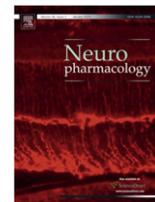




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Synaptic plasticity and addiction: Learning mechanisms gone awry

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ABSTRACT

Experience-dependent changes in synaptic strength, or synaptic plasticity, may underlie many learning processes. In the reward circuit for example, synaptic plasticity may serve as a cellular substrate for goal-directed behaviors. Addictive drugs, through a surge of dopamine released from neurons of the ventral tegmental area, induce widespread synaptic adaptations within this neuronal circuit. Such drug-evoked synaptic plasticity may constitute an early cellular mechanism eventually causing compulsive drug-seeking behavior in some drug users. In the present review we will discuss how different classes of addictive drugs cause an increase of dopamine release and describe their effects on synapses within the mesolimbic dopamine system. We will emphasize the early synaptic changes in the ventral tegmental area common to all addictive drugs and go on to show how these adaptations may reorganize neuronal circuits, eventually leading to behaviors that define addiction.

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1. Introduction: general concepts on synaptic transmission and plasticity

The adult human brain is estimated to contain anywhere from 100 to 500 trillion synapses. The word “synapse” comes from the Greek “syn-” (“together”) and “haptein” (“to clasp”), coined by Sherrington in the late 19th century. In the CNS most synapses are chemical: the presynaptic neuron releases a neurotransmitter into the synaptic cleft that interacts with specific receptors located in the membrane of the adjacent postsynaptic neuron. While the transduction from the presynaptic electrical signal into a chemical and back to an electrical is a complex and energy-consuming phenomenon, it has the advantage to allow for activity-dependent modulation, here simply referred to as synaptic plasticity.

The discovery of long-term potentiation (LTP) at excitatory synapses of the hippocampus (Bliss and Lomo, 1973) is the starting point for the exploration of the molecular and cellular correlates of memory. Moreover, LTP and the mirror phenomenon long-term depression (LTD) may also be involved in synaptogenesis and synaptic stabilization, and in postnatal fine-tuning of neural circuits (Malenka and Bear, 2004).

Since their initial discovery, many forms of LTP and LTD have been described, which can be classified by their specific mechanisms of induction (i.e. which type of activity is required to evoke plasticity) and expression (i.e. which molecular changes mediate the change in synaptic efficacy). A comprehensive discussion of the different forms of LTP and LTD is beyond the scope of the present review. Nevertheless, reviewing some major forms may help to understand synaptic plasticity in the context of drug exposure:

- N-methyl-D-aspartate receptor (NMDAR)-dependent LTP. This form of LTP is induced by releasing glutamate onto the depolarized NMDARs (active after the magnesium (Mg^{2+}) block has been relieved). This allows calcium (Ca^{2+}) to enter the postsynaptic terminal, which triggers an intracellular cascade of events, eventually leading to the increase of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) at the synapse, thus strengthening the excitatory transmission (Lüscher and Frerking, 2001).
- NMDAR-independent, presynaptic LTP. This requires an activity-dependent rise of Ca^{2+} in the presynaptic terminal that in turn activates adenylyl cyclase and protein kinase A (Nicoll and Schmitz, 2005). This leads to a persistent increase in glutamate release from the presynaptic terminal. One of the best-studied examples is the LTP of hippocampal mossy fibers.
- NMDAR-dependent LTD. This LTD is induced by a weak activation of NMDARs resulting in a small rise of Ca^{2+} in the postsynaptic terminal. Ca^{2+} -dependent intracellular signals,

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including activation of phosphatases, lead to the dephosphorylation of AMPARs and the subsequent removal of these receptors from synapses via a clathrin- and dynamin-dependent process (Selig et al., 1995; Lüscher et al., 1999; Morishita et al., 2005). In addition to NMDAR activation, LTD in the hippocampus requires voltage gated calcium channel (VGCC) activation (Christie et al., 1997). VGCCs have been suggested to play a role in both the induction and expression of this form of plasticity (Linden, 1999).

- Metabotropic glutamate receptor (mGluR)-dependent LTD. Here in response to the activation of mGluRs, Gq signaling events are engaged and Ca^{2+} released from intracellular stores. This leads to a decrease in synaptic strength through a variety of distinct mechanisms of AMPAR trafficking that are in part discussed later in the review (Bellone et al., 2008).

2. Synaptic plasticity in the ventral tegmental area

In the ventral tegmental area (VTA) several forms of synaptic plasticity have been described. For example when excitatory synapses onto DA neurons of the VTA are stimulated with the appropriate protocol they may undergo NMDAR-dependent LTP (Bonci and Malenka, 1999; Liu et al., 2005; Luu and Malenka, 2008), VGCC-LTD or protein kinase A (PKA)-dependent LTD (Jones et al., 2000; Thomas et al., 2000).

Interestingly already a first exposure to an addictive drug leads to long-lasting synaptic adaptations at these synapses, apparently similar to the forms of plasticity that can be induced *in vitro*. Here we will review the induction as well as the expression mechanism of such drug-evoked plasticity, and its implications in the behavioral traits characterizing addiction (Table 1).

2.1. Addiction: the hijacking of the mesolimbic dopamine system

Addictive substances facilitate behaviors and memories that are associated with drug use. As with natural rewards, drug consumption rapidly predicts positive outcomes. A large body of literature suggests that the increase in dopamine (DA) levels represents a common feature for both natural rewards and addictive substances with the latter able to promote abnormal changes that may ultimately lead to compulsive drug consumption despite negative consequences (Hyman and Malenka, 2001; Ikemoto and Wise, 2004).

2.2. The VTA as a common target of all drugs

The DA neurons located in the VTA project to the nucleus accumbens (NAc), the prefrontal cortex (PFC), the hippocampus,

Table 1
Different forms of activity-dependent synaptic plasticity observed in DA neurons of the VTA.

Transmission	Type of plasticity	Induction	Expression
Excitatory	LTP	Postsynaptic: NMDA	Postsynaptic: AMPAR insertion
	LTD	Postsynaptic: VGCC ^a	Postsynaptic: PKA-dependent AMPAR withdrawal
	LTD	Postsynaptic: mGluRs	Postsynaptic: De novo synthesis of low conductive AMPAR
Inhibitory	LTP	Postsynaptic: NMDA	Presynaptic: NO ^a
	LTD	Postsynaptic: mGluR + D2	Presynaptic: eCB ^a

^a VGCC = voltage gated calcium channels, eCB = endocannabinoids, NO = nitric oxide.

the amygdala and the olfactory tubercle (Swanson, 1982). In return DA neurons receive excitatory inputs from the PFC, the laterodorsal tegmental nuclei, the lateral hypothalamus, and the bed nucleus of stria terminalis (BNST) (Georges and Aston-Jones, 2001; Georges and Aston-Jones, 2002; Geisler et al., 2007; Omelchenko and Sesack, 2007). DA neurons receive inhibitory inputs from local GABAergic neurons (within the VTA), and distally from the NAc, and the ventral pallidum (VP) (Johnson and North, 1992; Ikemoto and Wise, 2004). Together, the VTA, the NAc and the PFC constitute the motivational circuit of which the crucial role in motivated behaviors and reward learning has been extensively reviewed (Berke and Hyman, 2000; Wise, 2004; Berridge, 2007).

Addictive drugs target the mesolimbic DA system and alter reward signaling through their action on DA and GABA neurons of the VTA. Despite their obvious chemical diversity, three distinct cellular mechanisms have been proposed to underlie their action on the mesolimbic DA system (Lüscher and Ungless, 2006). Morphine, cannabis, γ -hydroxybutyric acid (GHB) and benzodiazepines increase DA indirectly by removing the inhibitory control of GABA cells (Johnson and North, 1992; Cruz et al., 2004; Tan et al., 2010). Through their respective metabotropic Gi/o-protein coupled receptor (GPCR) and the GABA_A receptor respectively, they silence GABA neurons resulting in the disinhibition of DA neurons. Other addictive drugs such as nicotine directly depolarize DA neurons, eventually increasing DA release in the NAc (Maskos et al., 2005). Finally, cocaine, amphetamine and ecstasy target the DA transporters on axon terminals and dendrites of DA neurons. While cocaine blocks the reuptake of DA by DAT inhibition (Heikkila et al., 1975), amphetamine and ecstasy promote non-vesicular release of DA (Seiden et al., 1993).

2.3. Cellular substrate of drug-seeking behaviors

Experience-dependent plasticity that induces synaptic long-term changes has been widely studied in several brain regions including the barrel cortex, the hippocampus and the amygdala (McKernan and Shinnick-Gallagher, 1997; Finnerty et al., 1999; Whitlock et al., 2006). Similarly, drug-evoked synaptic adaptation in several brain regions implicated in positive reinforcement is suggested to be a critical cellular mechanism that may ultimately lead to addiction (for a review see Kauer and Malenka, 2007).

Indeed, much evidence links behavioral models of core components of addiction to synaptic plasticity. Pharmacological interventions that block the development of drug-induced behavioral adaptations in animal models of addiction are among the first demonstration that addictive drugs may override cellular processes implicated in reward learning. NMDAR blockade for example, which effectively blocks LTP and LTD in many brain regions (Malenka and Bear, 2004), also prevents many behavioral adaptations normally associated with drug reinforcement (i.e. conditioned-place preference, behavioral sensitization and self-administration) (Kalivas and Alesdatter, 1993; Schenk et al., 1993; Kim et al., 1996). When applied directly into the VTA, NMDAR blockers prevent both locomotor sensitization and CPP (Kalivas and Alesdatter, 1993; Harris and Aston-Jones, 2003). More recently advanced mouse genetics allowed for cell-type specific manipulations of NMDARs. When the obligatory NR1 subunit of NMDARs was deleted in adulthood selectively in DA neurons, CPP and behavioral sensitization were normal (Engblom et al., 2008; Luo et al., 2010). Interestingly the behavioral phenotype was apparent at a much later stage, when they failed to reinstate drug-seeking behavior. These results suggest that the VTA might be implicated in late-stage drug-seeking behavior rather than short-term ones (Engblom et al., 2008) but see (Zweifel et al., 2008).

3. *In vivo* drug exposure triggers synaptic plasticity

3.1. Excitatory synapses

A single *in vivo* cocaine exposure is enough to cause synaptic adaptations at excitatory inputs onto DA neurons of the VTA. 24 h after cocaine injection the ratio of AMPA- versus NMDA (*A/N*)-mediated excitatory postsynaptic currents (EPSCs) was significantly increased (Ungless et al., 2001). Since current amplitudes evoked by bath application of NMDA were not affected by the cocaine treatment, the increase of the *A/N* ratio was interpreted as a strengthening of AMPAR transmission.

This finding can still be observed after five days but not ten days post injection and detected within few hours after amphetamine or cocaine exposure *in vivo* and *in vitro* (Faleiro et al., 2004; Argilli et al., 2008). Mechanistically, cocaine-evoked plasticity relies on NMDAR activation and subsequently prevents the induction of activity-dependent LTP, suggesting a shared expression mechanism of the two types of plasticity (Ungless et al., 2001). Therefore *in vivo* cocaine exposure elicits long-lasting synaptic adaptations at excitatory synapses on VTA DA neurons. Furthermore, drug-evoked plasticity can be generalized to other addictive drugs. Additional experiments with amphetamine, morphine, ethanol, nicotine and benzodiazepines (Saal et al., 2003; Tan et al., 2010) lead to a similar potentiation of the *A/N* ratio 24 h after *in vivo* administration of a single dose. In the case of nicotine, a presynaptic increase in glutamate release through $\alpha 7$ -containing receptors may represent the trigger for a more enduring plasticity (Mansvelter and McGehee, 2000). On the other hand benzodiazepines trigger the plasticity by disinhibiting the DA neurons via a decrease in GABAergic tone from local interneurons (Tan et al., 2010). Further studies will have to establish the molecular mechanisms engaged by opioids and alcohol to produce long lasting synaptic adaptations.

This increase in *A/N* ratio seems to reflect an initial form of adaptive synaptic plasticity in response to all addictive drugs. Importantly, non-addictive psychotropes such as fluoxetine or carbamazepine do not alter the *A/N* ratio (Saal et al., 2003). Moreover, the *A/N* ratio does not change at hippocampal synapses or at excitatory synapses onto GABA cells of VTA, indicating that the effect of cocaine at excitatory synapses onto DA neurons is specific (Ungless et al., 2001). A similar plasticity occurs 24 h after acute exposure to stress (Saal et al., 2003). While stress-induced plasticity relies on NMDAR and glucocorticoids receptor (GR) activation, cocaine-evoked plasticity does not require GRs suggesting the existence of two independent pathways. Likewise, the corticotropin-releasing factor (CRF) strengthens excitatory synaptic inputs onto DA neurons and the CRF-glutamate interaction may represent a cellular substrate of stress-induced reinstatement (Ungless et al., 2003; Wang et al., 2005, 2007; Borgland et al., 2010).

In conclusion, all addictive drugs tested to date induced persistent changes at excitatory synapses on projection neurons of the VTA. These studies suggest that drug-evoked synaptic strengthening may be a phenomenon implicated in the cascade of events that could lead to compulsive behaviors.

3.2. Expression mechanism of cocaine-evoked plasticity in the VTA

Based on the conclusion that the *A/N* ratio increases because of a strengthening of the AMPAR-EPSC, an expression mechanism similar to hippocampal LTP has been proposed. In this model, cocaine administration would lead to the insertion of additional AMPARs, which then occludes subsequent LTP (Kauer and Malenka, 2007). In line with this interpretation, several groups reported that LTP could no longer be induced after cocaine treatment (Ungless et al., 2001; Liu et al., 2005; Luu and Malenka, 2008).

However, the expression mechanism of cocaine-evoked plasticity does not simply consist of the insertion of more AMPARs. When AMPAR-EPSCs were recorded after cocaine treatment at different holding potentials ranging from -70 mV to $+40$ mV (current–voltage relationship, *I–V* plot) the slope of the inward current at negative potentials was steeper than the slope of outward currents at positive potentials (Bellone and Lüscher, 2006). In other words, 24 hrs after cocaine injection, AMPAR-mediated EPSCs show an inwardly rectifying *I–V* relationship.

Canonical AMPARs are heteromers containing two GluA2 subunits that render them impermeable to Ca^{2+} while AMPARs lacking the GluA2 subunit are Ca^{2+} -permeable and also have a higher single channel conductance (Liu and Zukin, 2007). Inward rectification is the electrophysiological signature of the latter, because the absence of GluA2 allows polyamines to access their binding site on the cytoplasmic tail and to inhibit the current at positive potentials (Pellegrini-Giampietro, 2003).

These data suggest a redistribution of AMPARs after cocaine exposure. At baseline, all AMPARs contain GluA2 while after the cocaine treatment some synapses express GluA2-lacking AMPARs. Further investigations indicate that this AMPAR redistribution depends on PICK1, a trafficking protein specifically interacting with GluA2 (Bellone and Lüscher, 2006). Moreover, after the cocaine treatment the single channel conductance of sEPSCs almost doubled from 7.8 pS to 15 pS and evoked EPSCs were inhibited by 50% when the polyamine Jorospider toxin was bath applied, in line with the idea of an insertion of GluA2-lacking AMPARs (Bellone and Lüscher, 2006; Mameli et al., 2007). The presence of GluA2-lacking AMPARs after cocaine exposure was also confirmed in rats by controlling for rectifying AMPAR-EPSCs and sensitivity to external polyamines (Argilli et al., 2008; Good and Lupica, 2010). Whether cocaine-evoked AMPAR redistribution occurs at all inputs onto DA neurons remains elusive. However, a recent study employed 2-photon laser photolysis of caged glutamate to activate single synapses and generate unitary (u) AMPAR-EPSCs. Using this approach it was observed that only a subset of synapses presented rectifying currents upon cocaine treatment (Mameli et al., 2011). Interestingly, the excitatory projection from the pedunculopontine nucleus to DA neurons seems particularly sensitive in triggering GluA2-lacking insertion after cocaine and delta9-tetrahydrocannabinol administration (Good and Lupica, 2010). Furthermore, when measured with single synapse resolution, a decrease in NMDAR-mediated current was observed along with rectifying AMPAR-EPSC. As a consequence, this dual redistribution of glutamate receptors led to an inversion of the rules for synaptic plasticity at excitatory inputs onto DA neurons of the VTA (Mameli et al., 2011). While in slices of naïve animals, Hebbian NMDAR-dependent LTP was induced by a spike-timing dependent protocol, in slices from cocaine-treated mice anti Hebbian potentiation was elicited. In these cells a brief hyperpolarizing current injection led to a robust LTP. This plasticity was mediated by calcium influx likely passing through GluA2-lacking AMPARs (Fig. 1) (Mameli et al., 2011). In summary, this finding indicates that synapses onto DA neurons after cocaine treatment are no longer able to induce physiological LTP, but can be potentiated by an alternative form of synaptic plasticity. This may then have repercussions on neural circuit adaptation that may eventually underlie behavioral changes and lead to addiction.

3.3. Time course of cocaine-evoked plasticity in the VTA

The cocaine-evoked plasticity measured 24 h after a single cocaine injection lasts for about a week, after which both *A/N* and rectification index (a way to measure the presence of GluA2-lacking AMPARs, RI) return to baseline (Ungless et al., 2001; Bellone and

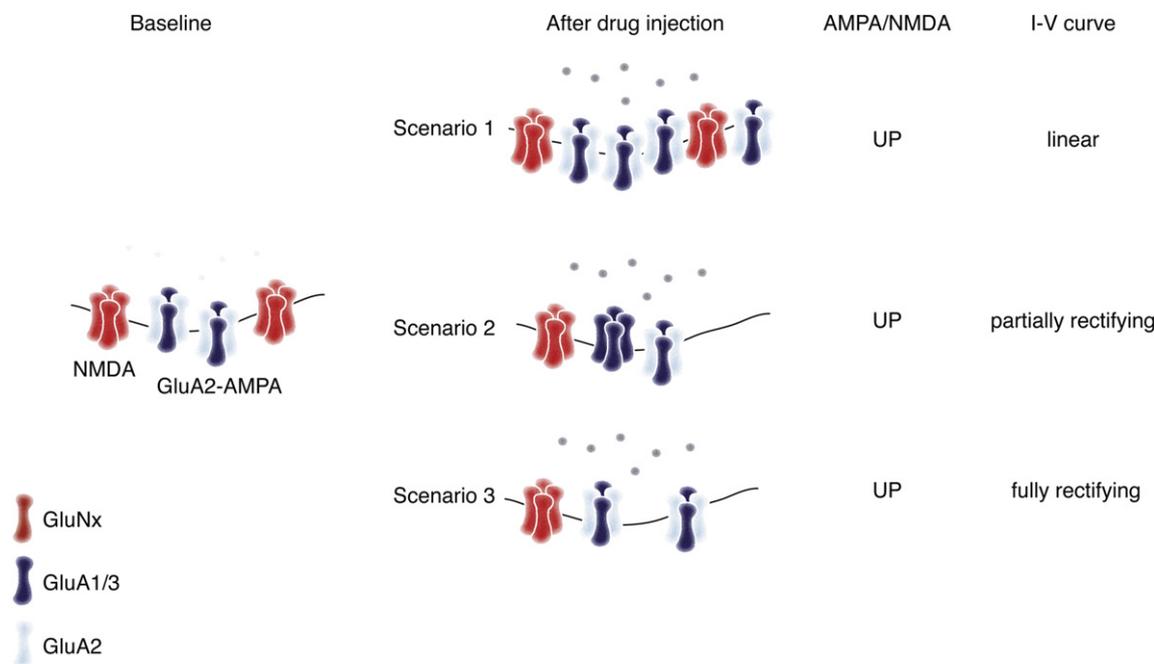


Fig. 1. AMPAR and NMDAR redistribution after drug exposure. At baseline synapses contain NMDAR and AMPAR containing the subunit GluA2. Three distinct scenarios can be envisioned. The first implicate an insertion of AMPAR without any change in subunit composition. This situation would explain the increase in A/N obtained in different studies (Ungless et al., 2001; Saal et al., 2003; Bellone and Lüscher, 2006), but cannot account for the insertion of GluA2-lacking AMPARs. A second scenario would consist of an exchange of some GluA2 containing for GluA2-lacking AMPAR along with a decrease in the NMDA component. This scenario will be in line with much of the previous work (Bellone and Lüscher, 2006; Mameli et al., 2007; Argilli et al., 2008; Good and Lupica, 2010) reporting partial rectification and a decrease in GluA2 expression at the membrane surface. A recent report monitoring unitary NMDAR epscs observes indeed a significant decrease (Mameli et al., 2011). An extreme scenario would be reduction of NMDAR function and a complete loss of GluA2-containing AMPARs. This could be the case in selected input that undergo the change. The partial rectification observed with extracellular stimulation experiments would then reflect an average of synapses that undergo drug-evoked plasticity and those that do not undergo plasticity.

Lüscher, 2006). Surprisingly, even after several daily injections the plasticity persisted only five days after the last cocaine injection but returned back to baseline after ten days. Moreover daily injections for seven consecutive days of cocaine increased the A/N ratios and RI to a similar extent as a single injection, suggesting for a “switch-like” mechanism (Borgland et al., 2004; Mameli et al., 2009).

When cocaine is self-administered the same type of plasticity described above (i.e. increase in A/N) persists for up to three months (Chen et al., 2008), suggesting a need for an associative learning mechanism. In this report, natural rewards also elicited synaptic adaptations at excitatory synapses onto DA neurons of the VTA, which lasted for about seven days. Moreover, and in apparent contradiction to the passive injection experiments described above, in the group of yoked rats (animals received injections in a non-contingent fashion) no changes in the A/N were observed. These results highlight the importance of the associations with the external stimuli and the motivation in driving the drug taking, further suggesting a role for drug-evoked plasticity as a cellular substrate for the learning of addictive-like behaviors.

In addition to affecting glutamatergic transmission, chronic cocaine treatment (5–7 days) may lead to a decrease of the GABAergic transmission, which may facilitate subsequent induction of LTP elicited by a spike-timing protocol (Liu et al., 2005). However, these results are controversial as several groups have reported that following cocaine administration (1 day or 5 days), a similar spike-timing dependent protocol or a pairing-protocol could not induce LTP (Ungless et al., 2001; Adams and Sweatt, 2002; Argilli et al., 2008; Luu and Malenka, 2008). These latter studies concluded that LTP was absent because of the occlusion by the drug-evoked strengthening *in vivo*, which had already saturated AMPARs at the synapse, such that no further potentiation could be elicited in the slice preparation.

3.4. Reversal of cocaine-evoked plasticity in the VTA

In order to return synaptic transmission back to baseline one week after cocaine-evoked plasticity, dedicated mechanisms may exist. The first indications stem from the characterization of mGluR-LTD in slices of the VTA. When mGluR1 are activated GluA2-lacking AMPAR are removed from the surface thus leading to LTD (Bellone and Lüscher, 2006; Mameli et al., 2007; Good and Lupica, 2010). The induction of the mGluR-LTD may be chemical using DHPG (group I agonist), mGluR1-selective positive modulators or through a succession of brief trains of action potentials that efficiently activate the extrasynaptically-located metabotropic receptors. The expression of mGluR-LTD depends on *de novo* synthesis of GluA2 and an exchange of GluA2-containing AMPARs for GluA2-lacking ones (Mameli et al., 2007). It is important to realize that mGluR-LTD in the VTA can only be observed when GluA2-lacking AMPARs are present at the synapse, which is typically the case after cocaine treatment (Bellone and Lüscher, 2006; Mameli et al., 2007, 2009; Good and Lupica, 2010). The initial study reporting mGluR-LTD in the VTA however was carried out in very young rats that did not receive any cocaine treatment (Bellone and Lüscher, 2005). The presence of GluA2-lacking AMPARs at baseline may have been due to the young age of the animals or because a specific synaptic input was selected. In line with the latter interpretation a recent study that aimed at selecting intra-VTA connections in drug-naïve rats also observed weak rectification at baseline (Argilli et al., 2008; Good and Lupica, 2010).

While mGluR-LTD is an established mechanism to reverse cocaine-evoked plasticity *in vitro*, additional evidence also suggests that mGluR1s are required for the *in vivo* reversal. For example, the same positive modulator of mGluR1 that readily induced mGluR-LTD in slices is also efficient *in vivo* at speeding up the reversal of

synaptic plasticity (Bellone and Lüscher, 2006; Mameli et al., 2009). Conversely, decreasing *in vivo* mGluR1 function by disrupting the mGluR1-Homer interaction will make cocaine-evoked plasticity in the VTA persistent (Mameli et al., 2009).

Taken together, mGluR1-dependent LTD has been identified as the mechanism by which cocaine-evoked plasticity is reversed, either physiologically in the situation when the plasticity disappears after a week or when an animal is treated with mGluR1 enhancers to pharmacologically reverse the effects of cocaine.

3.5. Drug-evoked plasticity of inhibitory synapses

As suggested above, addictive drugs may also affect inhibitory transmission in the VTA, which plays a critical role in controlling the firing rate of DA neurons. In fact, blockade of GABA_A receptors located in local GABA neurons strongly increases DA cell firing both *in vivo* and in slices (Johnson and North, 1992; Tan et al., 2010). For example, daily cocaine injections over a week decrease the size of GABA_A receptor-mediated miniature inhibitory postsynaptic currents (mIPSCs) on DA neurons as well as their maximal evoked GABA_A currents (Liu et al., 2005; Pan et al., 2008). As a consequence DA neurons have increased excitability in response to a given stimulus. These changes seem to rely on endocannabinoid (eCB) release after activation of mGluR5s.

DA neurons of the VTA can undergo GABA_A-mediated IPSC-LTP in slices from naive animals in response to high-frequency stimulation (I-LTP) (Nugent et al., 2007) that is NMDAR-dependent. Mechanistically, this form of plasticity relies on the postsynaptic release of nitric oxide (NO) from DA cells that feeds back on inhibitory terminals to activate guanylate cyclase, which in turn causes a long-lasting enhancement of GABA release. One day after a single dose of morphine, I-LTP was absent because the drug-treatment disrupts the coupling between NO and guanylate cyclase. In addition to the increased synaptic strength at excitatory synapses, the loss of I-LTP is expected to increase the firing of VTA DA neurons following morphine exposure (Saal et al., 2003; Nugent et al., 2007). Like drug-evoked plasticity of excitatory transmission, all substances tested so far (e.g. morphine, cocaine and nicotine) abolished LTP of GABA transmission with different time courses (Niehaus et al., 2010).

3.6. Drug-evoked plasticity in target regions of the VTA

If addictive drugs strengthen excitatory synapses onto VTA DA neurons this may increase DA release in target structures, such as the BNST, the amygdala and the PFC, ultimately modulating DA-dependent learning (Hyman and Malenka, 2001; Kalivas and Volkow, 2005). To understand the effects of such massive pharmacological stimulation, which are in contrast to the physiological reward associated changes in firing behavior of DA neurons (Schultz et al., 1993), the adaptive changes in the target regions need to be fully characterized and it will be necessary to establish the hierarchical relationship between the different types of adaptations.

While it is beyond the scope of the present review to discuss all the adaptive changes observed through out the mesolimbic system in detail, we review some essential mechanisms and discuss how they may be interconnected.

3.7. Bed nucleus of stria terminalis

The BNST is part of the “extended amygdala” involved in fear responses, anxiety-like behaviors, drug-seeking and stress induced relapse (Walker and Davis, 1997; Shaham et al., 2000; Sullivan et al., 2004). Addictive drugs increase DA levels in the BNST and activate

extracellular regulated kinase (ERK) through DA receptor activation (Carboni et al., 2000; Valjent et al., 2004). When D1 receptor-mediated (D1R) signaling in the BNST is disrupted, the reinforcing properties of psychostimulants and ethanol are attenuated (Epping-Jordan et al., 1998; Eiler et al., 2003). The BNST contributes to maintain the excitatory tone of DA neurons, therefore this might represent a loop that controls the reward signal and that is affected by drug-exposure (Georges and Aston-Jones, 2002).

A form of NMDAR-dependent LTP occurs in the BNST. Ethanol exposure blocks this form of long-term plasticity via a decrease of the NMDAR function (Weitlauf et al., 2004). In the case of psychostimulants, when rats self-administer cocaine, the A/N of excitatory afferents onto BNST neurons increases, suggesting that there are long-lasting synaptic adaptations similar to those present in the VTA (Dumont et al., 2005). However passive injections of cocaine do not trigger synaptic plasticity, highlighting the importance of the animal's motivational drive in taking the drug (Dumont et al., 2005). At these synapses, group I mGluRs trigger a LTD that depends on the ERK1 activation (Grueter et al., 2006). A chronic cocaine treatment (10 days) but not a single injection abolishes this mGluR-LTD, however whether this is due to occlusion or inhibition of induction mechanisms has not been investigated.

3.8. Amygdala

Synaptic strengthening at excitatory synapses onto principal neurons of the amygdala has been implicated in fear conditioning and emotional-related memories (Sigurdsson et al., 2007) and it is gated by DA inputs from the VTA, which modulate feed forward inhibition (Bissiere et al., 2003). LTP at cortical inputs to the lateral amygdala depends on NMDARs, while LTP at thalamic inputs relies on presynaptic mechanisms (Humeau et al., 2003; Krishnan et al., 2010). In addition, CRF regulates LTP in the amygdala specifically after exposure to psychostimulants (Krishnan et al., 2010). The synaptic adaptations in the amygdala (specifically in the basolateral nucleus (BLA)) may represent an important cellular mechanism underlying incentive motivation and reward-seeking. The excitatory inputs from BLA to NAc participate in integrating signal from limbic structures to motor structures (Shiflett and Balleine, 2010). Using a disconnection procedure, it has been demonstrated that BLA projections to core and shell of the NAc code for distinct processes underlying choice and decision-making during instrumental learning. Furthermore, BLA and VTA projections to NAc synergistically participate in shaping reward-seeking behaviors and may be important in cue-reward associations (Ambroggi et al., 2008). Further studies will need to provide information regarding the role of synaptic strengthening of BLA in drug- or reward-related behaviors.

3.9. Prefrontal cortex

In the pyramidal neurons of the medial PFC exposure to cues previously associated with heroin self-administration induces an acute decrease in the A/N ratio (Van den Oever et al., 2008). This synaptic depression relies on the reduction of the AMPAR component via reduced synthesis of GluA2 and GluA3 subunits of the AMPAR. In addition, NR2B synthesis is also reduced, albeit without any functional effects on the NMDAR EPSC (Van den Oever et al., 2008).

3.10. Nucleus accumbens

Arguably, the NAc is the VTA target where drug-evoked plasticity has been best characterized. The NAc receives a strong DA projection from the VTA and synaptic transmission is affected by chronic drug-exposure. For example, 24 h after a week of daily

cocaine injections the A/N is reduced. This synaptic depression switches back into a state where A/N ratios are enhanced after a short withdrawal period (Kourrich et al., 2007). After extended withdrawal from passive injections and self-administration, GluA2-lacking AMPARs appear at excitatory synapses (Conrad et al., 2008; Mameli et al., 2009). This finding has sparked much interest since a selective inhibition of the GluA2-lacking AMPARs in the NAc or selective ablation of the obligatory subunit of NMDAR (NR1) from DA neurons significantly reduces cue-induced cocaine seeking in mice, which is generally accepted as a model for relapse in humans (Conrad et al., 2008; Mameli et al., 2009). After prolonged periods of drug intake a fraction of rats show addiction-like behaviors such as continued drug-seeking even in the presence of footshocks. This lever pressing despite punishment in rodents may represent the consumption despite negative consequence in humans that defines addiction according to the DSM IV (DSM IV, 1994; Deroche-Gamonet et al., 2004). As a cellular correlate, the loss of NMDAR-dependent LTD of AMPAR-mediated transmission in the NAc was proposed (Kasanez et al., 2010). It will be interesting to see which cellular mechanisms underlie the loss of LTD. Are drugs blocking induction or are they interfering with expression mechanisms of this form of plasticity (e.g. AMPAR trafficking)? Moreover, to understand the repercussions for circuit function it will be necessary to test whether the loss of LTD affects inputs onto direct pathway neurons and indirect pathway neurons equally. Studies following up on these exciting findings will need to understand the cascade of molecular events engaged in this “anaplasticity” in order to unravel the biological basis of individual vulnerability.

3.11. A network perspective

While a large amount of data has already been obtained characterizing the different forms of drug-evoked plasticity in target regions of the VTA, little is known about the interplay between the different forms of drug-evoked plasticity. An appealing hypothesis however has emerged that is based on the anatomical connectivity between the midbrain and the striatum (Fig. 2). Based on work in monkeys and rodents (Haber and Rauch, 2010), ascending DA projections target descending GABAergic neurons that project to

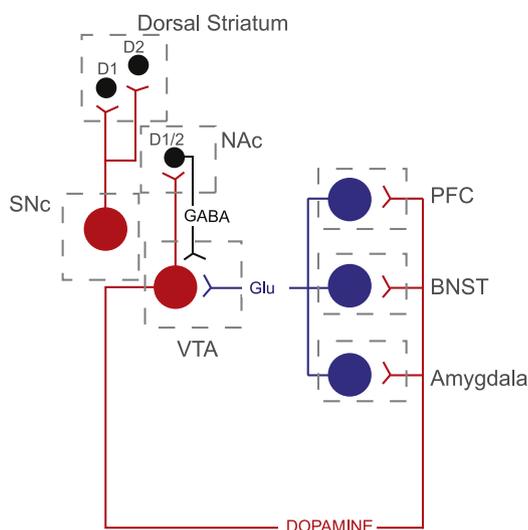


Fig. 2. Neural circuits reorganization after drug exposure. Synaptic connection of a number of interconnected regions where DA neuromodulation plays a crucial role, are susceptible to drug exposure. Drugs act at different level of such organization changing brain function and modulating behaviors, eventually leading to the loss of control over the drug.

more and more lateral DA neurons. For this reason, the term “spiraling” connectivity has been coined (Belin and Everitt, 2008). The VTA may therefore constitute the first leg of a complex spiral loop, which would undergo graded remodeling. First medial components would change, which then would recruit more dorsal structures. In direct support of such a staged remodeling is the observation that the synaptic depression in the NAc after chronic cocaine exposure takes place only if the drug-evoked plasticity in the VTA persists. In contrast, if each cocaine injection is paired with a mGluR1 enhancer even repetitive injections are without effect on transmission in the NAc, suggesting a hierarchical organization of synaptic adaptations (Mameli et al., 2009).

The recruitment of nigro-striatal projections by strong activation of VTA-NAc projections, which leads to behavioral changes, is supported by several reports. First, recent evidence suggests that reward circuits are interconnected with neuronal circuits controlling cognitive function and motor planning (Haber and Rauch, 2010). The dissociation in the function of ventral and dorsal striatum together with the related cortico-basal ganglia circuit has been proposed for reward-guided learning. If the nucleus accumbens mainly participates in pavlovian-type of learning, the dorsal striatum would mediate preferentially instrumental actions (Yin et al., 2008). In this context, reward-associated information could therefore be redirected through cognitive circuits to influence motor control circuits. Behavioral studies modeling drug seeking and electrophysiological evidence demonstrate that brain structures are recruited during early and late phases of drug-seeking behaviors. While the meso-accumbal connection is necessary during the initial drug-taking, the nigro-striatal spiral comes into play during late habit formation (Porrino et al., 2004; Belin and Everitt, 2008).

Such a model will need however to integrate drug-evoked synaptic plasticity in other brain regions.

3.12. Open questions

Despite considerable progress since the initial description of early cocaine-evoked plasticity in the VTA (Ungless et al., 2001) several important questions remain unanswered. First, the induction criteria are only partially elucidated. What is the precise role of DA, where is it coming from and which receptors need to be activated? If dendritically-released DA plays a key role, the induction mechanism could be limited to the VTA (Schilstrom et al., 2006; Brown et al., 2010).

The expression mechanism will also require further research. It seems contradictory for the A/N ratio measured at positive potentials to increase because of the insertion of GluA2-lacking AMPARs, since these receptors only minimally contribute to the current at positive potentials. The initial studies failed to use spermine as a source of polyamines in the pipette, which could explained the increase of the A/N ratio by the insertion of GluA2-lacking AMPARs with a relieved block due to washout of endogenous polyamines. However several studies have meanwhile confirmed the concomitant increase of A/N and RI in conditions where the polyamine block was maintained. It is possible that the interpretation of the change in A/N has to be reconsidered. Based on the observation that the current amplitude in response to NMDA was similar in slices from naïve, saline- and cocaine-treated rats, the conclusion was that the AMPAR-component must increase. However the bath-application of NMDA activated synaptic and extrasynaptic receptors, and specific changes in the synaptic population or a redistribution between synaptic and extrasynaptic NMDARs may not be detectable. The recent evidence obtained with single synapse resolution, suggests that insertion of GluA2-lacking AMPAR and decrease in NMDAR function are concomitantly occurring at the

same synapse leading to a change in the induction mechanisms for synaptoc plasticity (Mameli et al., 2011).

It will also be of interest to test how increased A/N and RI relate to other forms of drug-evoked plasticity in the VTA. For example, a single dose of amphetamine blocks a PKA-dependent form of LTD along with synaptic potentiation (Jones et al., 2000). Synaptic adaptations that influence LTP in the VTA also occur during drug withdrawal. For example, expression of c-FOS (a marker for neuronal activation) increased in rats re-exposed to an environment associated with withdrawal (Neisewander et al., 2000). In a related finding, brain-derived neurotrophic factor (BDNF) levels in the VTA increase during prolonged (10–15 days) drug withdrawal, which may facilitate further LTP through reduced inhibition (Pu et al., 2006).

Ultimately it will be crucial to understand how the function of the mesolimbic circuit is changed because of the increase of A/N and RI. Current techniques such as projection targeting with optogenetic methods can be used to probe specific inputs onto DA neurons. Which inputs express the synaptic changes in response to drug-exposure? Similarly it will be necessary to identify the projection site of the DA neurons that express the drug-evoked plasticity. Are DA neurons projecting to the PFC equally affected as those that project to the NAc?

Answers to these questions will help to eventually understand how the network changes in these target regions of the VTA. Initial studies suggest that drug-evoked plasticity is in fact a permissive step towards more long-lasting changes elsewhere in the brain. For example, only if synaptic changes (i.e. increase in the rectification index and A/N) in the VTA are rendered persistent are further adaptation at excitatory inputs onto medium spiny neurons of the nucleus accumbens triggered (Mameli et al., 2009).

Finally, the most difficult task lies in understanding the causal relationship between synaptic changes, circuit remodeling and addiction-relevant behavior. Initial assumptions such as the link to behavioral sensitization were proven incorrect as mice with a conditional and constitutive deletion of NMDARs in DA neurons exhibit perfectly normal sensitization, but an absence of cocaine-evoked plasticity (Engblom et al., 2008; Luo et al., 2010). Two papers implicate the synaptic changes in the reinstatement of drug-seeking behaviors (Conrad et al., 2008; Mameli et al., 2009). Finally BDNF, when injected into the VTA immediately after a regimen of cocaine self-administration, enhances drug-seeking behavior even after several weeks of cocaine withdrawal (Lu et al., 2004).

In summary, much evidence is converging to show that addictive drugs cause a redistribution of AMPARs at excitatory synapses onto VTA DA neurons. Such synaptic adaptations may constitute a first permissive step in a cascade of cellular events that ultimately lead to circuit remodeling and changes in behavior, which may eventually be diagnosed as addiction. However, the comprehensive dissection of the neurocircuitry that undergoes adaptation during the development of addiction is only at the beginning.

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