensive view of the various aspects of glutamatergic function might be different in the NAc core versus shell subregions. Some changes have been essentially examined in only one of the subregions, with many studies focusing primarily on the NAc core and other studies focusing on the shell, although in several cases both subregions have been examined. In addition, biochemical studies sometimes use tissues containing both NAc core and shell.

One *in vivo* cocaine exposure does not alter AMPAR activity in NAc neurons^{7,65} (but see Ref. ⁵³). However, one exposure to tetrahydrocannabinoids (THC) or cocaine does abolish the normally observed eCB-mediated NAc LTD. This is probably due to decreased surface levels of mGluR5^{42–44} (but see Ref. ⁶⁶). In addition, after chronic THC exposure, LTD induction can

occur, but through an mGluR2/3-dependent mechanism different from the normal mGluR5-dependent mechanism underlying NAcB LTD.⁴⁴

Like the VTA, repeated exposure to drugs of abuse can strongly modulate NAcB excitatory synaptic transmission. Glutamatergic plasticity has been examined primarily after repeated cocaine exposure, either passively through experimenter administration or actively through self-administration. Interestingly, several markers of AMPAR function are reduced in the NAcB shell during early withdrawal after repeated drug exposure.⁶⁷ Biochemical studies of NAcB AMPAR subunit levels during early withdrawal have produced more mixed results.^{68–73} Nonetheless, *in vitro* electrophysiological studies demonstrate that synaptic AMPAR-mediated currents in the NAcB are decreased during early withdrawal in the shell but not the core.^{47,67} Furthermore, the reduced AMPAR levels that can occur during LTD would allow a subsequent increase in the magnitude of LTP,^{27,74} and NAcB LTP is greater during early withdrawal.⁴⁶ Several ion channels in the NAcB are altered after repeated drug exposure, which decreases the intrinsic excitability of medium spiny neurons.⁷⁵ Interestingly, AMPA-mediated excitation of NAcB neurons *in vivo* is reduced during early withdrawal from cocaine,⁷⁶ which could be mediated by decreased AMPAR signaling or intrinsic excitability. Finally, repeated amphetamine exposure does not produce similar changes in NAcB AMPAR activity as are observed for cocaine.⁷⁷

Repeated drug exposure can also result in perhaps long-lasting changes in NAcB glutamatergic plasticity after protracted abstinence. Cocaine self-administration, but not yoked cocaine exposure, leads to a long-lasting disruption of induction of both LTD and LTP in NAcB neurons.^{78,79} LTD disruption is observed in the NAcB core but not the shell.⁷⁸ It has been proposed that disruption of LTD reflects loss of tonic mGluR5 signaling as a consequence of dysfunction in the cysteine–glutamate exchanger (see following discussion), whereas disruption of LTP reflects loss of tonic mGluR2/3 activation.⁷⁹ In addition, repeated passive cocaine exposure disrupts synaptic plasticity in hippocampal inputs to the NAcB.⁴⁸ Sensitization to cocaine is also associated with increased D1R inhibition of glutamate release in the NAcB,⁸⁰ although sensitization to amphetamine disrupts the DA receptor inhibition of NAcB LTP.²² Thus, short- and long-term neuroadaptations can occur in the NAcB during abstinence after repeated drug exposure.

Disruption of NAcB LTP induction after repeated drug exposure and abstinence could in part be mediated by an increase in the surface levels of AMPARs. Thus, if LTP expression requires trafficking of AMPARs to the surface membrane, this process could be occluded if AMPARs are already trafficked to the membrane as a result of repeated drug exposure. In fact, several lines of evidence indicate an increase in NAcB AMPAR activity after protracted abstinence. Biochemical studies have generally observed increased GluR cell surface expression and/or total GluR expression levels in the NAcB after repeated drug exposure^{68,70–73,81} (but see Refs. ⁶⁹ and ⁸²). Similar studies from the dorsal striatum have produced mixed results.^{73,83} Both GluR1 and GluR2 are increased at the cell surface in the NAcB after repeated passive drug exposure,⁷¹ in agreement with *in vitro* electrophysiological studies demonstrating an increase in NAcB AMPAR-mediated synaptic currents after sensitization with no change in the relative levels of synaptic GluR1- and GluR2-containing AMPARs.⁶⁷ In contrast, after active drug self-administration and protracted abstinence, cell surface levels of GluR1-type AMPAR subunits are increased in the NAcB,^{32,84} with a focus on the NAcB core³² and shell.⁸⁴ Increased surface AMPAR is confirmed by *in vitro* electrophysiological studies demonstrating the presence of GluR1 in the NAcB only after drug exposure.³² These studies also demonstrate that newly inserted GluR1 AMPAR subunits play a critical role in reinstatement of cocaine-seeking behavior. Interestingly, recent studies also demonstrate a role for altered GluR2 subunit phosphorylation and trafficking in both the NAcB core and shell in cocaine-primed reinstatement.^{85,86} Thus, studies generally agree that repeated passive or active drug exposure

and protracted abstinence are associated with increased NAc AMPAR signaling, although there are likely to be differences in the exact aspect of AMPAR function that is altered.

Repeated drug administration can also alter regulation of glutamate release in the NAc. Kalivas *et al.* have identified a series of neuroadaptations in the NAc after repeated cocaine and abstinence whereby a deficit in the cysteine–glutamate exchanger in glial cells leads to reduced uptake of glutamate and decreased basal levels of glutamate.^{75,87,88} Importantly, mGluR2/3 inhibition of NAc synaptic glutamate release depends tonically on this glial source of glutamate. Also, some groups have suggested that a reduction in basal glutamate signaling, perhaps in combination with reduced intrinsic excitability, may lead to homeostatic increases in AMPAR activity and glutamate release.^{75,89} Interestingly, restoring normal mGluR2/3 regulation of glutamate release can reduce cocaine reinstatement.⁹⁰ Finally, repeated drug exposure also decreases D2R inhibition of glutamate release in the NAc.⁹¹

Also interesting are recent studies suggesting that excitatory synaptic transmission in the NAc can be dynamically regulated by acute exposure to cocaine after abstinence from repeated drug exposure. Reexposure to cocaine during abstinence converts the increased NAc AMPAR function *in vitro* normally seen after sensitization to a decrease in AMPAR function that could reflect LTD.^{65,67} A switch in AMPAR function after cocaine reexposure is also observed in studies of locomotor activity after intra-NAc AMPA infusions¹⁵ and in biochemical studies of AMPAR expression.⁹² These studies raise the possibility that excitatory synapses in the NAc can be rapidly and strongly modulated by an animal's experience and that evidence for reduced AMPAR signaling during early withdrawal (described in the preceding) may reflect the fact that the animal has had recent exposure.

Recent studies have shown that glutamate receptors other than AMPAR may represent important neuroadaptations that contribute to drug-related behaviors after repeated drug exposure.⁸⁸ In particular, the expression of Homer proteins, which are scaffolding proteins that can bind to mGluRs and NMDARs, is altered in the NAc after repeated cocaine^{73,88}; protein levels of group I mGluRs (mGluR1 and 5) are also reduced. It has been suggested that group I mGluR activation can increase NAc glutamate levels and elicit locomotor activation, and thus these effects are blunted during abstinence from cocaine.

Drugs other than cocaine can also alter NAc AMPAR signaling.⁸⁸ Repeated morphine decreases expression levels of surface AMPARs⁹³ and prevents induction of LTD in the NAc.¹⁸ These findings perhaps concur with the observation that repeated morphine decreases NAc dendritic spine density⁹⁴ but that repeated psychostimulant exposure increases spine density.^{95–97} Repeated psychostimulants can also reduce presynaptic markers.⁹⁸

With the number of neuroadaptations that can occur in the NAc in relation to drug exposure, it is critical to understand the behavioral importance of any given change. In this regard, the studies described earlier have used agents, such as peptides selective for GluR1 and GluR2 AMPAR subunits, in order to understand the role of these particular AMPAR subunits in drug-related behaviors. Importantly, infusion of agents that interfere with GluR1 or GluR2 into the NAc significantly reduces reinstatement for cocaine,^{32,84–86} indicating that neuroadaptations in NAc GluR1s and GluR2s may be causally associated with drug-related motivation. In addition, longer periods of abstinence after repeated cocaine are associated with more NAc neurons' firing phasically in response to cocaine-predictive cues.⁹⁹

Plastic changes in NAc AMPARs described in the preceding may also help explain the results from other behavioral studies. For example, increased surface AMPARs after sensitization could underlie the enhanced ability of AMPA infusion into the NAc to increase locomotion⁸ or reinstatement.¹⁰⁰ On the other hand, a peptide that inhibits GluR2 trafficking disrupts NAc LTD induction *in vitro* and prevents the expression of behavioral sensitization

when injected into the NAc; NAc LTD could thus be necessary for this expression of behavioral sensitization.¹⁰¹ In addition, increasing GluR1 in the NAc by using viral overexpression can decrease reward processing,^{102,103} whereas increased NAc GluR2 can have the opposite effect and increase reward processing.^{102,104}

Taken together, these results suggest that exposure to drugs of abuse can have complex effects of NAc glutamatergic synaptic signaling. Nonetheless, several studies agree that neuroadaptations that enhance NAc AMPAR signaling or decrease basal glutamate release after repeated cocaine exposure and abstinence can contribute critically to reinstatement.^{32, 75,84}

Conclusion

The studies summarized in this review show that DA can modulate several forms of synaptic plasticity in the mesolimbic system. This may be particularly important for the modulation of excitatory synaptic transmission during and after exposure to drugs of abuse. In addition to providing information about the critical neural adaptations underlying reward-associated learning and maladaptive drug seeking, the types of studies reviewed here will probably produce a variety of novel targets for therapeutic drugs aimed at improving treatment of substance abuse and addiction.

References

- Schultz W. Predictive reward signal of dopamine neurons. *J Neurophysiol* 1998;80:1–27. [PubMed: 9658025]
- Mogenson GJ, Jones DL, Yim CY. From motivation to action: functional interface between the limbic system and the motor system. *Prog Neurobiol* 1980;14:69–97. [PubMed: 6999537]
- Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev* 1993;18:247–291. [PubMed: 8401595]
- Kalivas PW, McFarland K. Brain circuitry and the reinstatement of cocaine-seeking behavior. *Psychopharmacology* 2003;168:44–56. [PubMed: 12652346]
- Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* 2005;8:1481–1489. [PubMed: 16251991]
- Meredith GE, et al. The structural basis for mapping behavior onto the ventral striatum and its subdivisions. *Brain Struct Funct* 2008;213:17–27. [PubMed: 18256852]
- Thomas MJ, Kalivas PW, Shaham Y. Neuroplasticity in the mesolimbic dopamine system and cocaine addiction. *Br J Pharmacol* 2008;154:327–342. [PubMed: 18345022]
- Pierce RC, et al. Repeated cocaine augments excitatory amino acid transmission in the nucleus accumbens only in rats having developed behavioral sensitization. *J Neurosci* 1996;16:1550–1560. [PubMed: 8778304]
- Di Ciano P, et al. Differential involvement of NMDA, AMPA/kainate, and dopamine receptors in the nucleus accumbens core in the acquisition and performance of pavlovian approach behavior. *J Neurosci* 2001;21:9471–9477. [PubMed: 11717381]
- Parkinson JA, et al. Dissociation in effects of lesions of the nucleus accumbens core and shell on appetitive pavlovian approach behavior and the potentiation of conditioned reinforcement and locomotor activity by D-amphetamine. *J Neurosci* 1999;19:2401–2411. [PubMed: 10066290]
- See RE, Elliott JC, Feltenstein MW. The role of dorsal vs ventral striatal pathways in cocaine-seeking behavior after prolonged abstinence in rats. *Psychopharmacology* 2007;194:321–331. [PubMed: 17589830]
- Parkinson JA, et al. Nucleus accumbens dopamine depletion impairs both acquisition and performance of appetitive Pavlovian approach behaviour: implications for mesoaccumbens dopamine function. *Behav Brain Res* 2002;137:149–163. [PubMed: 12445721]
- Yun IA, et al. The ventral tegmental area is required for the behavioral and nucleus accumbens neuronal firing responses to incentive cues. *J Neurosci* 2004;24:2923–2933. [PubMed: 15044531]

14. Schmidt HD, Pierce RC. Cooperative activation of D1-like and D2-like dopamine receptors in the nucleus accumbens shell is required for the reinstatement of cocaine-seeking behavior in the rat. *Neuroscience* 2006;142:451–461. [PubMed: 16844308]
15. Bachtell RK, Self DW. Renewed cocaine exposure produces transient alterations in nucleus accumbens AMPA receptor-mediated behavior. *J Neurosci* 2008;28:12808–12814. [PubMed: 19036973]
16. Di Chiara G. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. *Behav Brain Res* 2002;137:75–114. [PubMed: 12445717]
17. Bonci A, Malenka RC. Properties and plasticity of excitatory synapses on dopaminergic and GABAergic cells in the ventral tegmental area. *J Neurosci* 1999;19:3723–3730. [PubMed: 10234004]
18. Robbe D, Bockaert J, Manzoni OJ. Metabotropic glutamate receptor 2/3-dependent long-term depression in the nucleus accumbens is blocked in morphine withdrawn mice. *Eur J Neurosci* 2002;16:2231–2235. [PubMed: 12473091]
19. Bellone C, Lüscher C. mGluRs induce a long-term depression in the ventral tegmental area that involves a switch of the subunit composition of AMPA receptors. *Eur J Neurosci* 2005;21:1280–1288. [PubMed: 15813937]
20. Liu QS, Pu L, Poo MM. Repeated cocaine exposure in vivo facilitates LTP induction in midbrain dopamine neurons. *Nature* 2005;437:1027–1031. [PubMed: 16222299]
21. Pennartz CM, et al. Synaptic plasticity in an in vitro slice preparation of the rat nucleus accumbens. *Eur J Neurosci* 1993;5:107–117. [PubMed: 7903183]
22. Li Y, Kauer JA. Repeated exposure to amphetamine disrupts dopaminergic modulation of excitatory synaptic plasticity and neurotransmission in nucleus accumbens. *Synapse* 2004;51:1–10. [PubMed: 14579420]
23. Argilli E, et al. Mechanism and time course of cocaine-induced long-term potentiation in the ventral tegmental area. *J Neurosci* 2008;28:9092–9100. [PubMed: 18784289]
24. Nugent FS, et al. High-frequency afferent stimulation induces long-term potentiation of field potentials in the ventral tegmental area. *Neuropsychopharmacology* 2008;33:1704–1712. [PubMed: 17851541]
25. Schotanus SM, Chergui K. Dopamine D1 receptors and group I metabotropic glutamate receptors contribute to the induction of long-term potentiation in the nucleus accumbens. *Neuropharmacology* 2008;54:837–844. [PubMed: 18272187]
26. Stuber GD, et al. Reward-predictive cues enhance excitatory synaptic strength onto midbrain dopamine neurons. *Science* 2008;321:1690–1692. [PubMed: 18802002]
27. Kauer JA, Malenka RC. Synaptic plasticity and addiction. *Nat Rev Neurosci* 2007;8:844–858. [PubMed: 17948030]
28. Lüscher C, et al. Role of AMPA receptor cycling in synaptic transmission and plasticity. *Neuron* 1999;24:649–658. [PubMed: 10595516]
29. Thomas MJ, Malenka RC, Bonci A. Modulation of long-term depression by dopamine in the mesolimbic system. *J Neurosci* 2000;20:5581–5586. [PubMed: 10908594]
30. Bellone C, Lüscher C. Cocaine triggered AMPA receptor redistribution is reversed in vivo by mGluR-dependent long-term depression. *Nat Neurosci* 2006;9:636–641. [PubMed: 16582902]
31. Mameli M, et al. Rapid synthesis and synaptic insertion of GluR2 for mGluR-LTD in the ventral tegmental area. *Science* 2007;317:530–533. [PubMed: 17656725]
32. Conrad KL, et al. Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. *Nature* 2008;454:118–121. [PubMed: 18500330]
33. Overton PG, et al. Long-term potentiation at excitatory amino acid synapses on midbrain dopamine neurons. *Neuroreport* 1999;10:221–226. [PubMed: 10203312]
34. Jones S, Kornblum JL, Kauer JA. Amphetamine blocks long-term synaptic depression in the ventral tegmental area. *J Neurosci* 2000;20:5575–5580. [PubMed: 10908593]
35. Ungless MA, et al. Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. *Nature* 2001;411:583–587. [PubMed: 11385572]
36. Saal D, et al. Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. *Neuron* 2003;37:577–582. [PubMed: 12597856]

37. Luu P, Malenka RC. Spike timing-dependent long-term potentiation in ventral tegmental area dopamine cells requires PKC. *J Neurophysiol* 2008;100:533–538. [PubMed: 18450581]
38. Gutlerner JL, et al. Novel protein kinase A-dependent long-term depression of excitatory synapses. *Neuron* 2002;36:921–931. [PubMed: 12467595]
39. Manzoni O, Michel JM, Bockaert J. Metabotropic glutamate receptors in the rat nucleus accumbens. *Eur J Neurosci* 1997;9:1514–1523. [PubMed: 9240409]
40. Calabresi P, et al. Coactivation of D1 and D2 dopamine receptors is required for long-term synaptic depression in the striatum. *Neurosci Lett* 1992;142:95–99. [PubMed: 1357611]
41. Kreitzer AC, Malenka RC. Dopamine modulation of state-dependent endocannabinoid release and long-term depression in the striatum. *J Neurosci* 2005;25:10537–10545. [PubMed: 16280591]
42. Fourgeaud L, et al. A single in vivo exposure to cocaine abolishes endocannabinoid-mediated long-term depression in the nucleus accumbens. *J Neurosci* 2004;24:6939–6945. [PubMed: 15295029]
43. Mato S, et al. A single in-vivo exposure to delta 9THC blocks endocannabinoid-mediated synaptic plasticity. *Nat Neurosci* 2004;7:585–586. [PubMed: 15146190]
44. Mato S, et al. Presynaptic homeostatic plasticity rescues long-term depression after chronic Delta 9-tetrahydrocannabinol exposure. *J Neurosci* 2005;25:11619–11627. [PubMed: 16354920]
45. Kombian SB, Malenka RC. Simultaneous LTP of non-NMDA- and LTD of NMDA-receptor-mediated responses in the nucleus accumbens. *Nature* 1994;368:242–246. [PubMed: 7908412]
46. Yao WD, et al. Identification of PSD-95 as a regulator of dopamine-mediated synaptic and behavioral plasticity. *Neuron* 2004;41:625–638. [PubMed: 14980210]
47. Schramm-Sapota NL, Olsen CM, Winder DG. Cocaine self-administration reduces excitatory responses in the mouse nucleus accumbens shell. *Neuropsychopharmacology* 2006;31:1444–1451. [PubMed: 16205778]
48. Goto Y, Grace AA. Dopamine-dependent interactions between limbic and prefrontal cortical plasticity in the nucleus accumbens: disruption by cocaine sensitization. *Neuron* 2005;47:255–266. [PubMed: 16039567]
49. Charpier S, Deniau JM. In vivo activity-dependent plasticity at corticostriatal connections: evidence for physiological long-term potentiation. *Proc Natl Acad Sci USA* 1997;94:7036–7040. [PubMed: 9192687]
50. Charpier S, Mahon S, Deniau JM. In vivo induction of striatal long-term potentiation by low-frequency stimulation of the cerebral cortex. *Neuroscience* 1999;91:1209–1222. [PubMed: 10391430]
51. Kreitzer AC, Malenka RC. Endocannabinoid-mediated rescue of striatal LTD and motor deficits in Parkinson's disease models. *Nature* 2007;445:643–647. [PubMed: 17287809]
52. Shen W, et al. Dichotomous dopaminergic control of striatal synaptic plasticity. *Science* 2008;321:848–851. [PubMed: 18687967]
53. Grignaschi G, et al. A single high dose of cocaine induces behavioural sensitization and modifies mRNA encoding GluR1 and GAP-43 in rats. *Eur J Neurosci* 2004;20:2833–2837. [PubMed: 15548228]
54. Wanat MJ, et al. Strain specific synaptic modifications on ventral tegmental area dopamine neurons after ethanol exposure. *Biol Psychiatry* 2009;65:646–653. [PubMed: 19118821]
55. Borgland SL, et al. Orexin A in the VTA is critical for the induction of synaptic plasticity and behavioral sensitization to cocaine. *Neuron* 2006;49:589–601. [PubMed: 16476667]
56. Schilstrom B, et al. Cocaine enhances NMDA receptor-mediated currents in ventral tegmental area cells via dopamine D5 receptor-dependent redistribution of NMDA receptors. *J Neurosci* 2006;26:8549–8558. [PubMed: 16914681]
57. Chen BT, et al. Cocaine but not natural reward self-administration nor passive cocaine infusion produces persistent LTP in the VTA. *Neuron* 2008;59:288–297. [PubMed: 18667156]
58. Bouton ME. Context and behavioral processes in extinction. *Learn Mem* 2004;11:485–494. [PubMed: 15466298]
59. Myer KM, Davis M. Mechanisms of fear extinction. *Mol Psychiatry* 2007;12:120–150. [PubMed: 17160066]

60. Margolis EB, et al. The ventral tegmental area revisited: is there an electrophysiological marker for dopaminergic neurons? *J Physiol* 2006;577:907–924. [PubMed: 16959856]
61. Lammel S, et al. Unique properties of meso-prefrontal neurons within a dual mesocorticolimbic dopamine system. *Neuron* 2008;57:760–773. [PubMed: 18341995]
62. Brischoux F, et al. Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. *Proc Natl Acad Sci USA* 2009;106:4894–4899. [PubMed: 19261850]
63. Nugent FS, Kauer JA. LTP of GABAergic synapses in the ventral tegmental area and beyond. *J Physiol* 2008;586:1487–1493. [PubMed: 18079157]
64. Pan B, Hillard CJ, Liu QS. Endocannabinoid signaling mediates cocaine-induced inhibitory synaptic plasticity in midbrain dopamine neurons. *J Neurosci* 2008;28:1385–1397. [PubMed: 18256258]
65. Thomas MJ, et al. Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine. *Nat Neurosci* 2001;4:1217–1223. [PubMed: 11694884]
66. Hoffman AF, et al. Functional tolerance and blockade of long-term depression at synapses in the nucleus accumbens after chronic cannabinoid exposure. *J Neurosci* 2003;23:4815–4820. [PubMed: 12832502]
67. Kourrich S, et al. Cocaine experience controls bidirectional synaptic plasticity in the nucleus accumbens. *J Neurosci* 2007;27:7921–7928. [PubMed: 17652583]
68. Churchill L, et al. Repeated cocaine alters glutamate receptor subunit levels in the nucleus accumbens and ventral tegmental area of rats that develop behavioral sensitization. *J Neurochem* 1999;72:2397–2403. [PubMed: 10349849]
69. Lu W, Wolf ME. Repeated amphetamine administration alters AMPA receptor subunit expression in rat nucleus accumbens and medial prefrontal cortex. *Synapse* 1999;32:119–131. [PubMed: 10231131]
70. Lu L, et al. Molecular neuroadaptations in the accumbens and ventral tegmental area during the first 90 days of forced abstinence from cocaine self-administration in rats. *J Neurochem* 2003;85:1604–1613. [PubMed: 12787079]
71. Boudreau AC, Wolf ME. Behavioral sensitization to cocaine is associated with increased AMPA receptor surface expression in the nucleus accumbens. *J Neurosci* 2005;25:9144–9151. [PubMed: 16207873]
72. Hemby SE, et al. Cocaine-induced alterations in nucleus accumbens ionotropic glutamate receptor subunits in human and non-human primates. *J Neurochem* 2005;95:1785–1793. [PubMed: 16363995]
73. 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;159:414–426. [PubMed: 19105975]
74. Fino E, Glowinski J, Venance L. Bidirectional activity-dependent plasticity at corticostriatal synapses. *J Neurosci* 2005;25:11279–11287. [PubMed: 16339023]
75. Kalivas PW, Hu XT. Exciting inhibition in psychostimulant addiction. *Trends Neurosci* 2006;29:610–616. [PubMed: 16956674]
76. White FJ, et al. Repeated administration of cocaine or amphetamine alters neuronal responses to glutamate in the mesoaccumbens dopamine system. *J Pharmacol Exp Ther* 1995;273:445–454. [PubMed: 7714800]
77. Nelson CL, et al. Behavioral sensitization to amphetamine is not accompanied by changes in glutamate receptor surface expression in the rat nucleus accumbens. *J Neurochem* 2009;109:25–51. [PubMed: 19183256]
78. Martin M, et al. Cocaine self-administration selectively abolishes LTD in the core of the nucleus accumbens. *Nat Neurosci* 2006;9:868–869. [PubMed: 16732275]
79. Moussawi K, et al. N-Acetylcysteine reverses cocaine-induced metaplasticity. *Nat Neurosci* 2009;12:182–189. [PubMed: 19136971]
80. Beurrier C, Malenka RC. Enhanced inhibition of synaptic transmission by dopamine in the nucleus accumbens during behavioral sensitization to cocaine. *J Neurosci* 2002;22:5817–5822. [PubMed: 12122043]

81. Zhang X, et al. Reversal of cocaine-induced behavioral sensitization and associated phosphorylation of the NR2B and GluR1 subunits of the NMDA and AMPA receptors. *Neuropsychopharmacology* 2007;32:377–387. [PubMed: 16794574]
82. Sutton MA, et al. Extinction-induced upregulation in AMPA receptors reduces cocaine-seeking behaviour. *Nature* 2003;421:70–75. [PubMed: 12511956]
83. Kim M, et al. AMPA receptor trafficking in the dorsal striatum is critical for behavioral sensitization to cocaine in juvenile mice. *Biochem Biophys Res Commun* 2009;379:65–69. [PubMed: 19070590]
84. Anderson SM, et al. CaMKII: a biochemical bridge linking accumbens dopamine and glutamate systems in cocaine seeking. *Nat Neurosci* 2008;11:344–353. [PubMed: 18278040]
85. Famous KR, et al. Phosphorylation-dependent trafficking of GluR2-containing AMPA receptors in the nucleus accumbens plays a critical role in the reinstatement of cocaine seeking. *J Neurosci* 2008;28:11061–11070. [PubMed: 18945913]
86. Ping A, et al. Contributions of nucleus accumbens core and shell GluR1 containing AMPA receptors in AMPA- and cocaine-primed reinstatement of cocaine-seeking behavior. *Brain Res* 2008;1215:173–182. [PubMed: 18486119]
87. Kau KS, et al. Blunted cystine-glutamate antiporter function in the nucleus accumbens promotes cocaine-induced drug seeking. *Neuroscience* 2008;155:530–537. [PubMed: 18601982]
88. Szumlinski KK, Ary AW, Lominac KD. Homers regulate drug-induced neuroplasticity: implications for addiction. *Biochem Pharmacol* 2008;75:112–133. [PubMed: 17765204]
89. Bossert JM, et al. Neurobiology of relapse to heroin and cocaine seeking: an update and clinical implications. *Eur J Pharmacol* 2005;526:36–50. [PubMed: 16289451]
90. Baker DA, et al. Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. *Nat Neurosci* 2003;6:743–749. [PubMed: 12778052]
91. Brady AM, O'Donnell P. Dopaminergic modulation of prefrontal cortical input to nucleus accumbens neurons in vivo. *J Neurosci* 2004;24:1040–1049. [PubMed: 14762122]
92. Boudreau AC, et al. Cell surface AMPA receptors in the rat nucleus accumbens increase during cocaine withdrawal but internalize after cocaine challenge in association with altered activation of mitogen-activated protein kinases. *J Neurosci* 2007;27:10621–10635. [PubMed: 17898233]
93. Glass MJ, et al. Chronic administration of morphine is associated with a decrease in surface AMPA GluR1 receptor subunit in dopamine D1 receptor expressing neurons in the shell and non-D1 receptor expressing neurons in the core of the rat nucleus accumbens. *Exp Neurol* 2008;210:750–761. [PubMed: 18294632]
94. Robinson TE, et al. Widespread but regionally specific effects of experimenter- versus self-administered morphine on dendritic spines in the nucleus accumbens, hippocampus, and neocortex of adult rats. *Synapse* 2002;46:271–279. [PubMed: 12373743]
95. Li Y, Acerbo MJ, Robinson TE. The induction of behavioural sensitization is associated with cocaine-induced structural plasticity in the core (but not shell) of the nucleus accumbens. *Eur J Neurosci* 2004;20:1647–1654. [PubMed: 15355332]
96. Lee KW, et al. Cocaine-induced dendritic spine formation in D1 and D2 dopamine receptor-containing medium spiny neurons in nucleus accumbens. *Proc Natl Acad Sci USA* 2006;103:3399–3404. [PubMed: 16492766]
97. Toda S, et al. Cocaine increases actin cycling: effects in the reinstatement model of drug seeking. *J Neurosci* 2006;26:1579–1587. [PubMed: 16452681]
98. Subramaniam S, Marcotte ER, Srivastava LK. Differential changes in synaptic terminal protein expression between nucleus accumbens core and shell in the amphetamine-sensitized rat. *Brain Res* 2001;901:175–183. [PubMed: 11368965]
99. Hollander JA, Carelli RM. Abstinence from cocaine self-administration heightens neural encoding of goal-directed behaviors in the accumbens. *Neuropsychopharmacology* 2005;30:1464–1474. [PubMed: 15856078]
100. Suto N, et al. Previous exposure to psychostimulants enhances the reinstatement of cocaine seeking by nucleus accumbens AMPA. *Neuropsychopharmacology* 2004;29:2149–2159. [PubMed: 15266353]
101. Brebner K, et al. Nucleus accumbens long-term depression and the expression of behavioral sensitization. *Science* 2005;310:1340–1343. [PubMed: 16311338]

102. Todtenkopf MS, et al. Brain reward regulated by AMPA receptor subunits in nucleus accumbens shell. *J Neurosci* 2006;26:11665–11669. [PubMed: 17093088]
103. Bachtell RK, et al. Role of GluR1 expression in nucleus accumbens neurons in cocaine sensitization and cocaine-seeking behavior. *Eur J Neurosci* 2008;27:2229–2240. [PubMed: 18430032]
104. Kelz MB, et al. Expression of the transcription factor deltaFosB in the brain controls sensitivity to cocaine. *Nature* 1999;401:272–276. [PubMed: 10499584]