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The Emergence of a Circuit Model for Addiction

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Keywords

cocaine, synaptic plasticity, metabotropic glutamate receptors, calcium-permeable AMPA receptors, deep brain stimulation, optogenetics

Abstract

Addiction is a disease of altered behavior. Addicts use drugs compulsively and will continue to do so despite negative consequences. Even after prolonged periods of abstinence, addicts are at risk of relapse, particularly when cues evoke memories that are associated with drug use. Rodent models mimic many of the core components of addiction, from the initial drug reinforcement to cue-associated relapse and continued drug intake despite negative consequences. Rodent models have also enabled unprecedented mechanistic insight into addiction, revealing plasticity of glutamatergic synaptic transmission evoked by the strong activation of mesolimbic dopamine—a defining feature of all addictive drugs—as a neural substrate for these drug-adaptive behaviors. Cell type-specific optogenetic manipulations have allowed both identification of the relevant circuits and design of protocols to reverse drug-evoked plasticity and to establish links of causality with drug-adaptive behaviors. The emergence of a circuit model for addiction will open the door for novel therapies, such as deep brain stimulation.

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INTRODUCTION: CLINICAL DEFINITION OF ADDICTION

A simple definition of addiction is “compulsive drug seeking and use, despite harmful consequences” (Volkow 2014, p. 5). Clinically, the American Society for Addiction Medicine defines addiction as “a primary, chronic disease of brain reward, motivation, memory and related circuitry” that is characterized by the “inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one’s behaviors and interpersonal relationships, and a dysfunctional emotional response” (American Society of Addiction Medicine 2011). The former simple definition has the appeal that it can be modeled in animals, whereas the latter captures the full complexity of the human disease more accurately. Moreover, addicts are also subject to aversive feelings, which may lead to negative reinforcement via motivational withdrawal (Koob 2009). Because the focus of the present review is on the neural basis of the disease in rodent models, the emphasis here is on the compulsivity and resistance to punishment.

Despite occasional alarming reports, the overall prevalence of addiction has remained constant during the past several decades. What is shifting are the specific substances used. In Western Europe, heroin was the most commonly used addictive drug during the 1980s; today, heroin use has decreased, but cocaine is on the rise. In the United States, particularly outside of the big cities, methamphetamine is the leading drug today. Prescription opioids leading to an epidemic of drug overdose pose an additional threat (Rudd et al. 2016). In Asia, recreational opioids have traditionally been the most commonly used drugs and are still number one (World Health Organization 2010).

Resistance to punishment test: a behavioral assay whereby a mild electric shock is delivered when an animal self-administers an addictive drug to assess its motivational value

Based on the US National Comorbidity Survey (Kessler et al. 2004), early longitudinal clinical studies demonstrate clearly that only a minority of recreational drug users eventually fulfill the diagnostic criteria for the disease (Wagner & Anthony 2002). This landmark work shows that about 15% of cocaine users develop addiction¹ within 10 years of first cocaine use; the corresponding values were 8% for marijuana users and 12–13% for alcohol users [for alcohol, which is consumed regularly by the large majority of the adult population, prevalence for addiction in Europe is estimated to not exceed 4%, albeit with a strong gender bias (Rehm et al. 2015)]. This indicates clearly that the majority of people can use even the most highly addictive drugs recreationally without ever becoming addicted.

One of the most striking features of drug relapse is its dependence on the environment. Addicts typically relapse in settings associated with prior drug use. Conversely, exposed to a different context, addicts typically find it easier to remain abstinent. Another landmark study demonstrated this effect on heroin-addicted Vietnam War veterans, who, when back in the United States, had a significantly higher success rate in rehabilitation programs compared to local addicts (Zinberg 1986). This remarkable finding was attributed to the fact that for the veterans, contextual drug cues were rare and thus relapse was less common.

Although an attempt to generate a general theory for addiction was greeted with criticism (Piazza & Deroche-Gamonet 2014), much research over the past two to three decades supports the notion of addiction as a brain disease, in which pharmacological substances exert their deleterious effect by usurping the neural reward system. Contrary to common beliefs, addiction is not a neurodegenerative disease, as neurotoxicity is not a common feature of addictive drugs. Here we present the preclinical evidence for the dopamine (DA) system as a common initial target for all addictive drugs and review the literature on adaptive synaptic plasticity as the addiction trace, which maintains compulsive behavior despite punishment and other negative consequences.

THE DOPAMINE HYPOTHESIS: STILL ALIVE AND KICKING

Addictive drugs constitute a group of chemically diverse pharmacological substances with distinct molecular targets. It is therefore not trivial to assume a common function that would trigger the induction of addiction. Yet accumulating evidence points to the DA system as the initial target of all addictive drugs.

The first evidence for involvement of the DA system in the acute rewarding effects of addictive drugs dates back to the 1970s (for a review, see Wise 2004) with the report that cocaine self-administration in rats was abolished when lesioning DA neurons but remained unaffected by a chemical destruction of the noradrenergic neurons (Roberts et al. 1977). Subsequently, a systematic characterization using microdialysis to measure DA after systemic administrations of morphine, methadone, ethanol, nicotine, amphetamine, and cocaine showed strong increases of DA for all these substances (Di Chiara & Imperato 1988). The transient increases in DA were particularly marked in the nucleus accumbens (NAc) compared to the caudate nucleus. These studies led to the hypothesis that addiction could arise from increased levels of mesolimbic DA, which was both necessary and sufficient to induce the disease (**Figure 1**). This model focuses on the mechanism of induction of addiction and needs to be distinguished from the hypothesis, which posits changes in DA signaling as the cause of adaptive behavior (for a review, see Melis et al. 2005).

NAc: nucleus accumbens, a nucleus of the ventral striatum that integrates dopamine inputs from the ventral tegmental area and glutamate projections from the prefrontal cortex, the amygdala, and the ventral hippocampus

¹The original publication uses the term dependence, which is now limited to describing the state defined by the withdrawal syndrome upon abrupt termination of drug exposure.

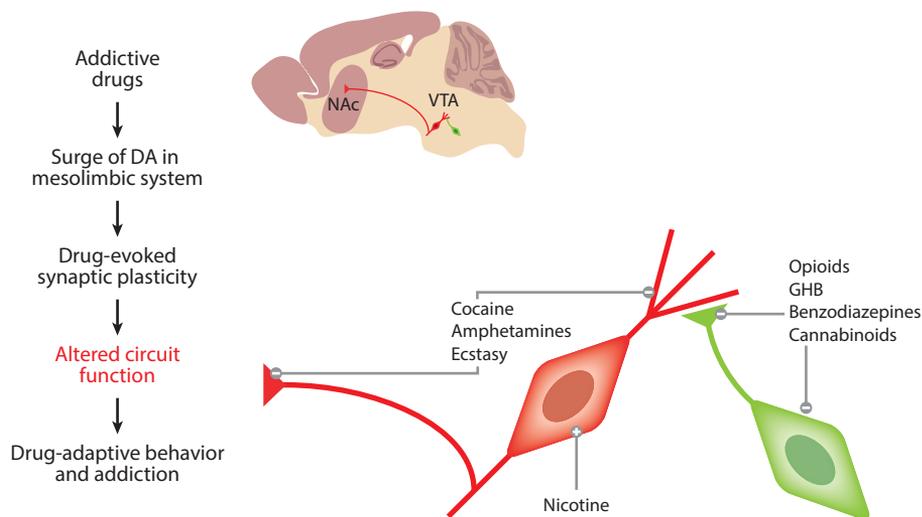


Figure 1

Overarching hypothesis of dopamine (DA)-evoked circuit adaptations leading to addiction. Schematics are shown of the mesolimbic DA system with its origin in the ventral tegmental area (VTA) and two primary projection sites, the nucleus accumbens (NAc) and the medial prefrontal cortex. Addictive drugs converge onto a minimally required circuit that may explain an increase in DA concentrations through three distinct cellular mechanisms. Nicotine can depolarize DA neurons (*red*) directly, whereas the psychostimulants cocaine, ecstasy, and amphetamines interfere with DA reuptake. Note that this mechanism also increases DA in the VTA because these neurons also release the transmitter from their dendrites. Drugs in a third group, including opioids, γ -hydroxybutyrate (GHB), cannabinoids, and benzodiazepines, have a disinhibitory effect, which is the result of the presynaptic release probability in combination with the hyperpolarization of VTA γ -aminobutyric acid (GABA) neurons (*green*). This minimally required circuit element is also modulated by afferent circuits (not shown) and subject to acute adaptations (e.g., desensitization of nicotine receptors). Modified from Lüscher & Malenka (2011) with permission.

DAT: dopamine transporter expressed on the cell membrane for the reuptake of the transmitter from the extracellular space

Conditioned place preference: a form of conditioning used to measure the motivational effects attributed to the environment in which addictive drugs are administered

GABA: γ -aminobutyric acid, inhibitory neurotransmitter

VTA: ventral tegmental area, a nucleus at the tip of the brainstem with DA projection neurons

Challenging the Dopamine Hypothesis of Drug Reward

Researchers have challenged the DA hypothesis of drug reward several times (Nutt et al. 2015). In the late 1990s, the observation that mice lacking the DA transporter DAT (DAT knockout mice) still self-administered cocaine received much attention (Rocha et al. 1998). It took the field a decade to understand the mechanism underlying this observation. In fact, in DAT knockout mice, a compensatory reuptake of DA through other monoamine transporters developed, and because these transporters were also inhibited by cocaine, DA still increased with drug exposure even in the absence of DAT. Double and triple monoamine transporter knockout mice (Sora et al. 2001) finally paved the way for the definitive experiment showing that self-administration of cocaine, but not amphetamine, was abolished in mice that carried a mutated DAT that no longer binds cocaine but is otherwise functional (Chen et al. 2006).

The observation that morphine still induced conditioned place preference in DA-deficient mice has also challenged the DA hypothesis (Hnasko et al. 2005). However, these animals suffered from severely reduced locomotion and other developmental adaptations, which precluded the testing for later-stage drug-adaptive behavior. Early studies also suggested that a major drive for morphine reinforcement originates in the tegmental pedunculopontine nucleus (TPP), a small brain-stem nucleus receiving γ -aminobutyric acid (GABA) projections from the ventral tegmental area (VTA) (Bechara & van der Kooy 1992). According to this model, in naive animals, the reinforcing effects of

opiates would be mediated by VTA GABA neurons projecting to the TPP. Conversely, in opiate-dependent but withdrawn animals, collaterals of the same GABA neurons projecting to VTA DA neurons would mediate the reinforcing effects. Opioid dependence would control the ambient chloride concentration of VTA GABA neurons such that the polarity of the GABA_A receptor signaling swaps from inhibitory to excitatory (Laviolette et al. 2002). How this then directs the information to one or the other target remains elusive, as does the locus of μ -opioid receptors that drives the effect of morphine. It is well established that VTA GABA neurons express these receptors in the somatodendritic as well as the axon-terminal compartment. μ -Opioid receptors in the former activate K⁺ channels of the G protein-coupled inwardly rectifying K⁺ (GIRK) channel family, whereas those in the latter inhibit calcium channels to reduce transmitter release (Lüscher et al. 1997). Therefore, a more straightforward model, initially proposed in the 1980s, is the disinhibition of DA neurons by opioids because VTA GABA neurons are shut down (Johnson & North 1992).

Researchers have proposed similar disinhibition models for γ -hydroxybutyrate (GHB) (Cruz et al. 2004) and benzodiazepines (Tan et al. 2010), both substances with addiction liability. For the former, the molecular target is the GABA_B receptor, expressed both on GABA and DA neurons of the VTA. However, DA neurons do not express GIRK1, and agonist concentrations an order of magnitude higher are therefore required to half-activate the GABA_B receptor effector channel currents (EC₅₀) (Labouèbe et al. 2007). Consequently, there is a concentration window in which the main effect of GHB is mediated through VTA GABA neurons, which leads to disinhibition of DA neurons. Benzodiazepines, which are positive allosteric modulators (PAMs) at GABA_A receptors, cause strong inhibition of VTA GABA neurons by virtue of a cell type-specific expression of receptor subunits (Tan et al. 2010). The GABA_A alpha 1 subunit is expressed exclusively in GABA neurons, conferring larger single-unit conductance to GABA_A receptors on GABA neurons compared to DA neurons, which express channels made of alpha 2/3. Benzodiazepines exacerbate this difference, and little transmitter is released from VTA GABA neurons. As a consequence, there is no GABA that can be amplified by benzodiazepines on DA neurons; this ultimately leads to disinhibition and enhanced release of DA.

The Mechanistic Classification of Addictive Drugs

Taken together, three distinct cellular mechanisms suffice to propose a mechanistic classification of addictive drugs (Lüscher & Ungless 2006). There are those drugs that can depolarize DA neurons directly (nicotine), those that interfere with reuptake (cocaine, amphetamines, and ecstasy), and a third group that leads to disinhibition (opioids, cannabis, benzodiazepines, and GHB). Thus, a comprehensive model is emerging, despite some remaining questions, most prominently how to classify ethanol. There is no doubt that ethanol stimulates DA neurons (Gessa et al. 1985) and increases mesolimbic DA (Di Chiara & Imperato 1988), but the relevant molecular target and the cellular mechanism remain elusive.

Increasing the levels of mesolimbic DA as a common pathway of addictive drugs is in line with the DA prediction error hypothesis (for recent reviews, see Keiflin & Janak 2015, Schultz 2011). Much experimental evidence indicates that under physiological conditions, the phasic activity of VTA DA neurons generates a learning signal when an unexpected reward occurs (Schultz et al. 1997). The purpose of this signal would be to promote learning such that reward can again be obtained. Once the reward becomes fully predictable, DA neurons will no longer be activated, and learning ceases (which makes sense as the behavior is now optimized). The sheer pharmacological power of addictive drugs can override this system, thus generating an inappropriate learning signal that ultimately leads to compulsive drug intake at the expense of all other behavior. In this model,

GHB:

γ -hydroxybutyrate, a commonly used club drug

NMDAR: ionotropic glutamate receptor defined by its selectivity for *N*-methyl-D-aspartate made of an obligatory GluN1 subunit that assembles with GluN2 or GluN3

addiction should be considered a gain-of-function disease, as an excessively strong increase of mesolimbic DA concentration is at the origin of the behavioral dysfunction.

If this is true, then direct, sustained stimulation of these neurons should have similarly reinforcing effects. Several studies using optogenetic approaches appear to confirm this prediction. Pairing an environment with optogenetic stimulation of VTA DA neurons leads to an immediate place preference that persists for several days (Adamantidis et al. 2011, Tsai et al. 2009). Self-stimulation of VTA DA neurons is reinforcing, and mice will press a lever several hundred times per hour just to receive burst-activation of DA neurons. That injection of an addictive drug strongly occludes optogenetic DA neuron self-stimulation (Pascoli et al. 2015) is another argument that the same system drives the underlying motivation.

Although addictive drugs target DA neurons without distinction, specific projections from the VTA probably contribute more than others do to the rewarding and ultimately addictive effects. Circumstantial evidence suggests a crucial role for VTA DA neuron projections to the NAc. A subset of DA neurons may also code aversive stimuli (Lammel et al. 2014). If this were the case, one might speculate that their strong activation may give rise to adaptations in circuits underlying the proposed opponent process, recently reviewed elsewhere (Koob 2009). Combining cell type specificity and projection targeting with optogenetic activators will help to resolve the issue of the relative contribution by subpopulations.

DRUG-EVOKED SYNAPTIC PLASTICITY: THE TRACE OF DRUG EXPOSURE

By definition, relapse occurs when subjects are off drugs. Any neural substrate conferring the risk to start taking drugs again must therefore be a trace that addictive substances leave behind once they have been cleared from the body. In 2001, a seminal study (Ungless et al. 2001) reported that a single dose of cocaine was sufficient to induce a trace at excitatory synapses onto VTA DA neurons that lasted for about a week, and in 2003, the same group showed that the trace could also be observed after a dose of morphine, nicotine, alcohol, or amphetamines (Saal et al. 2003). These two publications initiated much research on changes in glutamatergic transmission caused by exposure to addictive substances, a phenomenon called drug-evoked synaptic plasticity (Lüscher & Malenka 2011). Drug-evoked synaptic plasticity occurs at many other excitatory synapses of the mesocorticolimbic system and beyond as well as at GABAergic synapses, where it can affect the fast (Bocklisch et al. 2013, Liu et al. 2005, Nugent & Kauer 2008) and slow inhibitory postsynaptic current (Padgett et al. 2012). It is beyond the scope of the present review to provide a comprehensive list of all reports of drug-evoked synaptic plasticity. Here we focus on plasticities in the VTA and the NAc, which are affected most directly by the increase of DA caused by addictive drugs. We review their mechanism of induction, expression, and possible cellular reversal protocols. The epigenetic and transcriptional regulation that is part of the underlying molecular mechanisms are reviewed elsewhere (Kenny 2014, Robison & Nestler 2011).

One-Shot Plasticity in the Ventral Tegmental Area

In DA neurons of the VTA, particularly in those that project to the NAc, excitatory afferents from the laterodorsal tegmentum (a brain stem nucleus) are potentiated for several days, starting hours after the first exposure of the animal to any addictive drug (Lammel et al. 2012). The induction depends on *N*-methyl-D-aspartate receptors (NMDARs) and DA D1 receptors (D1Rs) (Ungless et al. 2001), which are activated when DA neurons become active and release DA from their dendrites. The NMDARs that drive the induction are located on DA neurons themselves, as the

plasticity is abolished in mice that have the obligatory NMDAR subunit GluN1 removed conditionally from DA neurons (Engblom et al. 2008). This finding was confirmed by a sophisticated pharmacological experiment in which a masked version of the NMDAR open-channel blocker is made cell membrane-permeable and then activated enzymatically in select DA neurons (Yang et al. 2015). The locus of the D1Rs has not been investigated fully, but the relevant receptors are most likely expressed on the presynaptic terminals of excitatory afferents. The induction of this form of plasticity is therefore a VTA-autonomous process.

The characterization of the expression mechanism took many years. Initial work suggested that the potentiation was due to the insertion of additional α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA), whereas the NMDARs would remain unaffected (Ungless et al. 2001). This interpretation was based on the observation that the ratio of the amplitude of AMPAR/NMDAR-mediated postsynaptic currents (A/N ratio), a parameter often used to quantify synaptic strength in the acute brain slice preparation, was higher than normal. However, the current model favors a more complex scenario, whereby native AMPARs are exchanged for receptors that lack the GluA2 subunit; conversely, canonical NMDARs are switched for receptors that contain the GluN3 subunit (Mameli et al. 2011, Yuan et al. 2013).

Canonical NMDARs are heteromers made from two GluN1 subunits and two GluN2 subunits, which can be of either the 2A or 2B splice variant (Paoletti et al. 2013). Such receptors do not flux current at negative potentials owing to magnesium block of the pore. When depolarized, the magnesium detaches and the receptors can readily flux calcium. By contrast, heterotrimeric NMDARs are assembled from two GluN1, one GluN2, and one GluN3 subunit (Pérez-Otaño et al. 2001). Such receptors flux hardly any calcium and are insensitive to magnesium. In the VTA of naive animals, canonical NMDARs are present and permeable to calcium when depolarized, which is essential for the induction of activity-dependent as well as drug-evoked synaptic plasticity. After cocaine exposure, changes in the current-voltage relationship, the sensitivity of subunit specific pharmacology, and the direct visualization of the reduced calcium influx are indicative of the presence of heterotrimeric NMDARs (Yuan et al. 2013). The observation that this form of drug-evoked synaptic plasticity is absent in GluN3 knockout mice confirms this.

Calcium-Permeable AMPA Receptors

AMPA receptors typically contain one or two GluA2 subunits, which, through posttranscriptional editing, exchange a glutamine residue for a larger and polarized arginine residue (Q/R editing) in the pore region (Liu & Zukin 2007, Wolf & Tseng 2012). As a result, AMPARs have a linear current-voltage curve that reverses at 0 mV and are virtually calcium impermeable. In fact, in DA neurons of drug-naive adult animals, all AMPARs are calcium impermeable (CI-AMPA). After drug exposure, although the total number of receptors remains constant, a substantial fraction of receptors are exchanged for calcium-permeable (CP) ones (Bellone & Lüscher 2006). Because CP-AMPA also have a higher single-channel conductance, this exchange results in a net potentiation of the AMPARs' excitatory postsynaptic current (EPSC). The presence of CP-AMPA is demonstrated by the inwardly rectifying current-voltage curve. Moreover, endogenous spermines inhibit the EPSC at positive potentials, whereas specific pharmacological substances, such as Joro spider toxin or 1-naphthyl acetyl spermine (nasp), can also block synaptic currents at negative potentials.

Given the dual redistribution of NMDARs and AMPARs, the increased A/N ratio receives a different interpretation. This ratio, when calculated by dividing the amplitudes of the EPSCs measured at +40 mV, increases because the decrease in NMDA current exceeds the partial reduction of the macroscopic AMPA current. The latter is due to the rectification, which yields smaller currents at positive potentials, even if the number of receptors remains identical. Functionally,

AMPA: ionotropic glutamate receptor defined by its selectivity for α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

RMTg: rostromedial tegmentum, a nucleus adjacent to the VTA made of GABA neurons that inhibit DA neurons

the switch of the synaptic source of calcium may impact the induction of activity-dependent plasticity (Mameli et al. 2011). In naive animals, afferent activity paired with a depolarization leads to a long-term potentiation (LTP)-like strengthening of transmission driven by calcium fluxing through canonical NMDARs. After cocaine exposure, this protocol becomes inefficient, but LTP can be rescued by pairing afferent stimulation with the hyperpolarization of the DA neurons, which facilitates calcium entry through CP-AMPARs. Although there is good evidence that such a scenario exists in acute brain slices, no experimental evidence has yet demonstrated the significance of this metaplasticity *in vivo*.

As already suggested by the initial publications, all addictive drugs tested to date induce this form of drug-evoked synaptic plasticity. Specifically, changes in A/N ratio, rectification, or both have been reported for cocaine, amphetamine, nicotine, morphine, heroine, diazepam, midazolam, ethanol, and cannabis (Good & Lupica 2010, Heikkinen et al. 2009, Saal et al. 2003, Tan et al. 2010, Ungless et al. 2001). The orexin system seems to play an additional modulatory role, as blocking orexin receptors also inhibits drug-evoked synaptic plasticity (Baimel et al. 2015, Borgland et al. 2006). No plasticity occurs with nonaddictive psychoactive substances such as carbamazepine or fluoxetine (Saal et al. 2003). The plasticity has even been observed *ex vivo* a day after 2-h optogenetic stimulation of DA neurons, mimicking the activity typically observed with opioids or nicotine (Brown et al. 2010). Intra-VTA application of a D1R antagonist blocked the induction of this optogenetically driven plasticity, in line with a VTA-autonomous process, just as with addictive drugs. Strong DA neuron stimulation is therefore sufficient to elicit the switch of AMPARs and NMDARs observed with addictive drugs.

The VTA is also the locus for plasticity in inhibitory circuits with opposing effects on DA neuron activity. VTA GABA neurons are the preferential target of inhibitory afferents from D1R medium spiny neurons (MSNs). These afferents enhance their release probability upon cocaine exposure [five daily injections (Bocklisch et al. 2013)], causing a disinhibition of DA neurons, which may play an important role in the progression of the plasticity to more dorsal parts of the striatum (Everitt & Robbins 2013).

Conversely, VTA GABA neurons [particularly those located in the tail of the VTA or rostromedial tegmentum (RMTg) (Jhou et al. 2009)] receive inputs from glutamate neurons of the lateral habenula (LHb). These cells are known to encode aversive stimuli (Matsumoto & Hikosaka 2009, Proulx et al. 2014). Cocaine exposure potentiates the LHb-VTA GABA neuron projection (Maroteaux & Mameli 2012) by inserting additional AMPARs and increasing intrinsic excitability of the cell bodies (Jhou et al. 2013, Meye et al. 2015). This plasticity may counteract the potentiation of direct excitatory afferents, as the net effect is an enhanced inhibition of DA neurons, which may contribute to aversive affect during withdrawal.

Delayed Plasticity in the Nucleus Accumbens

Drug-evoked synaptic plasticity also occurs at excitatory afferents onto MSNs of the NAc. Two elements are important in this context. First, whereas in the NAc, drug-evoked plasticity can be detected a day after the end of chronic drug exposure, it evolves during the first couple of weeks after withdrawal (Thomas et al. 2001). Most studies focus on this consolidated form, which coincides with specific drug-adaptive behavior (see below). Second, the two major classes of MSNs of the NAc—the ones that express D1Rs and those that express D2Rs—differ fundamentally. Drug-evoked synaptic plasticity in the two populations follows distinct induction rules, contrasting molecular expression mechanisms and opposing functional consequences.

Initial studies applied five injections of cocaine to find a decrease in the A/N ratio and an occlusion of the induction of long-term depression (LTD) in acute slices of the NAc a day after

the last injection (Thomas et al. 2001). Within two weeks, this situation reversed into a higher than normal A/N ratio (Kourrich et al. 2007). At this stage, LTD was enhanced, whereas LTP was occluded (Thomas et al. 2001). Moreover, a challenge dose of cocaine at the end of the withdrawal period reestablished the low A/N ratio. In other words, exposure to several injections of cocaine leads to a depression of synaptic transmission that reverses into a potentiation within a couple of weeks but decays within hours if cocaine is reapplied. This sequence of events can also be retraced with biochemical assays quantifying the pool of receptors on the membrane surface (Wolf & Ferrario 2010), confirming a postsynaptic expression mechanism.

The initial depression of transmission is associated with the appearance of many NMDAR-only—and therefore silent—synapses, which are then transformed gradually into functional units during the withdrawal period (Brown et al. 2011, Lee et al. 2013). Much biochemical evidence indicates that the concomitant activation of D1R and NMDARs engages a signaling cascade that, through the mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK), supports protein translation and the potentiation of the EPSC (Pascoli et al. 2011). In agreement with this idea, a stimulation protocol that induces LTP efficiently in acute NAc brain slices also activates ERK, and applying an ERK inhibitor blocks LTP in the NAc (Pascoli et al. 2012).

Similar to the VTA, there is good evidence for CP-AMPA receptors in neurons of the NAc following drug exposure. Although some researchers have claimed that CP-AMPA receptors appear only when cocaine is self-administered (Conrad et al. 2008, Wolf & Tseng 2012), other studies find CP-AMPA receptors also after noncontingent (i.e., experimenter-administered) drug exposure (Boudreau et al. 2007, Mameli et al. 2009). The application protocol and the cocaine dose seem to play a role in determining which neurons undergo plasticity (**Figure 2**). A recent study suggests that doses up to 0.75 mg/kg per injection in mice induce the plasticity in D1R-MSNs selectively, whereas higher doses recruit D2R-MSNs as well (Terrier et al. 2015). Researchers have not investigated the induction mechanism for the insertion of GluA2-lacking AMPARs in D2R-MSNs, but it is obviously not driven by the D1R as described above.

For almost all experimental work on drug-evoked synaptic plasticity in the NAc, researchers used cocaine, but similar adaptations also occur with morphine (Hearing et al. 2016). Moreover, 12 days of optogenetic self-stimulation of VTA DA neurons elicits a synaptic plasticity in D1R-MSNs that is indistinguishable from changes observed after cocaine self-administration (Pascoli et al. 2015), suggesting that strong stimulation of the mesolimbic DA system is ultimately the cause of the plasticity in the NAc as well.

Metabotropic Glutamate Receptor 1–Long-Term Depression to Reverse Drug-Evoked Synaptic Plasticity

In both the VTA and NAc, metabotropic glutamate receptors (mGluRs) are responsible for the removal of CP-AMPA receptors (Bellone & Lüscher 2006, McCutcheon et al. 2011). Owing to their location at the periphery of the postsynaptic density, activation requires trains of action potentials at frequencies above 10 Hz, such that glutamate transients in the synaptic cleft can reach the metabotropic receptors. The plasticity induced by mGluR1 activation causes a depression of the AMPA current as high-conductivity CP-AMPA receptors are replaced by low-conductivity CI-AMPA receptors. The signaling involves mammalian target of rapamycin and protein synthesis, most likely from prefabricated mRNA, among which some code for the immediate early gene *Arc* and the GluA2 subunit (Mameli et al. 2007, Waung et al. 2008).

In the slice preparation, as well as in vivo, PAMs can be used to facilitate this reversal process, and, at least for the VTA, there is good evidence that mGluR1 activation is the endogenous mechanism limiting the duration of the expression of cocaine-evoked synaptic plasticity (Mameli et al.

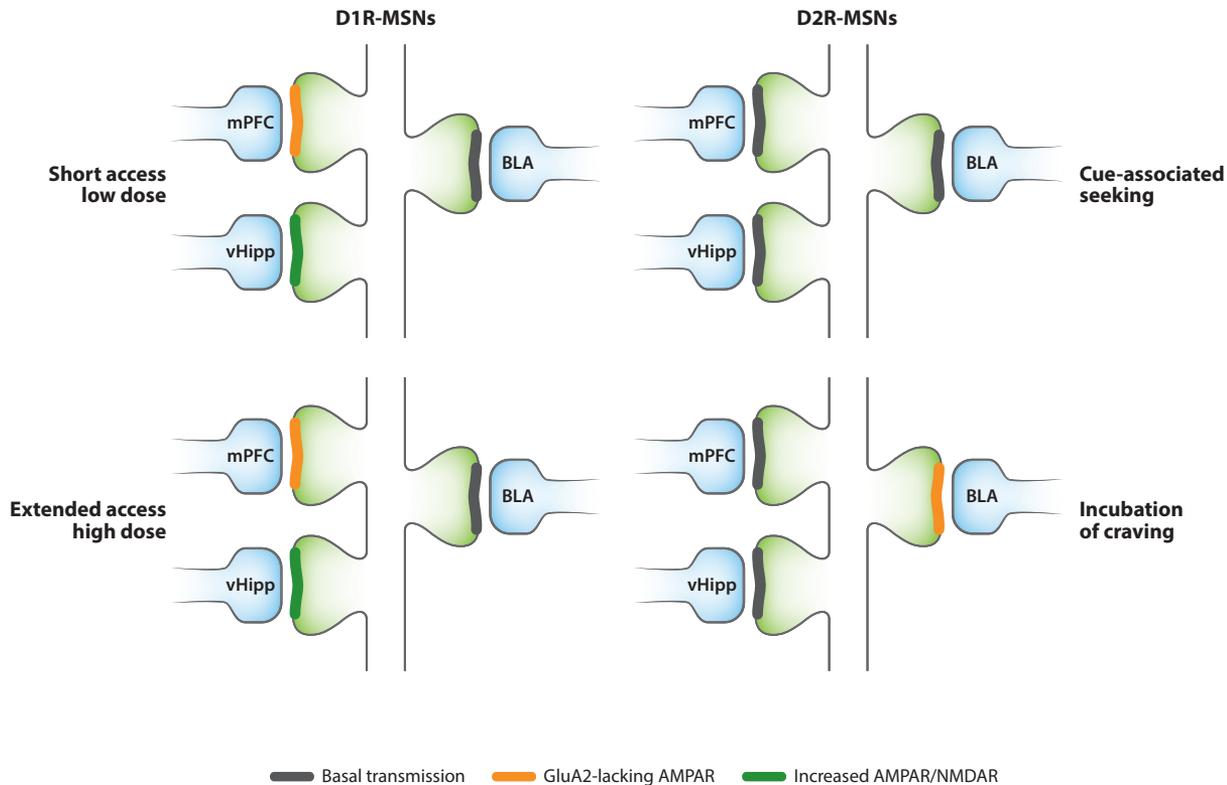


Figure 2

Synapse-specific plasticity in nucleus accumbens. Contrasting expression mechanisms of drug-evoked synaptic plasticity are shown in select projections. Note that the exposure to high concentrations of cocaine leads to insertion of GluA2-lacking AMPARs in both D1R- and D2R-MSNs, albeit at distinct inputs. Abbreviations: AMPAR, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BLA, basolateral amygdala; D1R, dopamine D1 receptor; D2R, dopamine D2 receptor; mPFC, medial prefrontal cortex; MSN, medium spiny neuron; NMDAR, *N*-methyl-D-aspartate receptor; vHipp, ventral hippocampus.

2009). Any deficit of mGluR1 function, be it by pharmacological inhibition or genetic alterations, may make the cocaine-evoked plasticity more permanent. Recent evidence also suggests that the surface expression of mGluR1 receptors may be downregulated by sustained exposure to cocaine (Scheyer et al. 2014).

Changes in Cortical Excitability

Drug-evoked synaptic plasticity in cortical areas may also depend on D1R signaling, with several investigators reporting changes in excitability of layer V pyramidal cells (some of which project to the NAc) (Buchta & Riegel 2015). For example, input-output curves in slices from animals that were exposed to cocaine are altered, reflecting a reduced excitability (Chen et al. 2013). Neither the molecular induction and expression mechanism nor the *in vivo* correlate are known, but the excitability changes are believed to drive plasticity at the target of the projection in the NAc. Major differences seem to exist between the medial prefrontal cortex (mPFC) (hypoexcitability) and the orbitofrontal cortex (OFC) (hyperexcitability) and even within the mPFC [infralimbic versus prelimbic parts (Kalivas et al. 2005, Peters et al. 2008)]. These changes in excitability

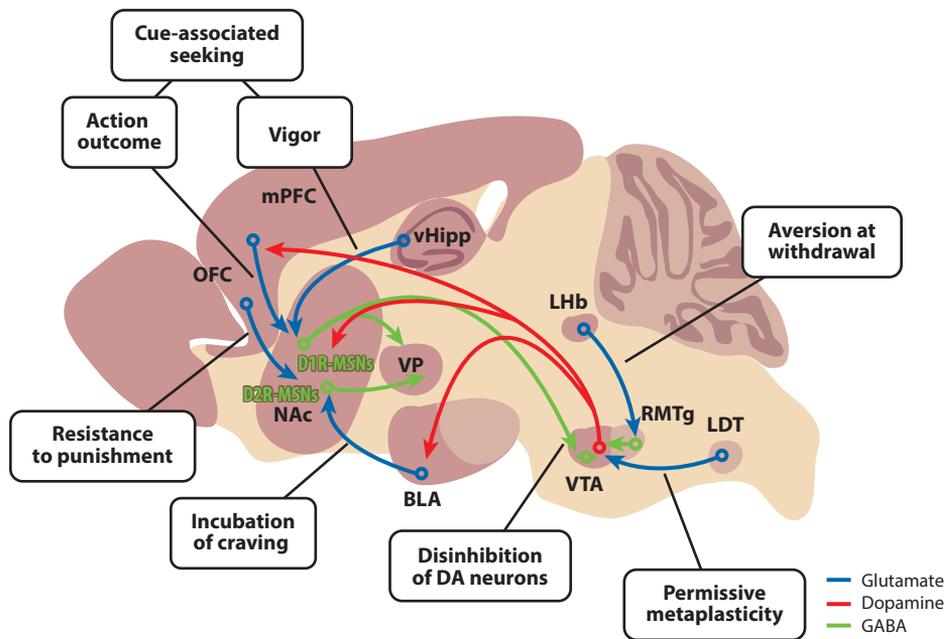


Figure 3

Disease-relevant circuits. Major connections undergoing drug-evoked synaptic plasticity and associated drug-adaptive behavior are shown on a sagittal section of the brain. Note that most of the connections where drug-evoked synaptic plasticity was characterized are glutamatergic, with the exception of the inhibitory afferents from the NAc onto VTA GABA neurons. Red indicates dopamine, blue indicates glutamate, and teal indicates GABA. Abbreviations: BLA, basolateral amygdala; D1R, dopamine D1 receptor; D2R, dopamine D2 receptor; LDT, laterodorsal tegmentum; LHb, lateral habenula; mPFC, medial prefrontal cortex; MSN, medium spiny neuron; NAc, nucleus accumbens; OFC, orbitofrontal cortex; RMTg, rostromedial tegmentum; vHipp, ventral hippocampus; VP, ventral pallidum; VTA, ventral tegmental area. Modified from Lüthi & Lüscher (2014) with permission.

are of particular interest because several studies (Chen et al. 2013, Kasanetz et al. 2012, Pascoli et al. 2015) suggest that the extent of plasticity may be bimodally distributed in the experimental population and reflect the resistance to punishment when self-administering cocaine (see below).

REMODELING CIRCUITS WITH DRUGS

A prerequisite to elucidating the functional consequences of the various forms of drug-evoked synaptic plasticity is the identification of the connection that has been modified. Recent functional tracing methods, and above all optogenetic projection targeting, have allowed decisive progress in dissecting the behaviorally relevant circuitry (Figure 3).

In the VTA, by targeting channelrhodopsin to specific inputs onto DA neurons, researchers have shown that cocaine potentiates inputs primarily from the brain stem, notably the laterodorsal tegmentum (Lammel et al. 2012). In contrast, inputs from the mPFC remain largely unchanged.

In the NAc, MSNs are the sites of convergence of several afferents that undergo cocaine-evoked synaptic plasticity. For example, after withdrawal from short-access, low-dose cocaine self-administration, the input from the ventral hippocampus (vHipp) onto D1R-MSNs becomes potentiated by the insertion of CI-AMPA receptors (Pascoli et al. 2014). In contrast, EPSCs elicited by

Locomotor sensitization: a process in which repeated injections of a given dose of cocaine result in the progressive amplification of the locomotor response

stimulation of afferents from the mPFC become rectifying, i.e., CP-AMPA receptors appear at different synapses on the same dendrite. Finally, afferents from the basolateral amygdala (BLA) to D1R-MSNs remain unchanged unless rodents are allowed extended access to a higher dose of cocaine, at which point CP-AMPA receptors start to appear at BLA synapses onto D2R-MSNs as well (Terrier et al. 2015). With morphine, CP-AMPA receptors appear at a thalamic input onto D2R-MSNs (Zhu et al. 2016).

Another aspect that remains only partially understood is the possible hierarchical organization of drug-evoked synaptic plasticity throughout the mesolimbic system. Evidence suggests that the potentiation at excitatory afferents in the NAc occurs only if the VTA afferent remains potentiated for more than a week (Mameli et al. 2009). For example, when a PAM of mGluR1 was used to reverse plasticity quickly in the VTA (see above), even several injections of cocaine failed to cause plasticity in the NAc. The signals governing the march of plasticity from the VTA to the NAc remain to be determined.

ESTABLISHING CAUSALITIES: THE LINK TO DRUG-ADAPTIVE BEHAVIOR

Knowledge of the molecular mechanisms underpinning specific forms of drug-evoked synaptic plasticity, together with the anatomical identification of the relevant connections, has enabled the design of specific reversal approaches. The goal of this work is to establish links of causality between drug-evoked synaptic plasticity at identified synapses and drug-adaptive behaviors. The blueprint for these experiments (Lüscher 2013) therefore starts with the *ex vivo* characterization of the drug-evoked synaptic plasticity, followed by the establishment of a reversal protocol that is first validated in the slice and then applied *in vivo* to monitor the effect on the drug-adaptive behavior. The reversal protocol can be pharmacological or a more specific optogenetic stimulation at a defined input. In both cases, the removal of CP-AMPA receptors by activation of the mGluR1 has proved particularly powerful.

Pharmacological Approaches

In the VTA, systemic application of an mGluR1 PAM restores baseline transmission efficiently by driving the synthesis of CI-AMPA receptors (Mameli et al. 2007). The behavioral impact of the drug-evoked synaptic plasticity is less clear. Most drug-adaptive behaviors with a similar time course remain unaffected, including locomotor sensitization and conditioned place preference. Mice in which NMDARs were abolished selectively on VTA DA neurons (and thus the cocaine-evoked plasticity in these cells failed to induce) self-administer cocaine normally, but they have a reduced cue-associated seeking behavior when tested weeks later (Engblom et al. 2008).

This temporal dissociation between plasticity that appears in the VTA within hours and the associated behavior, which manifests weeks later, suggests that the synaptic changes in the VTA may be merely a permissive metaplasticity (Creed & Lüscher 2013). In other words, the appearance of CP-AMPA receptors puts VTA DA neurons in a different state that allows changes in the NAc to occur eventually (Mameli et al. 2009). This idea is in line with the concept of a teaching signal function of DA neurons that stems from the temporal difference learning model (Keiflin & Janak 2015) discussed above. This model, although highly appealing, has not been tested fully, and recent systematic recordings in VTA neurons indicate a high degree of variability in the activation pattern of DA neurons (Cohen et al. 2012). Moreover, some drug-adaptive behavior may occur independently of plasticity in the VTA. For example, in GluN1 knockout mice conditional for

DA neurons, locomotor sensitization induced by cocaine is normal, which, as we see below, has been linked to plasticity in the NAc (Engblom et al. 2008).

The strongest links of causality have been established between cocaine-evoked synaptic plasticity in the NAc and two forms of drug-adaptive behavior: cue-associated drug seeking and incubation of craving. For the latter, infusion of naspm (an inhibitor of GluA2-lacking AMPARs) directly into the NAc reduces the increase of lever pressing typically observed during the time of withdrawal (Conrad et al. 2008). Similarly, boosting mGluR1 function with a locally applied mGluR1 PAM again reduces cue-associated seeking and incubation of craving (Loweth et al. 2014).

Optogenetic Approaches

Researchers have used optogenetic projection targeting to induce LTD and thus reverse cocaine-evoked synaptic plasticity to restore baseline transmission even more selectively. The first study implementing this approach looked at locomotor sensitization and found that an NMDAR-dependent LTD was sufficient to depotentiate inputs from the mPFC to the NAc and erase this form of drug-adaptive behavior (Pascoli et al. 2012). A similar approach applied to downregulate CP-AMPA receptors at amygdala-to-NAc synapses to resilience synapses after prolonged withdrawal attenuated incubation of cocaine craving (Ma et al. 2014). In the latter case, investigators chose a stimulation protocol that activated mGluR1 efficiently.

Both NMDAR-LTD and mGluR-LTD can be efficient at reversing individual components of drug-adaptive behaviors. Owing to the higher stimulation frequency (>10 Hz leading to spillover; see above), mGluR1-LTD also has a heterosynaptic component (Lüscher & Huber 2010). For example, a 12-Hz protocol applied to the vHipp to NAc input can remove CP-AMPA receptors at the mPFC to NAc input. In contrast, 1 Hz-evoked NMDAR-LTD applied at the same input removes CI-AMPA receptors at this input only (homosynaptic effect). By exploiting these protocols in mice after withdrawal from cocaine self-administration, researchers have deconstructed cue-associated seeking behavior (Pascoli et al. 2014). When cocaine-evoked plasticity was reversed selectively at the mPFC input, mice still showed a strong seeking behavior but were unable to predict the action outcome as they pressed the active lever (a previously cocaine-associated lever) or the inactive lever (a lever never associated with cocaine infusions) without distinction. Conversely, reversal of the vHipp input left lever discrimination intact but reduced the number of presses on the active lever, a reflection of the reduced seeking vigor. Normalizing transmission at both inputs erased seeking behavior. Importantly, in this study that used a short-access session to low doses of cocaine, no synaptic changes were observed at the BLA input, and mice did not show incubation of craving (defined as an increase in drug seeking during withdrawal).

Just as with addictive drugs, optogenetic DA neuron self-stimulation leads not only to reinforcement but also to cue-associated stimulation seeking and is sufficient to induce resistance to punishment in a fraction of mice (Pascoli et al. 2015). This fraction (65–75%) is substantially higher than what is observed typically with cocaine (20–30%, depending on the study). This indicates that VTA DA neuron self-stimulation is sufficient to induce addiction (at least a simple form of the disease in rodents), and it does so more efficiently than the most addictive drugs. The non-specific nature of the pharmacological activation (e.g., cocaine also increases monoamines other than DA) may in some way actually be protective.

In this study, resistance to punishment was found to segregate with enhanced excitability of pyramidal neurons of the OFC, and chemogenetic modulation of OFC excitability affected resistance to punishment, thereby establishing causality (Pascoli et al. 2015). These findings complement a study in which optogenetic activation of the prefrontal cortex inhibited cocaine seeking in resistant rats, whereas inhibition of the same area had the converse effect (Chen et al. 2013). As

Incubation of craving: cocaine seeking, when triggered by reexposure to drug-associated cues, progressively increases over the first two months after withdrawal from self-administration of the drug

argued above, research on the molecular and cellular mechanisms of cortical plasticity is still in its infancy, and much additional research will be needed to integrate these circuits in the emerging model. For example, OFC activity is inversely correlated with habitual learning (Gremel & Costa 2013a,b), which raises the question of whether habitual learning and compulsive drug use are sequential steps in the progression to addiction. This question is also of particular relevance in the context of the proposed shift from ventromedial to dorsolateral stratal circuits as compulsive drug consumption takes over (Everitt & Robbins 2013). The synaptic mechanisms governing the recruitment of more and more dorsal loops remain elusive, but they are likely to include plasticity of GABA transmission (Bocklisch et al. 2013) or modulation by cholinergic signaling covered elsewhere (Threlfell & Cragg 2011).

In models of adverse effects observed during acute withdrawal, the behavioral correlate of enhanced inhibition onto VTA DA neurons may be a depression-like state, as a dominant negative peptide inhibiting the insertion of GluA1 and thus preventing the potentiation from the LHb to the RMTg abolishes enhanced immobility significantly in the forced swim test. This is a marker of depression-like behavior typically observed during cocaine withdrawal (Meyer et al. 2015). Optogenetic reversal of the potentiation between the thalamus and the NAc attenuated the state of strong dysphoria observed during withdrawal from morphine (Zhu et al. 2016).

Taken together, these experiments provide compelling evidence for a link of causality between drug-evoked synaptic plasticity and drug-adaptive behavior. Current studies now aim to characterize the ensuing alteration in neural activity, starting with distinct populations in the NAc and cortical areas. Interestingly, researchers have used PET imaging to establish a positive correlation between craving and OFC activity, and the projection to the NAc has been implicated in the compulsive component of consummatory behavior (Volkow et al. 2005). In contrast, most of the preclinical literature describes drug-adaptive changes that occur in all animals. The exception is that the excitability changes in cortex are seen only in rodents that are resistant to punishment, thus coming closest to a simple definition of actual addiction.

THERAPEUTIC IMPLICATIONS: OPTOGENETICALLY INSPIRED DEEP BRAIN STIMULATION

Given the power of optogenetic reversal protocols to erase drug-adaptive behavior, one might be tempted to explore translational aspects of this approach. Wouldn't it be great to correct pathological circuit function, such that an addict could again control his or her decisions and lead a normal life? This may become possible eventually, yet, in our opinion, not in the near future (Lüthi & Lüscher 2014). Many obstacles remain, such as the need for cell type-specific targeting, the failure to express opsins stably for the intended duration of the therapy (typically years), or the threat of long-term toxicity. Much development will be required to overcome these limitations. There might, however, be a window in which to take advantage of optogenetics for the development of novel protocols of established circuit therapies. Two techniques come to mind: deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS). Compared to optogenetics, electrical and magnetic stimulation is, however, nonspecific, and the sought-after effects may be masked by activation of other neural structures and projections.

Characterizing pathological circuit function with optogenetics, with the goal to design blueprints for manipulations aiming at restoring normal circuit function, could constitute an alternate approach (Lüscher 2013). The initial step consists of reversing the pathological behavior, still with optogenetics, in preclinical disease models. Next, the challenge consists of establishing ways to emulate the optogenetic protocols with DBS, still in an animal model. The goal is to obtain a similar effect on behavior while validating the underlying mechanism, ideally also in nonhuman

primates. Then, and only then, clinical trials could be envisioned that start with tests for safety and efficacy. In other words, optogenetically inspired DBS may be the hic et nunc translation of optogenetics.

Only a few studies have been published that may provide proof of principle for this approach. A novel DBS protocol to reverse locomotor sensitization to cocaine is one example (Creed et al. 2015). As discussed above, this behavior is driven by a potentiation of excitatory afferents onto D1R-MSNs in the NAc. Optogenetic reversal through an mGluR1-dependent LTD mechanism (10–15 Hz stimulation for 10 min) erases the drug-adaptive behavior (Pascoli et al. 2012). Initial attempts with DBS in the NAc in mice applying a similar stimulation parameter (10–15 Hz for 10 min the day before the testing), however, failed to reverse locomotor sensitization, and classical DBS (130 Hz continuous stimulation) had only a transient, nonspecific effect. The ex vivo analysis in the slice preparation showed that neither of the DBS protocols were able to induce the mGluR-LTD required to restore baseline transmission (**Figure 4**). This is not surprising because the nonspecific electrical stimulation was also driving DA release from midbrain afferents that, when activating D1R, inhibited the signaling cascade required to express mGluR-LTD (Shen et al. 2008). This scenario was confirmed by the rescue of mGluR-LTD in the presence of a D1R antagonist (SCH 23390 or SCH 31166) and the ensuing erasure of the locomotor sensitization. The D1R antagonist, paired with short, low-frequency DBS protocols, was efficient when applied directly into the NAc, as well as when given systemically, demonstrating the locus of action and suggesting a translational approach, respectively. This optogenetically inspired DBS protocol differs fundamentally from currently used clinical DBS protocols, as they use intermittent stimulation, use a different frequency, and are paired with a pharmacological adjuvant to enhance specificity.

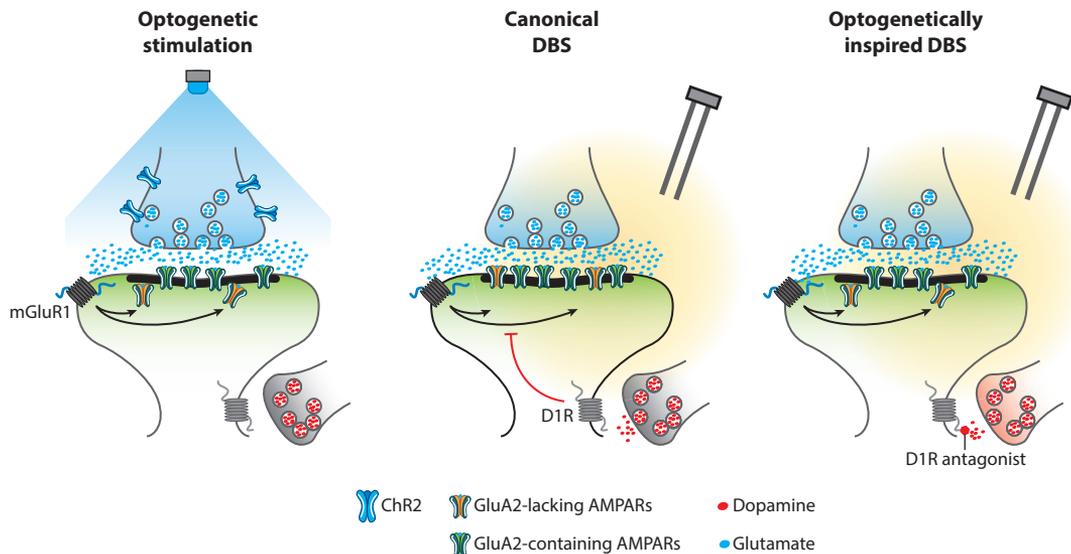


Figure 4

Optogenetically inspired DBS. Optogenetic stimulation causes selective release of transmitter from glutamate afferents (blue). With strong stimulation, glutamate reaches the perisynaptically located mGluR1s, which trigger an intracellular signaling cascade, eventually removing GluA2-lacking AMPARs (teal) inserted previously by cocaine exposure. Canonical DBS fails to trigger this process because the electrodes also stimulate DA afferents (red). As a consequence, D1R signaling inhibits the expression of mGluR1 depotentiation. Optogenetically inspired DBS associates electrical stimulation with a D1R antagonist (e.g., SCH23390, red hexagon), thus blocking the D1R signaling and rescuing mGluR1-depotentiation of the synapse. Modified from Creed et al. (2015) with permission.

Similar protocols can likely be established for addiction by targeting other nodes of the disease-relevant circuitry [in this regard, the superficial cortical areas may be a much better target for optogenetically inspired TMS protocols, as suggested by a recent pilot study (Terraneo et al. 2015)]. A comprehensive characterization of adaptive synaptic changes may reveal additional targets where circuit-breaking manipulations may be successful.

CONCLUSIONS AND PERSPECTIVES

In summary, the circuit model of drug addiction proposed here is based on much experimental evidence collected in rodents, taking advantage of simplified yet robust behavioral models for this brain disease. Various forms of drug-evoked synaptic plasticity represent the key mechanism underlying altered circuit function and eventually drug-adaptive behavior. The earliest forms are observed at the origin of the mesolimbic DA system, in DA neurons of the VTA, but with repetitive exposure then spread to the NAc. A commonality of many forms of drug-evoked synaptic plasticity is the appearance of CP-AMPA receptors, which may shape altered circuit function by changing the rules for the induction of experience-dependent plasticity. The identification of the disease-relevant changes in circuits has become possible with enhanced techniques of modern neuroscience, above all optogenetics. Ongoing studies focus on the determinants of individual vulnerability. Epigenetic mechanisms are likely to play an important role in the molecular mechanisms underlying drug-evoked synaptic plasticity or environmental factors that increase individual vulnerability (e.g., stress). Knowledge about circuit adaptations in addiction also allows probing of novel therapeutic approaches. Over the past few years, optogenetic strategies have thus emerged that treat drug-adaptive behavior in animals based on rational predictions. Although applicable exclusively in animal models, they may lead the way for circuit manipulations in humans using DBS or TMS, a strategy we call optogenetically inspired DBS and TMS, which may also extend to additional indications.

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