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Drug-evoked synaptic plasticity: beyond metaplasticity

Meaghan C Creed[1] and Christian Lüscher[1,2]

Addictive drugs such as cocaine induce synaptic plasticity in the ventral tegmental area and its projection areas, which may represent the cellular correlate of an addiction trace. Cocaine induces changes in excitatory transmission primarily in the VTA, which persists for days after a single exposure. These initial alterations in synaptic transmission represent a metaplasticity that is permissive for late stages of remodeling throughout the mesocorticolimbic circuitry, specifically in the NAc. Specific synaptic and cellular changes in the NAc persist following prolonged exposure to cocaine, and this remodeling may contribute to altered behavior. By manipulating synaptic activity in the NAc, it may be possible to reverse pathological synaptic transmission and its associated abnormal behavior following exposure to addictive drugs.

Addresses
[1] Department of Basic Neuroscience, Rue Michel-Servet 1, University of Geneva, 1211 Geneva, Switzerland
[2] Clinic of Neurology, University of Geneva, 1211 Geneva, Switzerland

Corresponding author: Lüscher, Christian (christian.luscher@unige.ch)

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Introduction

Addiction is a disease that evolves in multiple steps, from an initial high to casual use, which may transition into compulsive drug consumption with repetitive exposure [1]. While addictive drugs have different initial pharmacological mechanisms, they ultimately remodel the brain's reward circuitry, which may underlie behavioral changes associated with later stages of the addiction cycle. Here we review current evidence suggesting that drugs of abuse induce a staged form of plasticity. This process starts with permissive changes in the ventral tegmental area (VTA) caused by the first exposure to an addictive drug, which allow for subsequent changes throughout the mesocorticolimbic system, in particular the nucleus accumbens (NAc). In this sense, early forms of drug-evoked synaptic plasticity qualify as metaplasticity that alters the rules for activity-dependent plasticity, rather than encoding specific events. We argue that with insight into the molecular mechanism of drug-evoked synaptic plasticity, it may become possible to design interventions to restore normal synaptic transmission, which may provide valuable treatment strategies for addiction.

Convergence on common mechanism of addictive drugs

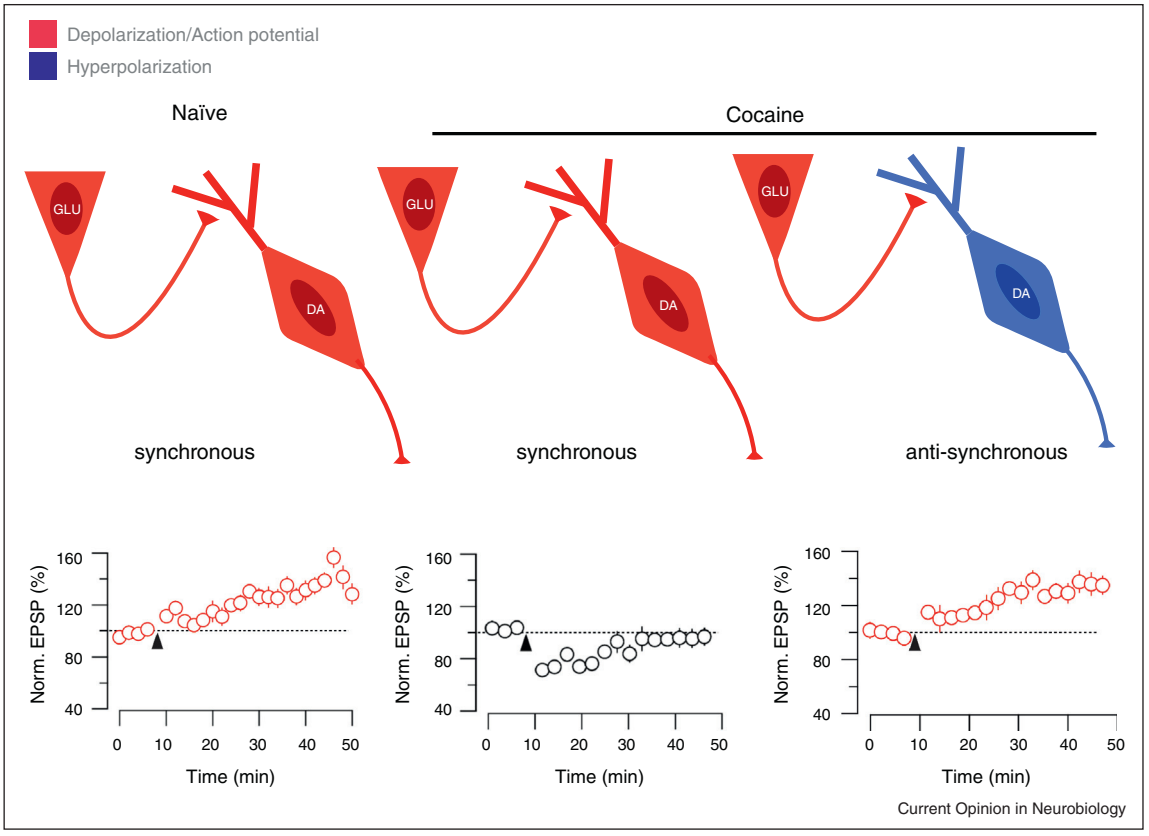
Despite their chemical diversity and individual molecular targets, all addictive drugs act on the VTA to increase mesolimbic dopamine (DA) levels [2,3] through distinct mechanisms [4]. Nicotine increases firing of DA neurons through $\alpha4\beta2$-containing nicotinic receptors that are expressed on these DA neurons [5], whereas opioids [6], γ-hydroxybutyrate [7], cannabinoids [8], and benzodiazepines [9] decrease activity of GABAergic interneurons in the VTA and thus disinhibit dopamine neurons. Finally, psychostimulants (cocaine, amphetamines, and ecstasy) target the DA transporter (DAT), increasing DA in the VTA as well as in its projection regions, the NAc and prefrontal cortex (PFC). Moreover, we have reported that optogenetically driving activity of VTA DA neurons can mimic the synaptic effects of addictive drugs [10], further suggesting that this increase in DA is sufficient for drug-induced synaptic effects.

However, the drug-induced increase in DA is transient, whereas the switch to compulsive drug use is driven by neural changes that outlast the actual presence of the drug in the brain. Given the role of DA as a neuromodulator, drug-induced increases in phasic DA release (i.e. a quick and strong release of DA caused by a burst of action potentials) may encode changes in glutamate or GABA transmission, which in turn may reflect a so-called 'memory trace' left by addictive drugs after they have been cleared from the brain [11]. Below, we discuss how serial changes in excitatory transmission in the VTA and NAc contribute to the development of addiction and how reversing drug-induced plasticity modifies pathological behavior.

An early form of metaplasticity in the VTA

Changes in excitatory transmission onto DA neurons of the VTA occur after a single injection of cocaine, and are permissive for later stages of plasticity in the mesolimbic reward system (Figure 1). An increase in excitatory synaptic strength, measured as an increase in the AMPA:NMDA ratio *ex vivo*, has been reported within hours of a single exposure to cocaine [12••,13]. An occlusion of spike-dependent long-term potentiation (LTP) normally observed in naïve animals is observed following a single cocaine injection, which is attributed to a saturation of AMPAR following cocaine [12••,14]. This plasticity is induced by all addictive drugs tested to date and persists for a week following noncontingent

Figure 1



Cocaine inverts rules for activity-dependant plasticity in the VTA. In the naïve state, synchronous presynaptic and postsynaptic depolarization elicits LTP in the postsynaptic neurons (left). After a single cocaine exposure induction criteria are altered (center and right panel). A classical protocol of presynaptic activity combined with postsynaptic depolarization is no longer capable of inducing LTP (center). However, LTP can be rescued in these neurons by an antihebbian form of plasticity, in which LTP is induced by presynaptic release paired with hyperpolarized membrane potentials (right). This metaplasticity induced by cocaine is likely to occur with other addictive drugs and inverts rules for activity-dependent synaptic potentiation in the VTA. Data from Ref. [25••].

administration [15,16] or months following self-administration [17]. The increase in AMPA:NMDA ratio occurs through a dual expression mechanism involving both AMPA and NMDA receptors.

Several pieces of evidence indicate that cocaine drives the insertion of AMPA receptors that lack the subunit GluA2 [18]. Specifically, cocaine treatment increases expression of GluA1 subunit in DA neurons of the VTA [19,20]. In midbrain slices *ex vivo* prepared after cocaine treatment, the amplitude of inward currents measured at negative potentials is larger than the amplitude of outward currents at corresponding positive potential. This leads to a change in slope of the current voltage relationship and is referred to as inward rectification. In addition, GluA2-lacking AMPA receptors are sensitive to polyamines, such as the toxin from the Joro spider or the wasp venom philantotoxine [18]. There are two major functional consequences of the insertion of GluA2-lacking receptors. AMPARs become calcium permeable and the current amplitude increases because of the higher single channel conductance. Cocaine therefore switches transmission close to resting potential from calcium impermeable (AMPARs are impermeable and NMDARs not sufficiently depolarized) to calcium permeable glutamate transmission.

Cocaine therefore not only increases efficacy of synaptic transmission, but this switch in subunit composition may alter associated signaling cascades, which has been implicated in behavioral sensitization [21]. GluA1 overexpression seems in fact sufficient to elicit sensitization in drug-naïve rats, an effect that can be blunted when GluA2 is overexpressed [22•]. Furthermore, in mice lacking GluA1, context-dependent associative components of sensitization and CPP are abolished [23].

Since GluA2-lacking AMPA receptors have a larger single channel conductance than GluA2-containing receptors, insertion in DA neurons could be sufficient to cause both

inward rectification and increase in AMPA:NMDA ratio. However, since GluA2-lacking AMPARs conduct poorly at positive potentials, their insertion alone cannot explain the increase in AMPA:NMDA ratio measured at depolarized potentials (+40 mV). Alterations in NMDA receptor subunit and function have also been documented in the VTA following acute cocaine exposure, and may also contribute to the increased AMPA:NMDA ratio [24].

We confirmed this NMDA involvement using two-photon laser photolysis of caged glutamate to evoke unitary EPSCs and pharmacologically isolated NMDAR currents [13]. In this preparation, we found that unitary AMPA EPSCs amplitudes were larger after cocaine treatment along with rectifying current voltage curves, while unitary NMDARs were reduced [25••]. The noncanonical NR2B receptor subunit has been implicated in these NMDA effects; following cocaine exposure, newly synthesized NR2B subunits are incorporated into synaptic NMDARs [26]. These NR2B subunits contribute to the increase in AMPA:NMDA ratio, since antagonism with ifenprodil attenuated the increase cocaine-induced increase in AMPAR/NMDAR ratio [24]. As a consequence of these receptor alterations, plasticity that relies on calcium influx through AMPARs independently of NMDARs becomes possible in VTA neurons following cocaine [25••]. This form of permissive plasticity requires pairing presynaptic activity with postsynaptic hyperpolarization [27], and inverts rules for activity-dependent synaptic plasticity in the VTA (Figure 1).

In summary, the capacity of acute cocaine exposure to induce a metaplasticity, allowing for a further strengthening of these drug-potentiated synapses, relies on GluA2-lacking AMPAR activation and NDMA receptor subunit redistribution in favor of NR2B-containing receptors. As we will discuss, this cocaine-evoked plasticity in the VTA, when present for prolonged periods of time, can trigger synaptic changes downstream in the NAc [28••,13].

A chain of staged forms of drug-evoked synaptic plasticity

Synaptic strengthening of the VTA following a single cocaine exposure can be observed as early as 4 hours after the injection [29], and returns to baseline within approximately 7 days. After several noncontingent cocaine injections, the plasticity is also reversed within 5–7 days following cessation of cocaine exposure [16]. This reversal is due to endogenous activation of mGluR1, which elicits a form of synaptic long-term depression (LTD) by removing GluR2-containing AMPA receptors from the synaptic membrane [18]. However, plasticity in the NAc typically takes multiple cocaine treatments over several days to arise [30,31].

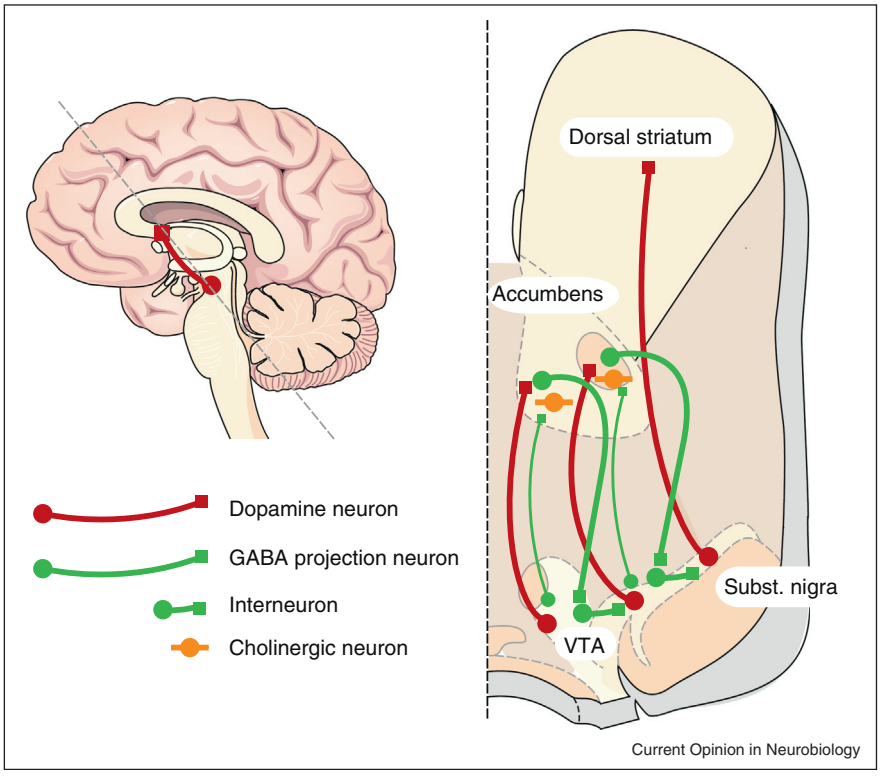
The midbrain and the striatum are connected by a series of spiraling projections (Figure 2). DA neurons in the medial VTA project to the medial shell of the NAc. Back-projections are GABAergic and reach the VTA more laterally, which after several loops reaches the substantia nigra, from whether the DA projections go to the dorsal striatum [32•,33•]. The immediate targets of the VTA DA neurons are medium spiny neurons (MSNs) in the NAc, which themselves project to the VTA with a preference for GABA interneurons [34]. Recently, we have shown that in addition to providing local inhibition, VTA GABA neurons project to cholinergic interneurons in the NAc, where they pause cholinergic interneuron firing [35]. In this way, inhibitory neurons of the VTA modulate dopaminergic and cholinergic tone in the NAc, and powerfully influence MSN activity (Figure 2). Disrupting this spiraling connectivity, either physically or pharmacologically, attenuates cocaine-seeking behavior [36••,37]. The spiral is engaged sequentially during the development of addiction with synaptic plasticity induced early in the spiral amplifying signals as they pass through the system and makes it easier to induce plasticity later in the spiral. If this were the case, one would predict that the changes in the plasticity in the nucleus accumbens (described below) would take place late in the development of addiction and would be contingent on plasticity in the VTA. Indeed, we have shown that initial plasticity in the VTA triggers changes in the synaptic plasticity of NAc MSNs [13]. Moreover, reversing cocaine-induced changes in the VTA also leads to the reversal of enhanced plasticity in the NAc [13].

Plasticity in the nucleus accumbens

Over 95% of the cells within the NAc are GABAergic MSNs, which receive excitatory inputs from the PFC, the ventral subiculum of the hippocampus, the basolateral amygdala, and the thalamus, as well as dopaminergic input from the VTA [38]. These excitatory synapses can express multiple forms activity-dependent plasticity [39], which has been implicated in the behavioral adaptations elicited by administration of drugs of abuse [40,41].

Specifically, following acute cocaine exposure, the AMPA:NMDA ratio in NAc MSNs is decreased [31,42] and LTD is occluded [43]. However, several weeks following withdrawal, surface levels of AMPA [44] and the AMPA:NMDA ratio are increased [31]. A day after a challenge dose of cocaine, terminating this withdrawal, both the surface levels of AMPARs and the AMPAR/NMDAR ratio in NAc MSNs are decreased, although both parameters recovered and stabilized at an enhanced level during subsequent protracted withdrawal [45]. A further synaptic adaptation occurring in the NAc following protracted withdrawal is the exchange of subunit GluA2 in a proportion of AMPA receptors [28••]. As discussed above, the removal of GluA2 subunits renders

Figure 2



Spiraling connectivity between the midbrain and striatum. The VTA and accumbens are connected by a series of spiraling connections, where the ascending limbs are long range DA and GABA projections and the back-projections are GABAergic. The VTA sends both DA and GABAergic projections to the accumbens, with dopaminergic neurons projecting primarily to MSNs, and GABAergic neurons preferentially innervating cholinergic interneurons. Cholinergic interneurons in the accumbens regulate firing of MSNS; in this way the VTA orchestrates MSN activity through both cholinergic and dopaminergic modulation. MSNs in turn project back to GABAergic neurons of the VTA, which provide local inhibitory control in the midbrain. Modified from Ref. [53].

receptors permeable to calcium which has implications for synaptic efficacy and signaling. As in the VTA, this change in subunit composition in MSNs may involve the membrane insertion of NMDA receptor rich in the NR2B subunit [26].

Just as in the dorsal striatum, MSNs of the accumbens fall into two classes based on the DA receptor they express [46]. Using transgenic mice expressing reporter proteins exclusively in the D1 or D2 containing neurons, we reported that cocaine occluded the induction of LTP in D1, but not D2 positive MSNs [47••]. By analyzing unitary events, this study confirmed that cocaine selectively potentiates cortical afferents onto D1 MSNs. These results are consistent with studies demonstrating expression of the plasticity-related gene, p-ERK, in D1but not D2 MSNs following cocaine treatment [48]. In an initial experiment linking this potentiation to behavior, pharmacological inhibition of ERK phosphorylation in D1-MSNs reversed locomotor sensitization to cocaine [49].

Reversal of drug induced plasticity

Having determined that cocaine-induced synaptic potentiation is dependent on ERK phosphorylation, and this plasticity mechanism underlies locomotor sensitization to cocaine, we sought to develop an *in vivo* stimulation protocol that would allow us to restore normal transmission in behaving mice [47••]. Our strategy was to optogenetically depotentiate cortical afferents onto D1-expressing MSNs.

Since D1-expressing MSNs receive their strongest input from cortical output neurons, in particular from the infralimbic and prelimbic cortices [50,51], we injected an AAV-virus expressing channelrhodophsin in these divisions of the prefrontal cortex, and implanted optogenetic fibers in the shell of the NAc. This allowed us to apply a classical NMDAR-dependent LTD protocol (1 Hz, 10 min) selectively on coritco-accumbal fibers. The magnitude of synaptic depression induced by this protocol was significantly larger in the cocaine treated mice, in line with the interpretation that on top of the LTD we also depotentiated these synapses. To determine the beha-

vioral significance of this depotentiation, we applied the stimulation protocol *in vivo* before a challenge dose of cocaine following 10 day withdrawal from 5 noncontingent cocaine administrations. We found that in addition to reversing cocaine-induced synaptic potentiation at D1-expressing MSNs, this optogenetic depotentiation abolished locomotor sensitization. Laser treatment was also effective when administered 5 days before the challenge dose of cocaine, which confirms that the optogenetic depotentiation acted by reversing cocaine-induced plasticity, and not by short term effects that may alter the locomotor response to the cocaine challenge [47••,52].

Conclusions

We have outlined a model by which drugs of abuse, such as cocaine, converge to enhance dopaminergic neurons of the VTA. Cocaine induces a permissive form of metaplasticity in the VTA that allows staged changes in synaptic plasticity in the mesolimbic reward circuitry, particularly in the NAc with further drug exposure. By restoring normal synaptic transmission, it is possible to erase drug-adaptive behavior. Results of optogenetic studies are promising, and suggest that by using a strategy of selective depotentiation, it may be possible to develop neuromodulation therapies for addictive disorders.

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