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Disease focus:

Drug-evoked synaptic plasticity causing addictive behavior.

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Introduction. The clinical manifestations of drug addiction are the subject of medical literature and fiction alike. In the “Novel with Cocaine”, first published almost 80 years ago under a pseudonym and only recently rediscovered, Mark Levi provides a disturbing account of a young Russian man becoming addicted to cocaine. Vadim, the novel’s antihero reflects: “Before I came in contact with cocaine I assumed that happiness was an entity, while in fact all human happiness consists of a clever fusion of two elements: the physical feeling of happiness, and the external event providing the psychic impetus for that feeling”.

This statement eloquently describes a core element of the addiction process. An initially neutral stimulus becomes attractive when associated with drug consumption, and even after prolonged periods of abstinence, this cue may trigger craving and cause the subject to relapse (Stewart et al., 1984; Childress et al., 1988). The risk for relapse that remains high for years of abstinence, which constitutes a major challenge for treating drug addiction.

Therefore, many researchers have argued that the secret to understanding addiction lies in the elucidation of the “memory trace” that links the cue to the compulsive drug use. The implicit underlying hypothesis is that addictive drugs generate an inappropriate learning signal that leads to the encoding of a unique trace, which when reactivated has a strong behavioral impact (Redish et al., 2008; Schultz, 2011).

Here we will review emerging evidence that the cellular correlate of the drug memory trace are the various forms of synaptic plasticity, mainly of glutamatergic transmission, in the circuits of the mesolimbic system, which we have previously called “drug-evoked synaptic plasticity” (Lüscher and Malenka, 2011). We will review the literature reporting drug-evoked synaptic plasticity in animal models of addiction and argue for a staged remodeling of the mesolimbic circuitry (Kalivas and O'brien, 2008) that is eventually responsible for relapse and compulsive drug use.

Animal models. The study of the neurobiological mechanisms underlying additive behavior requires animal models. While the basis of behavioral pharmacology were laid out using non-human primates and rats, more recently genetically modified mice have become extremely useful tools. There is general agreement that no animal model fully

reflects the complexity of the human disease. Many behavioral studies, however, reproduce core components of addiction, starting with the self-administration (SA) of the substance (Clarke et al., 1961). Depending on the substance involved, SA can be oral (e.g. ethanol or benzodiazepines, (Licata and Rowlett, 2008; Vengeliene et al., 2009)), intravenous (e.g. cocaine through a jugular catheter in rats or mice, (Gerber and Wise, 1989; Jackson et al., 1998)) or even directly into a specific brain region (e.g. morphine into the ventral tegmental area, VTA, Bozarth and Wise, 1981). While SA is a necessary condition to demonstrate the reinforcing nature of a given substance, it is by no means sufficient (Collins et al., 1984). SA translates well to clinical reports of drug liking; however, used in its most basic form, it does not fully mimic core features of addiction including loss of control or relapse after periods of extended withdrawal (O'Connor et al., 2011). What are needed for mechanistic investigations of the synaptic drug trace are tests, which demonstrate drug-adaptive behavior associated with an external stimulus. Locomotor sensitization, often used as a proxy of incentive saliency, refers to the enhanced locomotor effect of cocaine and other psychostimulants, which can be observed already at the second injection of the drug (Robinson and Berridge, 2001). Locomotor sensitization also has an associative component, as its magnitude depends on the environment (the effect is enhanced in a novel environment, Badiani et al., 1995). Importantly, locomotor sensitization is already observed several days after a single injection (Valjent et al., 2010) and many weeks after repeated injections. A direct measure of the association with the environment can be obtained in the conditioned place preference (CPP) test. In this paradigm, using an apparatus with two distinct compartments, one side is paired with the drug injection, the other with saline. Already after a first session a preference for the compartment where the drug was received can be measured. Both locomotor sensitization and CPP, however, have the disadvantage that the drug is injected by the experimenter, which strongly contrasts with the clinical reality. A more accurate model therefore is cue-induced cocaine seeking (De Wit and Stewart, 1981; Shaham et al., 2003), where lever pressing or nose poking for a drug-injection is paired with a cue (light or sound). After acquisition of the SA, the simple presentation of the cue will prompt a seeking behavior even though the drug is no longer available. This effect can be observed up to several weeks after the last SA session in rats (Kruzich et al., 2001) and mice (Highfield et al., 2002). One interesting feature is that the seeking behavior becomes stronger over the first few weeks of withdrawal, an observation called "incubation of craving" (Grimm et al., 2001).

Dopamine hypothesis. What is the pharmacological effect defining addictive drugs eventually responsible for the adaptive behavior? They all increase mesolimbic DA levels, which mediate their reinforcing effect (Wise, 1987; Di Chiara and Imperato, 1988). While this statement is supported by many experiments, particularly early behavioral pharmacology studies, it has been challenged, most prominently by genetic manipulations. For example, even though cocaine increases mesolimbic DA by inhibiting the dopamine transporter (DAT); mice lacking the dopamine transporter (DAT) still readily self-administer cocaine (Rocha et al., 1998). Arguably, this observation is incompatible with the DA hypothesis. However, subsequent work during the last decade has demonstrated that in these DAT-lacking mice, abnormally high levels of DA during development induce adaptations in the mesolimbic DA system. Consequently, the results of cocaine self-administration in these mice require reinterpretation. Rather than a complete knock-out, a more subtle manipulation consisting of point mutations renders the DAT insensitive to cocaine but induces only minimal effects on DA reuptake (Chen et al., 2006). With the cocaine unable to bind this mutated DAT, these knock-in mice no longer self-administered cocaine. This observation supports the DA hypothesis, that DA increases are necessary for the reinforcing effects of cocaine. As a side note, a similar knock-in approach has identified the $GABA_A$ receptor subtype containing the α1 subunit in VTA GABA neurons as the initial target responsible for the addictive properties of benzodiazepines (Tan et al., 2010). Amplification of of GABAA receptors in VTA GABA neurons leads to disinhibition of DA neurons, a cellular mechanism shared with opioids, γ-hydroxybutyrate, and cannabinoids (Fig. 1, modified from Lüscher and Ungless, 2006). By contrast, nicotine can directly stimulate DA neurons and psychostimulants exert their effect by interfering with DA reuptake as discussed above. The DA hypothesis; therefore, is still relevant and has received even more direct support from optogenetic manipulations of VTA DA neurons, which confirmed that their activation is sufficient to support self-administration and conditioned place preference (Tsai et al., 2009; Adamantidis et al., 2011; Lammel et al., 2012). Whether DA neuron activity is also sufficient to drive long-lasting adaptive behavior remains to be explored.

Drug-evoked synaptic plasticity. While the requirement for increased DA may explain the acute reinforcing effects of addictive drugs, it does not provide an explanation for craving and relapse. After all, these key features of addiction manifest long after the drugs have been cleared from the brain. Given the established modulatory role of DA on glutamatergic and GABAergic transmission, the synaptic trace of addictive drugs may

actually be expressed at these synapses and not necessarily involve a change in DA modulation. The experimental demonstration of such a trace was achieved over a decade ago using a clever *ex vivo* approach. Briefly, slices of the VTA were prepared one day following a single injection of cocaine and glutamatergic transmission at α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor **(**AMPAR) and N-methyl-D-aspartate receptor **(**NMDAR) was recorded in VTA DA neurons. Since the number of synapses stimulated in this preparation is beyond the control of the experimenter, the ratio of AMPAR- and NMDAR-mediated synaptic currents was calculated and found to be increased after the cocaine treatment (Ungless et al., 2001). Subsequent investigations revealed that this early drug trace can be observed with all addictive drugs tested to date, including ethanol, morphine, nicotine, but also amphetamines and benzodiazepines (Saal et al., 2003; Das et al., 2008; Heikkinen et al., 2009). The plasticity was also observed after a two hour long optogenetic stimulation of the VTA DA neurons, mimicking the increased firing typically observed with a single dose of morphine or nicotine (Brown et al., 2010). This increased AMPA to NMDA ratio is due to an enhanced AMPA transmission in conjunction of a decreased NMDA transmission. The molecular expression mechanism therefore involves a redistribution of both AMPARs and NMDARs. While the absolute number of AMPARs remains unchanged (Mameli et al., 2007), the GluA2-containing receptors at baseline are exchanged for GluA2 lacking ones (Bellone and Lüscher, 2006; Argilli et al., 2008). At the same time, GluN3A containing NMDARs appear in exchange for GluN2A containing NMDARs, again leaving the total number of NMDARs unchanged (Yuan et al., 2013). After a single injection this plasticity persists for about a week, after which transmission is normalized. This normalization requires the presence of mGluR1 receptors, which are located peri-synaptically and are most efficiently activated with a short burst of activity. mGluR1 activation engages mTOR-dependent local protein synthesis (Mameli et al., 2007). Interestingly, mGluR1-driven reinsertion of GluA2-containing AMPARs has also been observed at synapses in multiple brain areas (Clem and Huganir, 2010; McCutcheon et al., 2011), suggesting a conserved mechanism for neurons to eliminate GluA2-lacking AMPARs from the synapse.

The case for a permissive meta-plasticity. The complexity of the expression mechanisms of drug-evoked synaptic plasticity in the VTA indicates that the effect of addictive drugs on the mesolimbic circuit is not a straightforward potentiation of transmission, but suggests a shift of synaptic calcium signaling from NMDARs to AMPARs (Creed and Lüscher, 2013). In naïve mice, glutamatergic transmission can cause synaptic

entry of calcium, provided the DA cell is depolarized, which relieves the NMDARs from the magnesium block. In contrast, after cocaine treatment, GluN3A-containing NMDARs have a very low permeability for divalent cations and are inefficient conductors of calcium. In contrast, the GluA2-lacking AMPARs readily conduct calcium. In fact, owing to the inward rectification, the greater the hyperpolarization, the more calcium enters the cell. In other words, in naive animals, the postsynaptic neurons must be depolarized to engage calcium signaling, whereas after cocaine, hyperpolarization is required. As a consequence, the rules for activity dependent potentiation of synaptic transmission are inverted (Mameli et al., 2011). This can be experimentally demonstrated by using a spike timing dependent potentiation protocol (STDP), where the postsynaptic neuron either receives a depolarizing or a hyperpolarizing current injection (Figure 2). In slices from cocaine-treated animals, depolarizing STDP was no longer able to potentiate transmission; however, the potentiation could be rescued by switching to a hyperpolarizing STDP. Taken together, these findings strongly suggest a permissive role for this early form of drug-evoked synaptic plasticity . In this sense, the AMPA and NMDA receptor alterations induced by drug exposure can be considered a meta-plasticity, enabling specific forms of subsequent activity-dependent synaptic plasticity.

Causal role of drug-evoked synaptic plasticity in behavior. Establishing a causal relationship between drug-evoked synaptic plasticity and drug-adaptive behavior has been challenging, in part because of the temporal discrepancy between these two phenomena. A single injection already leaves a synaptic trace (discussed above) that lasts for approximately a week, but may not drive many behavioral adaptations. Interestingly, a recent study using retrograde tracing techniques has provided that the VTA DA neurons that project to the NAc are particularly prone to undergo drug-evoked synaptic plasticity (Lammel et al., 2012). These early forms of drug-evoked plasticity are merely building blocks of circuit remodeling, which, after repetitive exposure, eventually lead to behavioral alterations. In line with this interpretation, in mice where NMDA receptors were selectively abolished in DA neurons (DAT-Cre ERT2 x GluN1flox, Zweifel et al., 2008) the behavioral repercussions of drug exposure are only observed after a delay and following several injections. Specifically, reinstatement of drug seeking was reduced, which involves an extended circuitry including the nucleus accumbens (NAc, Engblom et al., 2008).

Further evidence for a stepwise remodeling of mesolimbic circuitry comes from experiments suggesting a hierarchical organization of drug-evoked synaptic plasticity

between the VTA and the NAc. Quick and efficient reversal of cocaine-evoked plasticity in the VTA by local or systemic application of a positive allosteric modulator of the metabotropic glutamate receptor 1 (mGluR1) prevented some drug-evoked synaptic adaptations in the NAc (Mameli et al., 2009). Lesion experiments and pharmacological manipulations implicate connections to and from the NAc in the integration of rewarding drug effects and contextual environmental cues (Sesack and Grace, 2010). The crucial plasticity that presumably mediates this integration occurs at the excitatory afferents onto medium spiny neurons (MSNs), which represent 95 % of neurons in the NAc and are a interface between limbic and motor functions (Mogenson et al., 1980). There are two populations of MSNs that are divided into two equal sized classes depending to the type of dopamine receptors (either D1R or D2R) they express and their projection sites (Gong et al., 2007). Both D1R-MSNs and D2R-MSNs receive excitatory afferents from the prefrontal cortex (mPFC), the ventral hippocampus (vHippo) and the basolateral amygdala (BLA, Papp et al., 2012). Previous studies have attributed the emotional valence to the BLA input (Cador et al., 1989), which when selectively stimulated is reinforcing (Stuber et al., 2011). The activation of the mPFC to NAc projection has been implicated in the initiation of action and the actual seeking behaviour and there is evidence linking the hypoactivity of cortical projection neurons to compulsive cocaine consumption (Chen et al., 2013). Finally, the afferents from the vHippo would code for the context (Sesack and Grace, 2010). Regardless of the origin, synaptic plasticity at glutamatergic transmission onto MSNs has been correlated with cue-induced relapse to cocaine seeking (Conrad et al., 2008). Given the proposed functions of these specific inputs, cocaine may evoke distinct forms of plasticity at excitatory synapses onto MSNs, which would contribute to specific components of adaptive behavior. What will be needed to address this hypothesis, is the selective manipulations at identified synapses. With the advance of cell type-specific optogenetic control of neuronal activity, such experiments are now possible. The blueprint of this approach consists of exposing the animal to the drug, such that a drug-adaptive behavior can be observed (e.g. repetitive injections of cocaine to cause locomotor sensitization) and characterize drug-evoked synaptic plasticity *ex vivo* (e.g. potentiation of mPFC afferents onto D1R MSNs). Since most forms of plasticity can be reversed by an appropriate stimulation protocol, the next step consists of finding a protocol that can normalize transmission *in vitro* (e.g. 1Hz NMDAR-dependent depotentiation). This protocol can then be applied *in vivo* after transfecting the appropriate upstream neurons and activating the afferent axons by terminal illumination (e.g. injection of optogenetic effector channelrhodopsin ChR2 into the mPFC shining light into the NAc) to test the effect of

depotentiation on drug adaptive behavior (e.g. erasure of sensitization). A proof of principle study (Pascoli et al., 2011) has shown that this approach is feasible, but further experiments must be done in order to understand the role of drug-evoked synaptic plasticity at identified synapses in more complex behavior (e.g. cue-induced cocaine seeking modelling relapse).

The challenge of individual vulnerability. One of the striking features of addiction is only poorly understood: the individual vulnerability. At equal levels of drug consumption, some people readily lose control while others maintain a controlled recreational use for many years. Just think of alcohol, a drug legal in many countries that the overwhelming majority can enjoy recreationally during an entire adult lifetime without ever losing control. This is also well documented for nicotine and cannabis, and even holds true for "harder" drugs such as amphetamines and cocaine, the latter leading to addiction in approximately 20% of regular users over the span of more than ten years (Wagner and Anthony, 2002). While several genetic variations have been associated with drug use (Goldman et al., 2005), a causal relationship remains to be established. Moreover most studies described above focus on generic mechanisms that underlie the behavioral changes and little is known about the neurobiology underlying individual vulnerability. One requirement is certain; individual vulnerability can be observed only after prolonged drug exposure. This requirement is not met in most animals models presented above, which is why behavioral pharmacology screens show very little variability. However, pioneering work using self-administration (SA) for several months in rats have demonstrated that animal to animal variability can also be observed in rodents (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004). In a subsequent study it has been argued that high impulsivity predicts the development of addiction-like behavior in rats (Belin and Everitt, 2008).

Emerging ideas for rational addiction treatments. A more comprehensive understanding of the precise nature of circuit remodeling caused by addictive drugs resulting from specific forms of drug-evoked synaptic plasticity may help us design novel rational treatments for the human disease. Such treatments may be pharmacological in nature or use neuromodulatory approaches such as deep brain stimulation or transcranial magnetic stimulation. The former may target specific types of receptors known to appear only after drug exposure, such as the GluA2-lacking AMPARs or the GluN3-containing NMDARs, but this type of pharmacological interventions are really only in their infancy. It may also be possible to exploit and enhance the physiological mechanism of reversing

drug-evoked synaptic plasticity. A focus on this regard may be on the mGluR1 receptors, which can reverse the redistribution of AMPARs and NMDARs.

Perhaps a more selective intervention would be to target specific areas of the reward circuitry, such as the NAc, with deep brain stimulation. However, novel protocols would have to be developed, as current high-frequency stimulation (>100Hz) is unlikely to affect plasticity. Transcranial magnetic stimulation (TMS) may have the appeal of being non-invasive. If we succeed to determine the cortical afferents undergoing drug-evoked synaptic plasticity to develop efficient reversal protocols, TMS may emerge as a promising treatment option.

Ultimately, the understanding of drug-induced plasticity at specific synapses must be furthered in order to develop a therapy that reverses plasticity and associated drug-induced adaptive behavior. The goal is to provide a cure for addiction and to prove Aaron Sorkin wrong when he recounted in a 2012 interview with the W magazine: "...the hardest thing I do every day is not take cocaine. You don't get cured of addiction—you're just in remission."

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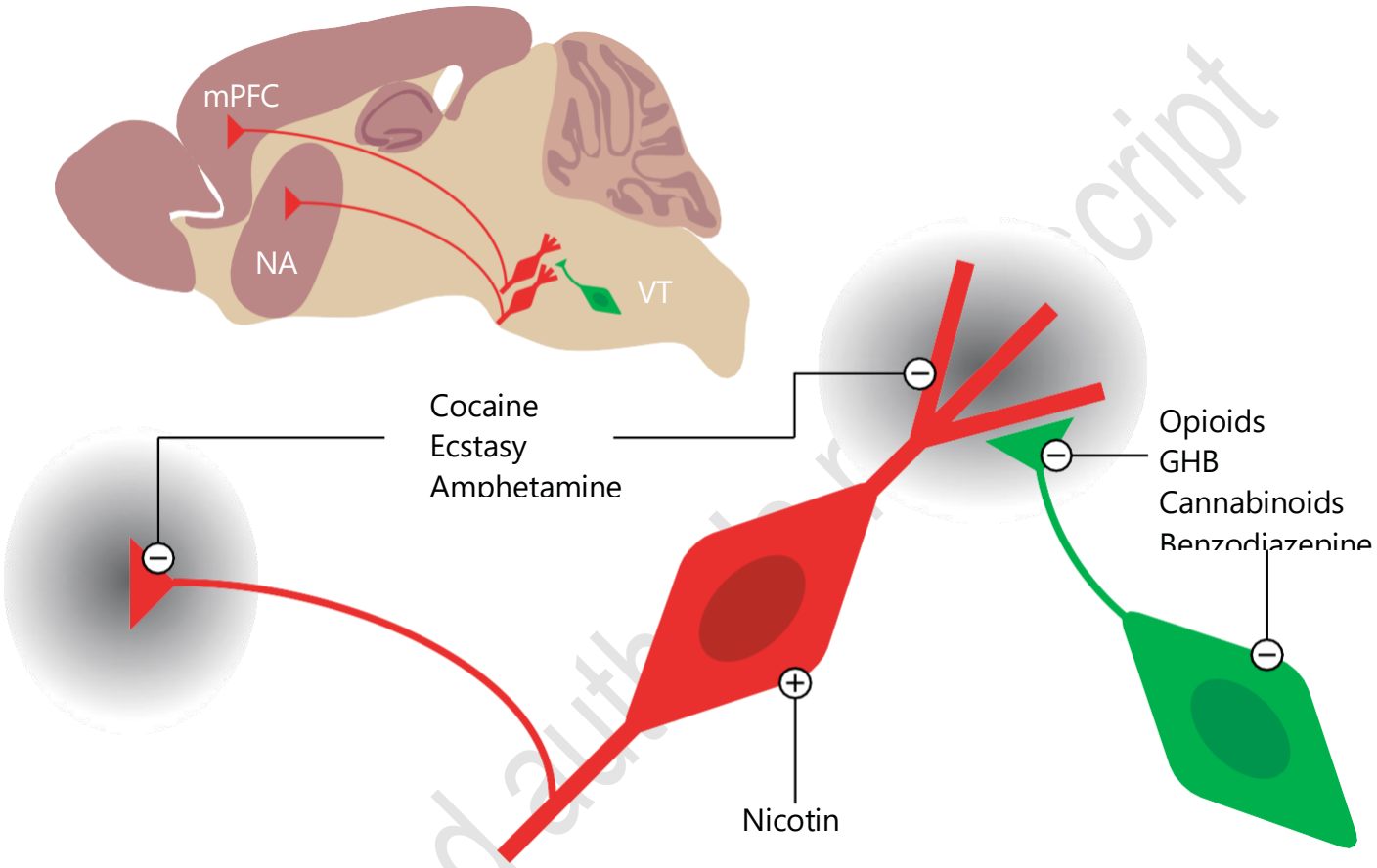
Legends:

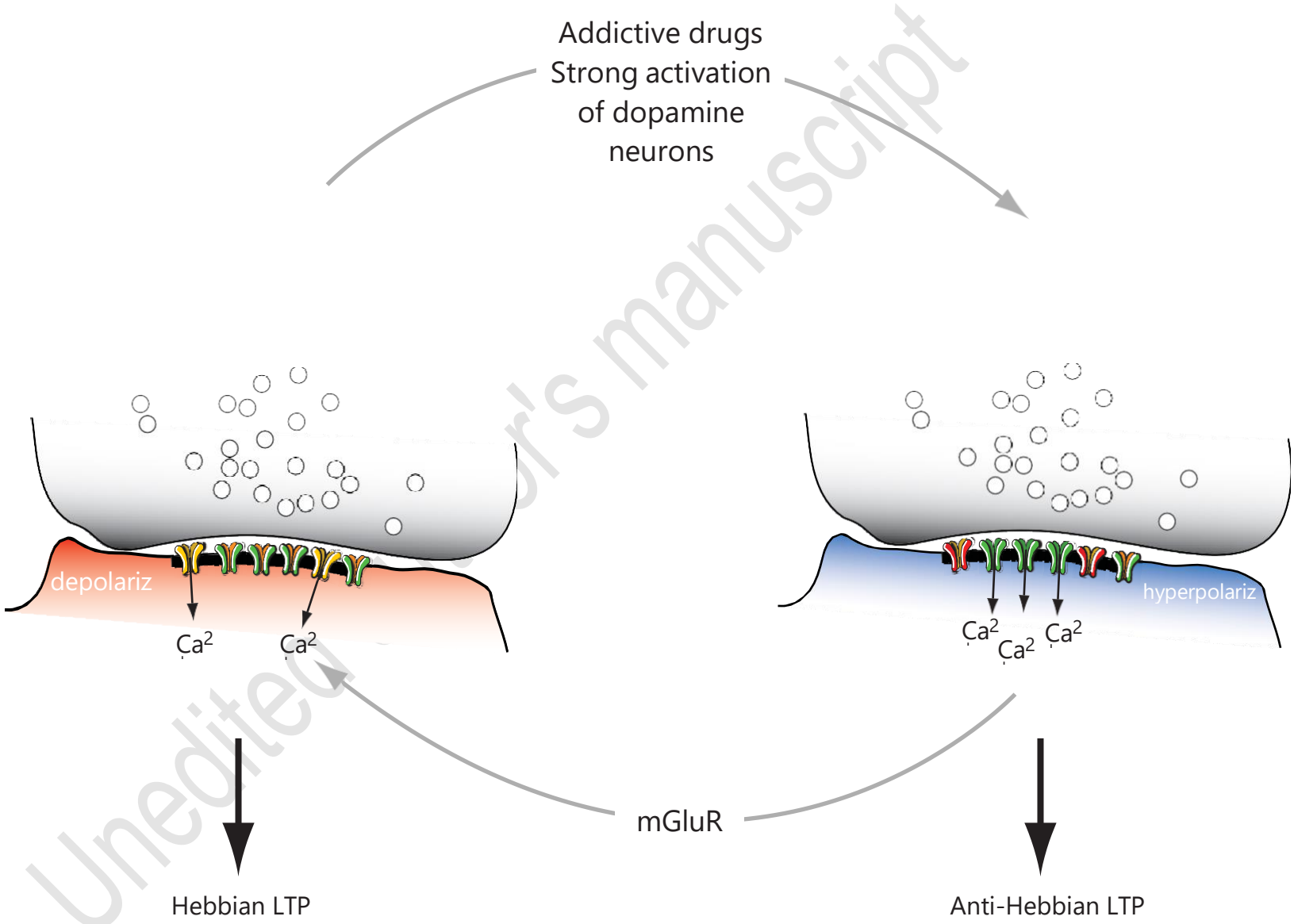
Figure 1. The meso-cortico limbic dopamine system as an initial target of addictive drugs. The VTA, at the origin of the meso-cortico limbic system, is composed of dopamine projection neurons that are under inhibitory control of GABA interneurons (somtimes described as an independent nucules at the tail of the VTA, the rostromedial tegmentum, RMTg). The main targets are the nucleus accumbens (NAc) and the medial prefrontal cortex (mPFC). Addictive drugs cause an increase in mesocorticolimbic dopamine through three distinct cellular mechanism: direct activation of dopamine neurons (e.g. Nicotine), indirect disinhibition of dopamine neurons (Opioids, GHB, cannabinoids and benzodiazepines), as well as interference with dopamine reuptake (cocaine, ecstasy and amphatamines). Note that the latter group also increases dopamine in the VTA itself owing to the perturbation of the reuptake of dendritically released doapmine (for details see Lüscher and Ungless, 2006).

Figure 2. Drug-evoked synaptic plasticity in dopamine neurons of the ventral tegmental area. Addictive drugs or strong stimulation of dopamine neurons causes a synaptic plasticity on the excitatory afferents. This plasticity is expressed by the dual exchange of AMPA and NMDA receptors: GluA2-lacking AMPA receptors and GluN3A containing NMDA receptors are inserted. As a consequence clacium enters the postsynaptic cell more readily when the membrane is hyperpolarized, which inverts the rules for activity-dependent synaptic plasticity. At baseline LTP is induced when glutamate is released onto a depolarized dopamine neurons (Hebbian LTP that is NMDAR dependent), while after cocaine exposure LTP can be observed when glutamate transmission conincides with a hyperpolarization (anti-Hebbian LTP that is AMPAR dependent). Normal transmission is restored by the activation of mGluR1. Taken together, addictive drugs evoked a permissive metaplasticity at excitatory afferents onto VTA dopamine neurons, which gates subsequent adaptations downstream (see text).

Lüscher, FIgure 1



Lüscher, Figure 2




GluN3-lacking

GluN3-containing

NMDAR


GluA2-lacking

GluA2-containing

AMPAR