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Cross-talk between the epigenome and neural circuits in drug addiction

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Abstract

Drug addiction is a behavioral disorder characterized by dysregulated learning about drugs and associated cues that result in compulsive drug seeking and relapse. Learning about drug rewards and predictive cues is a complex process controlled by a computational network of neural connections interacting with transcriptional and molecular mechanisms within each cell to precisely guide behavior. The interplay between rapid, temporally specific neuronal activation, and longer-term changes in transcription is of critical importance in the expression of appropriate, or in the case of drug addiction, inappropriate behaviors. Thus, these factors and their interactions must be considered together, especially in the context of treatment. Understanding the complex interplay between epigenetic gene regulation and circuit connectivity will allow us to formulate novel therapies to normalize maladaptive reward behaviors, with a goal of modulating addictive behaviors, while leaving natural reward-associated behavior unaffected.

Keywords

Dopamine; Addiction; Reinforcement; Epigenetics; Circuits

1 INTRODUCTION

Drug addiction is a chronic relapsing disorder characterized by maladaptive learning about drugs and predictive cues that leads to compulsive drug seeking (Leshner, 1997). The major goal of addiction treatment is to correct these maladaptive behaviors and minimize relapse events without disrupting normal reward-seeking behaviors (e.g., seeking food or water). Because drugs hijack endogenous reward circuitry to elicit their rewarding and reinforcing effects, this has proved difficult (Dackis and O'Brien, 2005; Leshner, 1997). For example, simply pharmacologically inhibiting receptors or circuits involved in these pathways often has side effects that suppress the rewarding value of natural stimuli, making them undesirable and ineffective as long-term treatments (Aberman and Salamone, 1999; Leshner, 1997; Salamone et al., 2002). Thus, it is critical to understand the different neural codes that encode information about rewarding stimuli and drug stimuli, and the neural basis of how

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these types of behaviors become dysregulated for long-periods of time to drive drug addiction.

While a large body of work has focused on neural circuit dysfunction as well as genetic factors contributing to addiction (Koob and Volkow, 2010; Kreek et al., 2005; Nestler and Aghajanian, 1997; Volkow et al., 2013), less work has taken a broad scale multidisciplinary approach to understand how genes, circuits, and complex behaviors act together to control acute and chronic responses to drugs. Thus, to develop new targets we propose work aimed at understanding the complex interplay between genetic and circuit factors, as modulating each in isolation will likely lead to ineffective treatment strategies.

Here, we will outline how epigenetic factors converge with changes in neural circuit activity and connectivity to control complex behaviors and drug addiction.

2 DRUG ADDICTION IS A BEHAVIORAL LEARNING DISORDER

2.1 LEARNING ABOUT RESPONSE CONTINGENCIES

DRUG SELF-ADMINISTRATION AS AN ANIMAL MODEL OF ADDICTION

Currently, a large amount of what we know about drug-induced plasticity comes from work using noncontingent acute drug administration. For example, the acute effects of many drugs are commonly modeled with intraperitoneal injections, subcutaneous pellets, and other forms of passive drug delivery. However, the acute effects of drugs are not what characterize human drug addiction. Additionally, animal models that rely on passive drug delivery do not reflect other equally crucial aspects of the addiction phenomenon. Similarly, while different paradigms are often used for studying the rewarding properties of addictive substances, reward is in fact a subjective measure difficult to interpret in many animal paradigms frequently used in the field. Importantly, other, equally crucial aspects of addiction such as social context of drug use are not assessed by animal models that still mostly rely on passive drug delivery (Heilig et al., 2016).

To model these aspects of drug addiction in animals, we use drug self-administration where animals are given access to a lever that when pressed results in the delivery of an intravenous injection of drug. The delivery of drug can be paired with discrete and contextual cues that allow for studies that assess how drug consumption changes over time, how predictive cues enhance motivation, and how cues can precipitate release.

Unlike genetic disorders, drug addiction is, primarily, a behavioral disorder that only develops after repeated exposure to a drug of abuse (Dackis and O'Brien, 2005; Koob and Volkow, 2010; Leshner, 1997). It is characterized by an inability to inhibit inappropriate behavioral responses to drugs and associated stimuli (Goldstein and Volkow, 2002). Both the consumption of natural rewards and drug rewards relies on reinforcement learning, where a stimulus (e.g., a reinforcer such as food) acts to maintain a particular behavior (such as eating) (Skinner, 1958). In the case of drug reinforcers, drug taking is driven initially by positive reinforcement, where an individual takes drug for the positive euphoric effects (i.e., the "high") (Everitt and Robbins, 2005). This positive experience reinforces the previous

behavior (smoking, consuming, or injecting the drug), driving the individual to learn to seek out and take the drug again to get the “high.” This same process occurs with natural rewards, and the ability to learn effective strategies for seeking reinforcers is critical to survival. Accordingly, many of these behavioral processes and the neural circuits controlling them are evolutionarily conserved across many species ranging from honey bees to humans (Balleine and O’Doherty, 2010; Gil, 2010; Tobler et al., 2006).

Because reinforcement learning relies on learning contingencies between actions and outcomes, it is a plastic process that requires quick adaptations changes in the environment, internal state, and need (Kandel and Schwartz, 1982; Kauer and Malenka, 2007; Shimizu et al., 2000). This behavioral process requires the ability to rapidly recall information, process information in real time, and reconsolidate this information. This is encoded by precise neural connections between brain regions and relies on both circuit connectivity and molecular and transcriptional factors to rapidly update information, and then maintain this information for when it is needed subsequently (Maren and Baudry, 1995; Sweatt, 2004). Evidence has shown that repeated drug exposure acts on some circuits to prevent plasticity and impair the ability of individuals to update these types of information (O’Brien et al., 1998). For example, with natural rewards, if the reward is no longer presented, or is very difficult to obtain, individuals will reduce the behavior because the effort or cost required to obtain the reward is too great (Bouton and Todd, 2014; Todd et al., 2014a, b). This adaptive response allows animals to learn new contingencies and allocate their behavior toward other scenarios and contexts that have a greater likelihood of resulting in rewards being obtained. This results in synaptic remodeling in the form of altered excitability and changes in cellular morphology in reward-related brain regions such as the nucleus accumbens (NAc) and prefrontal cortex (PFC) (Robinson, 1999; Robinson and Kolb, 2004). However, in the case of drug reinforcers these processes are often dysregulated, where drug seeking and taking can become compulsive and do not adapt to changing contingencies at both the behavioral and brain level (Everitt, 2014). Accordingly, individuals put enormous amounts of disproportionate effort into working to obtain drug at the expense of other adaptive behaviors. Thus, the inability to update information and extinguish mal-adaptive behavioral responses forms the basis of pathological drug seeking that often underlies relapse.

2.2 LEARNING ABOUT DRUG-ASSOCIATED CUES

In addition to learning about instrumental responses and outcomes, individuals also incorporate information about cues and contexts that inform about drug availability and guide environmentally appropriate behavioral responses (Schultz, 2006). In healthy individuals, associations between salient experiences and the environments within which they occur are the basis of decision-making and guide behavior toward advantageous outcomes. These learning processes play a critical role in survival and are essential for animals to successfully navigate their environment (Schultz, 2006). In drug addiction, discrete cues, such as drug paraphernalia, are associated with consummatory processes and can begin to acquire value on their own (Everitt, 2014; O’Brien et al., 1998). In human imaging studies, the presentation of these drug-associated cues has been shown to activate reward pathways (Young et al., 2014), and they can act to increase craving and drug seeking/ motivation for consuming the drug (Goldman et al., 2013).

An organism's ability to learn about these associations relies on a complex learning processes where information is encountered, consolidated within the brain, and upon exposure to the stimulus again the same neural circuits need to be reactivated. The number of times a memory is reconsolidated makes the strength of that memory stronger and makes the ability to reorganize the synaptic architecture that encodes that information less plastic. In the case of drug addiction, the presentation of the drug cues happens many times each day, making these associations particularly strong (Everitt, 2014; Lee et al., 2006b). These strong associations contribute not only to enhanced neural responses to these stimuli, but also create an ability to replace them with new information as it becomes available.

An inability to extinguish these associations facilitates reinstatement of drug seeking and taking when the stimulus is encountered even after a period of abstinence and it is thought to be a predominant process precipitating relapse (Everitt, 2014; Goldman et al., 2013; O'Brien et al., 1990; Weiss, 2010; Young et al., 2014). Thus, identifying the specific neuronal ensembles/subpopulations that drive these behaviors, and determining strategies to manipulate their activity to promote extinction of drug associations, is critical to understand the mechanisms of addiction.

3 DRUG-INDUCED PLASTICITY: HOW IS DRUG-ASSOCIATED INFORMATION STORED FOR LONG PERIODS OF TIME IN THE BRAIN?

A major focus of neuroscience research is understanding how information is stored in the brain and how we access that information later to guide behavior. Behavior in general is a complex process controlled by neural circuits that integrate information across a wide range of sensory modalities and balance that information with ever changing internal states. Precise networks of neural circuits that are sensory, homeostatic, attribute value to stimuli, and coordinate motor outputs all synchronously activate to guide the precise behavior that is necessary in that very moment (Anderson, 2016; Betley et al., 2013; Delgado et al., 2004; Fu et al., 2014; Schultz, 2006). Predictive cues and new information can change the neural code and behavioral response on a subsecond timescale, which requires tight and temporally specific signaling from all of the neurons involved.

This is controlled by a complex computational network of neural connections, the temporally specific activity of which guides behaviors toward appropriate outcomes. However, in psychiatric disease, especially drug addiction, these systems are dysregulated in an activity-dependent manner. Enhanced activation of specific reward and reinforcement pathways, such as the dopamine system, can lead to remodeling of these circuits as well as changes in synaptic connectivity that increase specific connections while decreasing others (Creed et al., 2016; MacAskill et al., 2014; Pascoli et al., 2014). The question at hand is how drug-induced changes in circuit dynamics, cell identity, and responsive gene expression interact with each other to produce these effects. Because addiction results in long-term changes in responses to drug-associated cues, that last long beyond the lifetime of any single protein or transcript in a given cell the question remains: how are these maintained long-term and how can we reverse them?

Tightly regulated control of DNA conformation and modification can increase or decrease the expression level of a particular gene over long periods (Jaenisch and Bird, 2003). This process termed epigenetic remodeling (discussed in Section 5) allows for potent and precise activity-dependent control over gene expression and it is via this mechanism that long-lasting, stable effects on gene expression can outlive an initial transient signal. This is important because protein turnover and posttranslational modifications, while relatively stable, only last a matter of weeks (Pratt et al., 2002). This allows for protein production that can change the activity of a cell, and its cellular response to a stimulus over the course of years. Conversely, repeated activation of a particular cell type can also change the epigenetic landscape of the cell to increase or decrease the probability of subsequent activation (Sweatt, 2009). It is through these complementary processes that organisms learn information and are able to update it quickly, efficiently, and for long periods of time.

The interplay between quick temporally specific neuronal activation and longer-term changes in transcription is of critical importance in the expression of appropriate, or in the case of drug addiction, inappropriate behaviors (Fig. 1). Thus, both of these factors and their interaction must be considered together, especially in the context of treatment. Understanding the complex interplay between these two factors will allow us to formulate novel epigenetic therapies that are likely to normalize mal-adaptive reward behaviors, with a goal of modulating addictive, but not natural reward behaviors.

Below, we will review three main points: (1) What neural circuits control learning about drugs and associated stimuli, (2) How changes in these pathways drive epigenetic reorganization and (3) How chromatin changes drive long-lasting changes in neural circuit function to dysregulate reward-related behaviors indefinitely.

4 THE NEURAL CIRCUITS CONTROLLING MOTIVATED BEHAVIORS AND THEIR DYSREGULATION IN DRUG ADDICTION

4.1 THE SHIFT FROM ACUTE PHARMACOLOGY TO REMODELED NEURAL CIRCUITS

The initial component of drug addiction is the “high” induced by the drug. These euphoric effects are what initially reinforces drug taking and drives individuals to seek out the drug again. While drugs of abuse have a variety of mechanisms of action, nearly all of them increase dopamine transmission in reward-related brain regions (Di Chiara and Imperato, 1988). Stimulants, such as cocaine and amphetamine, inhibit dopamine uptake and drive active dopamine release from nerve terminals, respectively (Seiden et al., 1993). Other drugs of abuse, such as nicotine or opioids, act indirectly to enhance VTA firing rate. (Laviolette and van der Kooy, 2004; Nader and van der Kooy, 1997; Pierce and Kumaresan, 2006).

This ability to increase dopamine signaling has been shown to be critically involved in reinforcement processes as dopamine depletion or pharmacological blockade of dopamine receptors reduces motivation for food and drug (Aberman and Salamone, 1999; Aberman et al., 1998; Salamone et al., 2002; Woolverton and Virus, 1989). Most stimulant drugs of abuse like cocaine increase dopamine levels by binding to and inhibiting the dopamine transporter. The ability of cocaine to bind to the dopamine transporter is directly linked to

the rewarding and motivational value of the drug (Chen et al., 2006; Siciliano and Jones, 2017), the consummatory process of drug taking (Roberts et al., 1977), and the ability to form associations between predictive cues and the rewarding effects of the drug (Calipari et al., 2017). Indeed, inhibiting the ability of drugs to increase dopamine levels, either by depleting dopamine, or altering the ability of cocaine to bind to the dopamine transporter, can completely block the ability of animals to associate cocaine with predictive cues. Therefore, the ability to increase dopamine levels initially is critical to the reinforcement process that begins the cycle of drug taking that ultimately results in addiction.

Drug-induced increases in dopamine signaling are typically long lasting. For example, DAT inhibition and the resulting “high” from a single cocaine injection can last 30min or more (Volkow et al., 1997a); however, neural signals in the brain that encode information are temporally specific and time-locked to behavioral events (Hart et al., 2014, 2015; Hollon et al., 2014; Howe et al., 2013). In the case of dopamine, it acts to predict reward availability and value (Lak et al., 2014, 2016; Medic et al., 2014; Sackett et al., 2017; Saddoris et al., 2015, 2017). When an individual encounters something that will likely be rewarding, dopamine is released and acts to coordinate downstream circuits to initiate action generation to obtain the rewarding stimulus (Ko and Wanat, 2016). Therefore, drugs enhance reinforcement learning by increasing dopamine and increasing the probability that animals will continue to execute behaviors that result in the drug being delivered. However, in addition to encoding information about rewards and their value, dopamine acts to update information and refine future behavior. The way this is achieved is by error signal (Schultz and Dickinson, 2000; Schultz et al., 1997). When a cue predicting a reward of a particular value is presented, dopamine is increased to reflect that value. However, if the value of the reward was not similar to that previously predicted, there will be a subsequent dopamine signal to the reward itself (Schultz et al., 1997). If the reward was smaller than expected, dopamine will decrease and if it was larger than expected, dopamine will increase. This acts as feedback to change the neural response to the cue and therefore refine expectation to allow for adaptive behaviors. The administration of drugs of abuse, including ethanol, cocaine, nicotine, and amphetamine, has all been shown to potentiate the amplitude of transient dopamine signals in the NAc (Cheer et al., 2007; Covey et al., 2016; Howard et al., 2013; Robinson et al., 2009). Thus, in the presence of a drug that increases dopamine signaling, the error signal will always be enhanced, making the neural representation of the reward greater than the value of the reward itself. The next time the cue is presented, the prediction will be that the reward is even bigger than the subsequent encounter. Thus, one major issue with drugs is not the initial high induced, but rather the ability of these drugs to hijack the reward prediction system to change reward circuits so that they respond maximally to drug predictive cues.

This dopamine reward signal is not only critical in predicting future rewards, but also in driving an organism to choose one reward over another (Lak et al., 2014, 2016; Medic et al., 2014). The predictive dopamine signal allows for the rank ordering of available rewards and allows organisms to make decisions between them. This has been shown in monkeys where electrophysiological recordings were conducted during the presentation of three separate juice rewards. The VTA dopamine signal to each cue was largest for each monkey's preferred juice and guided the animal to choose that reward over the others available (Lak et

al., 2014). In drug addiction, because the dopamine prediction signal is augmented, it guides animals to bias choices toward the drug over alternative reinforcers, and even in the face of negative consequences. Indeed, this has been seen in humans as well as in animal studies. For example, monkeys with a history of drug self-administration will choose heroin over a food reward (Negus and Rice, 2009) and will even administer drug to the point of death (Downs et al., 1979). Similar effects can be seen in rodent models, where a subset of rats will choose cocaine over sucrose rewards (Lenoir et al., 2013). Recent work has aimed at trying to find treatment interventions that shift choice away from maladaptive, and toward more adaptive rewards (Vandaele et al., 2016).

The ability of drug-associated stimuli to enhance motivated behaviors and drive drug seeking is a critical aspect of drug addiction (O'Brien et al., 1990, 1998). In addition to guiding decision making and choice, following long-term exposure, these cues can act as reinforcers in their own right, highlighting the powerful control they exert over motivation (Everitt and Robbins, 2005). These cue responses can be elicited even after long-term abstinence of many years and have been implicated in precipitating relapse. Cue-elicited neural responses highlight that the key factor in the development of addiction is not simply the pharmacological action of the drug. The drug binding to its site of action is critical to the initial reinforcement (Thomsen et al., 2009); however, this sets in motion a complicated circuit of learning that recruits not only the system the drug acts on, but other systems across the brain (Pascoli et al., 2015). Eventually, the ability of drugs to enhance reward circuits becomes an auxiliary component of motivation. Thus, to understand drug addiction we must focus on pinpointing the precise neural circuits in the brain that control this type of learning, understanding how they are initiated, and how they interact with the pharmacological effects of drugs to become pathological.

4.2 CHANGES IN DOPAMINERGIC ENCODING OF INFORMATION IN ADDICTION

While dopamine signaling is critical for self-administration and controls the motivation to self-administer drugs, long-term cocaine intake leads to increased motivation paired with paradoxical reductions in dopamine function. In the striatum, human imaging studies have shown reduced responses to dopaminergic challenges (Park et al., 2013; Tomasi et al., 2010; Volkow et al., 1997b). Analogous neurochemical alterations have been particularly well documented in the dopamine system of rodents with effects that include hypodopaminergia, tolerance to cocaine, and enhanced responsivity to cues (Calipari et al., 2013a,b, 2014; Ferris et al., 2012, 2013a,b, 2015). Thus, leading to the hypothesis that dopamine signaling is initially critical to the development of addiction; however, the maintenance of craving and seeking is driven by information being shifted to other neural circuits. Indeed, even after long-term abstinence from cocaine, animals still show tolerance to the effects of cocaine (Siciliano et al., 2016). This hypofunctional dopamine system is observed across many striatal regions as well as at varying periods of withdrawal (Park et al., 2013; Tomasi et al., 2010; Volkow et al., 1997a,b, 2007, 2013). In addition to presynaptic release being altered in the VTA to NAc projections, other studies have also seen decreases in D2 receptor expression levels which could contribute to further reductions in the ability of dopamine to update information about drug contingencies, thus impairing dopamine-dependent learning

processes such as extinction (Ferris et al., 2012; Park et al., 2013; Tomasi et al., 2010; Volkow et al., 1997a,b, 2007, 2013).

In addition to reductions in the ability of the dopamine system to respond to salient stimuli and update new information about drug rewards, the primary locus of control shifts from ventral regions of the striatum to more dorsal regions. Initially, reward and reinforcement is controlled by the posterior dorsomedial striatum and NAc, but shifts to the anterior dorsolateral striatum (Murray et al., 2012), a structure that is considered a critical mediator of habit control. This anatomical shift is thought to underlie the transition from goal-directed to habitual drug seeking (Belin and Everitt, 2008; Dackis and Gold, 1985). Therefore, not only are there changes in dopaminergic responsivity, but wide-scale reorganization of the circuits controlling motivated behaviors. This is a critical consideration as these types of changes prevent further learning-induced plasticity and can drive compulsive behaviors. However, this is even more important in the context of other glutamatergic circuits across the brain, where changes in striatal circuits lead to more widespread alterations in other brain regions (Baler and Volkow, 2006; Decot et al., 2017; Kalivas and Volkow, 2005; Koob and Volkow, 2016; Moeller et al., 2010).

4.3 DOPAMINE-INDUCED CHANGES IN THE NEURAL CIRCUIT REMODELING OF DOWNSTREAM INPUTS

While dopamine signaling plays a critical role in reward learning, its function in the brain is largely neuromodulatory. Dopamine acts on D1-type and D2-type receptor families, which are G protein-coupled receptors (Surmeier et al., 2007). Because these are metabotropic receptors the signaling occurring through them does not trigger action potentials on their own, but rather modulates the probability of converging glutamatergic inputs to drive action potential firing as well as altering many other aspects of cellular metabolism and function via complex signaling cascades. Dopamine acts as a high pass filter increasing the probability that high frequency inputs will generate action potentials and decreasing background low frequency firing (Surmeier et al., 2007). This serves one of two functions: (1) To increase the activity of downstream neurons in driving behavior and (2) Increasing the strength of these specific inputs via changes in plasticity. This can occur in all of the projection regions of the VTA, has been seen in the PFC, NAc, and amygdala, and gives further support that these initial dopaminergic changes can induce widespread circuit dysfunction in a range of circuits across the brain to drive maladaptive behaviors (Decot et al., 2017).

4.3.1 Enduring changes in synaptic connectivity—The dopamine signaling pathway involved in reward learning is illustrated in Fig. 2. These regions have been shown to be critical in learning about aversive and rewarding stimuli, and are dysregulated in drug addiction. The NAc is a region of particular interest in drug addiction as it integrates information from VTA dopamine projections with glutamatergic inputs from the hippocampus, basolateral amygdala (BLA), PFC, and a number of inputs from sensory and motor regions onto medium spiny neurons (MSNs) and neighboring interneurons. Thus, the NAc integrates information about internal state, reward, aversion, and motivation to guide appropriate decision making. In the NAc, dopaminergic signals are integrated by two largely

nonoverlapping populations of GABAergic projection neurons (MSNs) that project to downstream regions such as the ventral pallidum (VP) and back to the VTA (Surmeier et al., 2007).

The GABAergic projections neurons in the NAc are most often defined by their expression of D1 and D2 dopamine receptors. D1 dopamine receptors are Gq coupled and activation of these receptors increases the probability of action potential generation by excitatory inputs in this population, while D2 receptors are Gi coupled and are inhibitory (Surmeier et al., 2007). Indeed, work with in vivo calcium imaging has shown that increasing dopamine levels via cocaine injection leads to a suppression of the population activity in D2 MSNs, while increasing the activity of D1 MSNs (Calipari et al., 2016; Luo et al., 2011). D1 and D2 MSNs have been proposed to control discrete aspects of behavior as optogenetically stimulating D1 MSNs can result in a place preference and reinforcement while stimulating D2 MSNs results in aversion (Kravitz et al., 2012; Lobo et al., 2010). Thus, increases in dopamine activate D1 MSNs to drive animals toward rewarding stimuli. However, it is likely more complicated than just D1 or D2 signaling controlling reward and aversion, and rather is more likely controlled by a complex regulatory process that finely tunes the activity of these two populations (Soares-Cunha et al., 2016). This is highlighted by the overlapping inputs of sensory and cortical systems in both populations of neurons (Guo et al., 2015, see Fig. 3). In addition, D1 and D2 MSN populations were recently shown to have lateral inhibitory effects on each other (Dobbs et al., 2016), which allows activation in one pathway to regulate the output of the other, further refining signaling. As a result of this tightly controlled neuronal regulation, there is an interest in how repeated drug exposure alters the synaptic connections and excitability of these two pathways in isolation and how they contribute to behaviors associated with drug addiction.

The role of D1 and D2 MSNs in reward and aversion sheds light onto how rewarding and aversive stimuli alters the balance of signaling through these two neuronal populations to guide behavior (Calipari et al., 2016; Creed et al., 2016; Kravitz et al., 2012; Lüscher, 2016; MacAskill et al., 2014; Pascoli et al., 2014); however, even more important is the nature of signaling that occurs in response to drug-associated stimuli and how this is changed following repeated drug exposure (Bock et al., 2013; Creed et al., 2016; Lüscher, 2016; MacAskill et al., 2014; Pascoli et al., 2014). Temporally specific signaling originating from D1 MSNs in the NAc was identified to be critical in the encoding of information about drug associations. The extent to which this D1 signal was increased to predictive cues was positively correlated with drug seeking. Chronic cocaine exposure enhanced drug-cue evoked D1 signals to both prevent extinction and facilitate reinstatement (Calipari et al., 2016). Further, these increased responses to drug-associated contextual cues by D1 MSNs were still present after a 2-week withdrawal period, suggesting that the changes in the population activity were stable and long-lasting (Calipari et al., 2016). This is particularly interesting because recent work with food self-administration has shown that both D1 and D2 MSN activity is stimulated, suggesting that something is fundamentally different about the encoding of food and drug rewards (Natsubori et al., 2017).

The cell type-specific neuroadaptations that increase responses to drugs and associated cues are of interest not only in the NAc, but across the brain. In the case of D1 and D2 MSNs not

only have increases in activity been observed, but increases in the synaptic connectivity of specific glutamatergic inputs onto each population of neurons. Initially, a large body of work found that changes in glutamate signaling and extrasynaptic glutamate levels within the NAc were associated with relapse and withdrawal from cocaine self-administration (Baker et al., 2003; Kalivas et al., 2003; Kau et al., 2008; Pierce et al., 1996; Reid and Berger, 1996). These spine changes are consistent with increases in synaptic strength observed during the same period, where α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/*N*-methyl-D-aspartate (AMPA/NMDA) ratio is increased in these neurons following withdrawal (Conrad et al., 2008; Kourrich et al., 2007). The increase in AMPA receptor levels after withdrawal has been shown to be mediated by the insertion of AMPA receptors that lack the GluR2 subunit, thus rendering the receptors calcium permeable (Conrad et al., 2008). Indeed, calcium entry into these dendritic spines is potentiated during withdrawal from cocaine self-administration (Ferrario et al., 2012). Further, blocking the insertion of these calcium-permeable AMPA receptors in a nonspecific or projection-specific fashion is capable of blocking drug seeking (Lee et al., 2013). These changes highlight the long-term reorganization of receptor composition that could act to guide signaling via specific signaling cascades at specific times during withdrawal. This shift to allow more calcium-mediated signaling cascades could change the transcriptional landscape to promote different gene networks and could have potent effects on drug craving.

This work was further refined to show that specific projections from the PFC were critical in controlling drug seeking and relapse. Activity in the infralimbic cortex suppresses cocaine seeking and inactivation drives cocaine seeking (Lalumiere et al., 2012). Further, cocaine self-administration results in depressed prelimbic cortex excitability, which is associated with cocaine seeking. Rescuing this hypoactivity was capable of ablating this compulsive seeking, highlighting the causal role of reduced PFC activity in the process (Chen et al., 2013). However, following these studies, it was unclear as to which cells in the NAc these cortical projections were synapsing on. Recent work has demonstrated that drug seeking is associated with reduced AMPA/NMDA ratio (signifying reduced synaptic strength) at medial pre-frontal cortex (mPFC) to D1 MSN synapses. Conversely, increased AMPA/NMDA ratio was observed in ventral hippocampal inputs to this D1 population (Pascoli et al., 2014). Other studies have also shown specific potentiation of glutamatergic inputs onto D1 MSN. For example, cocaine exposure selectively enhances amygdala inputs to D1, but not D2 MSNs (but see: Pascoli et al., 2014), further highlighting cell type and pathway-specific adaptations that underlie cocaine-associated behaviors (MacAskill et al., 2014). These data demonstrate that remodeling of synaptic inputs is a complicated process that relies on converging factors in the environment to activate specific input circuits at specific times to induce long-term potentiation (LTP) in these circuits, but not others.

In addition to the inputs onto D1 and D2 MSNs, the outputs are also differentially altered by cocaine and show functionally distinct effects. Both D1 and D2 MSNs have been shown to project to the VP (Kupchik et al., 2015) rather than through direct and indirect pathways like in more dorsal regions of the striatum. Chronic cocaine exposure was shown to enhance D1 outputs to the VP while weakening outputs from D2 neurons (Creed et al., 2016), which is consistent with previous imaging work showing enhanced signaling through D1 pathways relative to D2 (Calipari et al., 2016). Interestingly, this work also showed that D1 and D2

projections to the VP had distinct roles in controlling behavioral outputs of cocaine, with the D1 pathway being more involved in locomotor sensitization and D2 in motivational deficits associated with cocaine exposure. It is likely that these two projection populations are responsible for balancing motivation and external information with changing internal states to help animals to make decisions; however, this is dysregulated in addiction. Further, work with reinforcement tasks has shown that reducing plasticity in the D2 pathway, or increasing its activity acts to alter cue-driven seeking behaviors (Bock et al., 2013; Heinsbroek et al., 2017). Importantly, the dysfunction in both of these pathways results from dysregulated plasticity, suggesting that increasing the ability of these cells to adapt to changing environments would have advantageous effects on addictive behaviors.

4.3.2 Enduring changes in morphology maintain new synaptic connections—

Changes in afferents and efferents on specific populations of neurons are maintained for long periods of time through stable changes in neuronal morphology. Dendritic spines are protrusions of the dendritic membrane upon which a majority of excitatory synapses are formed in the brain. Spine shape and size is often indicative of LTP or long-term depression (LTD) in glutamatergic projection populations (Okamoto et al., 2004). Spine head size is reflective of synaptic strength such that spines with large heads typically have a larger content of functional surface AMPA receptors than spines with small heads (Heinsbroek et al., 2017). Thus, LTD is often associated with shrinkage and atrophy of spines, while LTP is associated with both the formation of new spines and the enlargement of existing spines.

Spine changes are induced by activity-dependent signaling within each neuron which starts a molecular cascade that rapidly recruits the polymerization of actin and cytoskeletal-associated proteins to change spine size and alter stability (Blanpied and Ehlers, 2004; Lisman, 2003; Matus, 2005; Rao and Craig, 2000). The process by which spines can increase and decrease size and synaptic function is particularly important in drug addiction, as it provides a mechanism by which stable changes in circuit dynamics can be maintained so that activation of the pathway is more or less sensitive to environmental stimuli and subsequent drug exposure. Indeed, changes in spine morphology have been directly associated with the propensity to seek out drugs in animal models (Cahill et al., 2016; Dietz et al., 2012; Gipson et al., 2013; Li et al., 2004; Robinson et al., 2001; Russo et al., 2010). Furthermore, changes in the ability to remodel synaptic connections in reward-related brain regions are critical to responding to and recognizing drug-associated stimuli (Shen et al., 2009; Dumitriu et al., 2012; Gipson et al., 2013). These spine changes have been observed with concomitant changes in excitatory glutamatergic inputs (Conrad et al., 2008; Kourrich et al., 2007), and, as mentioned previously, with associated changes in excitability (Lee et al., 2013), extrasynaptic glutamate levels (Baker et al., 2003; Kalivas et al., 2003; Kau et al., 2008; Pierce et al., 1996; Reid and Berger, 1996), and enhanced connectivity of specific glutamatergic inputs from cortical areas (MacAskill et al., 2014; Pascoli et al., 2014).

Acute withdrawal from cocaine exposure results in increases in thin dendritic spines; however, following a withdrawal period there is a persistent and long-lasting change in spine size and dendritic branching in both the NAc and more dorsal regions of the striatum (Jedynak et al., 2007; Shen et al., 2009). It is likely that this maturation of spines acts to solidify the synaptic connections that contain information about cocaine and associated

stimuli (Bourne and Harris, 2007). Indeed, work on projections from the amygdala to the NAc has shown that over withdrawal, immature synapses were strengthened to form functional synaptic connections. Preventing this process from occurring was capable of preventing drug seeking (Lee et al., 2013).

While the stability and size of these spines is interesting, even more interesting is the rapid plasticity that they undergo upon presentation of a drug- or reward-cue stimulus. Both contingent and noncontingent cue presentation produces rapid changes in spine head diameter in the NAc (Gipson et al., 2013; Stankeviciute et al., 2014). Cue presentation results in rapid increases in spine head diameter within 15min, which is directly correlated with cocaine seeking. These spine head changes are associated with enhanced AMPA/NMDA ratios, suggesting that these proteins were “primed” to be inserted into the cellular membrane upon cue presentation. Further supporting the hypothesis of priming, an acute injection of cocaine following withdrawal from self-administered cocaine rapidly induces the surface expression of calcium permeable AMPA receptors (Anderson et al., 2008). These data together suggest that the ability of synapses to remodel quickly and efficiently is critical to learning-related processes and is altered following cocaine exposure in a way that potentiates the ability to rapidly upregulate proteins involved in synaptic connectivity.

While the ability of synapses and circuits to rapidly upregulate activity is enhanced following drug exposure, potentially more interesting is a concomitant decrease in the ability to induce LTD within these same brain regions (Martin et al., 2006). Therefore, cocaine experience seems to “prime” some responses while “desensitizing” others. Together, these changes converge to control an enhanced ability to respond to cues and drugs, and a reduced ability to inhibit these responses with changing environments. This could explain the deficits in drug-addicted individuals in appropriately extinguishing drug-associated behaviors. The question currently remains whether these changes are occurring within the same circuit or in a cell type or projection-specific manner. As mentioned previously, the maturation of synapses in the amygdala to NAc projection was shown to be critically involved in drug seeking. Further, changes over withdrawal from cocaine exposure have been shown to occur initially in both D1 and D2 MSN populations (Lee et al., 2006a), however, after a long withdrawal period only the D1 MSNs show an increase in the number of spines.

An important thing to note is that the changes in dendritic spines seem to be different to some extent across drug classes. Cocaine has been shown to increase the number and density of spines in the NAc, VTA, PFC, and OFC (Robinson and Kolb, 2004; Robinson et al., 2001). Conversely, opiates have been shown to decrease the number of spines in the NAc, hippocampus, and PFC (Russo et al., 2007; Sklair-Tavron et al., 1996). These findings are paradoxical as the behavioral phenotypes are similar. The changes in spines are interesting in this context, but are not surprising given the diverse roles of different cell types and projections in controlling these behaviors. For example, if the output of the NAc is driven by the balance between D1 and D2 MSNs, then both an increase in D1 and a decrease in D2 activity could potentially drive the same behavior. Therefore, moving forward it will be important to determine the source of the plasticity in order to make conclusions about how to effectively target these systems.

Together, effects of some drug classes may differ from others in some ways, however, these studies have a fundamental degree of overlap: there is a lack of dynamic plasticity across the brain that prevents adaptive learning processes. Thus, in order to make progress, we must understand the molecular basis for this activity-dependent morphological and circuit reorganization that underlies reward learning.

5 HOW ARE CHANGES IN NEURAL MORPHOLOGY AND FUNCTION MAINTAINED?

The behavioral, circuit, and morphology data point to one important adaptation in drug-addicted individuals. Synapses are strengthened for long periods of time that last far beyond the life span of any individual protein involved in the process (McPherson, 2015). These long-lasting changes in synaptic strength are critical mediators of drug seeking and relapse, thus understanding how they are maintained is of critical importance, both on a basic neuroscience and drug abuse treatment level.

At the heart of experience-dependent plasticity lies the capacity of neural circuits to undergo activity-induced structural and functional changes. The maintenance of such permanent change requires efficient posttranslational and transcriptional regulation (Sweatt, 2013). The ability to turn genes on and off is controlled by epigenetic regulation, where the structure of DNA is modified to increase or decrease the probability of gene expression. This process is emerging as the primary molecular mechanism underlying plasticity in postmitotic neurons. Thus, understanding how this process is dysregulated in disease will shed light onto the basic process, its importance in behavioral control, and provide potential targets for treatment of these complex disorders.

5.1 THE EPIGENOME AS THE MOLECULAR HUB OF INFORMATION ENCODING IN ADDICTION

EPIGENETICS

The term epigenetics was coined by Conrad Waddington to describe a conceptual solution to a fundamental consideration—and conundrum—in developmental biology. All the different types of cells that make up our body, bar exceptions in our reproductive and immune systems, have exactly the same genome. Yet, how can the identical DNA template produce vastly different gene products and yield distinct cell types like myocytes or neurons? Waddington reasoned there must be a mechanism above the level of DNA that controls the readout of genes encoded in its nucleotide sequence—coining the term epigenetics. These epigenetic mechanisms specify certain sets of genes that are turned into functional products in neurons, for instance, yet not in myocytes. Diverse epigenetic marks are set up during early cell fate decisions, in due course forming a memory system that perpetuates cellular phenotypes over the lifespan of our bodies. In view of that, classic epigenetics is the study of a change in gene expression or cellular phenotype that is stably inherited by a cell and that is not associated with changes in DNA sequence. Today, many epigenetic modifications are known to be highly dynamic

with critical functions in neuronal plasticity that are implicated in neurodegenerative and psychiatric disorders.

Although many cellular phenomena may be considered epigenetic, the primary focus of the field has been to illuminate environment–genome interactions at the level of chromatin. Chromatin describes the DNA–protein packaging complex that determines the accessibility of DNA in eukaryotic cells, making it the focal point of transcriptional gene regulation. The basic repeating unit of the chromatin structure is the nucleosome: ~146 base pairs of genomic DNA wrapped around a protein octamer, assembled from two molecules each of histone H2A, H2B, H3, and H4. In essence, the nucleosome constitutes a platform for complex chemical modifications—i.e., epigenetic marks—that dynamically regulate chromatin architecture and gene transcription (Rivera and Ren, 2013). The entirety of these epigenetic features has been denoted the epigenome—it defines neuronal identity and expresses the regulatory channels that operate at the interface of genome and environment (Day and Sweatt, 2011).

Posttranslational modifications of histones elicit structural and functional changes within chromatin and regulate various epigenetic processes. To date, numerous histone modifications have been identified and include acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, and ADP-ribosylation (Berger, 2007; Kouzarides, 2007). Acetylation, for instance, along with methylation, is the most extensively studied histone modification, and has broad effects on chromatin function and nuclear signaling pathways (Berndsen and Denu, 2008; Shahbazian and Grunstein, 2007). Histone acetylation is regulated by the opposing actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs acetylate-specific lysine residues of histone proteins, which neutralizes their positive charge, and can thus help to decondense chromatin leading to active gene transcription (Berndsen and Denu, 2008). Additionally, histone acetylation marks can be bound by small protein modules called bromodomains, often referred to as “readers.” These domains are conserved within many chromatin-associated proteins—including HATs themselves—that regulate transcription-mediated biological processes, and whose aberrant activities are correlated with several human diseases (Bannister and Kouzarides, 2011; Burdge and Lillycrop, 2010; Filippakopoulos and Knapp, 2014).

Indeed, drug addiction is one of these syndromes. Epigenetic remodeling has emerged as a potent regulator of drug-induced plasticity and has been implicated in addiction to stimulants, opiates, ethanol, and nicotine (Walker et al., 2015). For example, hypermethylation of the dopamine transporter gene has been observed in human alcoholics and was shown to be predictive of addiction severity (Ponomarev, 2013). In human heroin addicts, impairments in both glutamatergic neurotransmission and chromatin remodeling were observed, including increased enrichment of lysine-27 acetylated histone H3 (H3K27) that affected GluR2, the subunit of the AMPA receptor that confers calcium permeability (Egervari et al., 2017). Similar changes were seen in rodents that underwent heroin self-administration and these changes were directly linked to self-administration behavior. Other work with cocaine has shown reduced levels of H3K9 dimethylation in the nucleus NAc, which was found to be mediated through the repression of G9a, a methyltransferase (Maze

et al., 2010). These reductions led to increases in immediate early gene expression, and thus, could act to prime these genes to respond quickly and to a greater extent upon cellular activation. Together, changes in the ability of transcription to dynamically respond to the changing cellular microenvironment is important as it dysregulates not only the protein composition of cells, but their ability to quickly respond in a temporally specific fashion to information.

6 EPIGENETIC REGULATION IS THE KEY TO A CENTRAL PROPERTY OF NEURAL NETWORKS: PLASTICITY

The exact mechanisms by which circuit activity can directly manipulate chromatin structure in its participating neurons remain opaque. Neurons continually adapt to a changing environment, and thus require an acutely responsive system that adjusts chromatin structure and gene transcription. Epigenetic changes can be transient, such as histone acetylation or phosphorylation, or long-lived, such as specific histone methylation and DNA methylation, and both of these processes are likely involved in addiction (Fass et al., 2013; Peña et al., 2014; Robison and Nestler, 2011; Rudenko and Tsai, 2014). Importantly, modification of the epigenetic landscape provides a mechanism by which the transcriptional response to stimuli can be permanently altered, thus providing a molecular route to lasting modifications of neuronal and circuit functions.

Several types of epigenetic modifications have been associated with cognitive functions, including DNA methylation, and the posttranslational modification of histone proteins by acetylation, methylation, and phosphorylation (Alarcón et al., 2004; Dulac, 2010; Gräff and Tsai, 2013a; Korzus et al., 2004; Levenson et al., 2004; Nelson and Monteggia, 2011; Wood et al., 2006). Yet histone acetylation in particular has spurred considerable interest, and is most robustly associated with promoting associative learning and memory formation, which, as discussed previously, is one of the critical learning processes dysregulated in drug addiction.

As early as 1979, it was found that the acetylation state of histones is altered when rats undergo memory consolidation (Schmitt and Matthies, 1979). More recent evidence confirmed these findings, showing that specific forms of associative learning about cues and predicted outcomes correlate with increased histone acetylation (Levenson et al., 2004). For example, following contextual fear conditioning, acetylation of H3K14 was significantly increased in the hippocampus, whereas acetylation of H4 was unchanged (Levenson et al., 2004). Conversely, H4 acetylation was selectively increased after latent inhibition training (Schmitt and Matthies, 1979). Latent inhibition involves a process where a familiar stimulus takes longer to acquire a new meaning because of extended experience with the stimulus (Lubow and Moore, 1959). Thus, with latent inhibition the ability to update information about that stimulus is particularly difficult. Interestingly, H4 hyperacetylation is observed within 30min of a single cocaine injection, highlight that related processes are recruited with paradigms of drug exposure (Kumar et al., 2005). Thus, this specific modification could underlie some of the difficulty with replacing cocaine-associated memories with new and updated information. These early results not only highlight that histone acetylation

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accompanies memory consolidation and learning about drug rewards, but show that different learning paradigms elicit distinct epigenetic signatures in the brain. Given what we know about the processes involved in these different memory types (i.e., extinction vs latent inhibition, vs reinforcement learning) interventions could be targeted at specific epigenetic marks that help to enhance specific types of learning.

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Many follow-up studies have corroborated the implied link between histone hyperacetylation and memory formation for different memory types and phases, such as reconsolidation and extinction learning, which as discussed previously, are basic learning processes that are critical mediators of volitional drug consumption (Bannerman et al., 2014; Gräff et al., 2012; Oliveira et al., 2011; Rogge and Wood, 2013; Schneider et al., 2013; White and Wood, 2013; Wood et al., 2006). Newer studies using chromatin immunoprecipitation have revealed that memory-induced histone acetylation is specific to certain genes (Alarcón et al., 2004; Fischer, 2014; Korzus et al., 2004). These include genes that are important for neuronal plasticity, such as the immediate-early genes *Erg1*, *Creb*, and *Bdnf*, which showed an increase in expression following contextual fear learning, concomitant with the increase in histone acetylation (Bannerman et al., 2014; Korzus et al., 2004; Oliveira et al., 2011). Indeed, all of these molecules have been shown to be critically involved in different stages of the addiction process and the expression of maladaptive reward behaviors (Go et al., 2016; Hoffmann et al., 2017; Li et al., 2016; Rovaris et al., 2017; Sun et al., 2015; Zhang et al., 2016). Relevantly, during this time window, Ca^{2+} -induced cAMP signaling that engages the ERK and PKA pathways in the hippocampus and the amygdala directly phosphorylate and thus activate the transcription factor cAMP-response element-binding protein (CREB), a process critical to long-term memory (Dash et al., 1990; Freytag et al., 2017; Serita et al., 2017; Stevens, 1994). In fact, windows of CREB serine 133 phosphorylation coincide with sensitive periods during which inhibition of transcription impairs memory storage, highlighting the importance of regulated gene expression in learning and memory (Bourtchouladze et al., 1998). Aptly, acute administration of cocaine phosphorylates and thus activates CREB to induce transcription-dependent neuroplasticity in the reward pathway, most prominently in the NAc. Work has shown that overexpressing CREB enhances cocaine reinforcement and increasing CREB following withdrawal potentiates cocaine-induced seeking behavior, showing a potentiation of both drug effects and seeking (Larson et al., 2011).

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It is tempting to attempt to identify a single gene that controls the addictive phenotype, yet the complex nature of a disorder involving learning mechanisms make it more likely that a complex network of interconnected genes regulates the connectivity of neurons across the brain. Accordingly, recent evidence showed that CREB phosphorylation alone is not sufficient to drive such gene expression. Instead, it is the interaction between phosphorylated CREB and the histone acetyltransferase CREB-binding protein (CBP) that is critical for memory formation (Fischer et al., 2010; Gräff and Tsai, 2013b; Haettig et al., 2011; Levenson et al., 2004; Stefanko et al., 2009). This finding highlights the importance of dynamic chromatin regulation in neuroplasticity in response to drugs of abuse: CBP catalyzes the acetylation of histone H3 lysines through its HAT domain, resulting in chromatin remodeling and relaxation of chromatin structure that enables the transcription of CREB target genes (Wang et al., 2013). Learning-induced transcription occurs rapidly and is

restricted to precisely timed windows of dynamic histone acetylation and is dependent on a number of signaling cascades converging simultaneously (Dulac, 2010; Fischer, 2014; Gräff and Tsai, 2013a; Hsieh and Eisch, 2010; Sharma, 2010; Tsankova et al., 2007). Accordingly, the sudden increase in acetylation was found to be critically dependent on production of the cofactor acetyl-CoA by ACSS2, which “fuels” CBP-mediated acetylation and effective induction of genes functioning in experience-driven synaptic change, including Fos, Arc, and Egr2 (Mews et al., 2017). Thus, CREB acts in concert with a wider range of other factors to induce learning-related plasticity.

Similarly, following cocaine self-administration, rapid increases in CREB levels are linked to dynamic increases in promoter-proximal H3K9 and H3K14 acetylation at the Cdk5, Bdnf, and Fosb genes, which have key functions in neural plasticity and become upregulated by virtually all drugs of abuse (Bibb et al., 2001; Graham et al., 2007; Hope et al., 1994). As mentioned earlier (see Section 4.3.2) repeated exposure to cocaine leads to persistent alterations in spine morphology and synaptic strength that involve increases in calcium permeable AMPA-receptor levels. Because CREB is activated through calcium-dependent signaling within the cell, this provides a potential mechanism by which epigenetic modifications could control plasticity specifically in the neurons recruited into the drug-reward circuit, putatively constituting a molecular feedforward loop that could work to potentiate responses to drug-associated stimuli.

7 THE INTERFACE BETWEEN NEURONAL ACTIVATION AND EPIGENETIC REMODELING

Together, a large body of work has shown that both changes in neural circuit dynamics and epigenetic regulation can alter reward-related behaviors (Dudai and Morris, 2013; Russo and Nestler, 2013). A major question in neuroscience is how these activity-dependent changes at the level of the circuit interface with DNA changes to guide behaviors. The first step is understanding how information is transmitted from a synaptic signal, in the form of an action potential or receptor activation, to the nucleus to trigger the necessary molecular machinery for epigenetic remodeling on a fast time scale. In this view, epigenetic regulation is a gating device that arbitrates acute and transient gene expression in response to upstream neural activity. Circuit activity triggers intracellular signaling cascades such as the PKA or MAPK/ERK pathways that are activated by G protein-coupled receptors and calcium, and therefore, transmit circuit activity information to the nucleus (Ménard et al., 2015). In the nucleus, epigenetic signatures demarcate and regulate genes with functions in synaptic remodeling for memory circuit formation (Sweatt, 2013). Remarkably, but not surprisingly, the plasticity mechanisms linked to drug addiction correspond to well-described neuronal and circuit plasticity in learning and memory, and involve most of the same brain regions (outlined in Fig. 2).

7.1 DRUG-INDUCED TRANSIENT CHANGES IN CHROMATIN STRUCTURE

Epigenetic modifications serve two major functions in differentiated neurons. First, they act to determine which genes are upregulated on a transient timescale upon cellular activation. Second, they act to control stable gene expression on a timescale that extends beyond the

initial transient signal. The interplay between these two types of epigenetic modifications is relatively unstudied. Thus, better insight into how drug-induced transient changes in chromatin structure lead to stable and long-lasting epi-genetic regulation of gene expression is needed.

The focus of recent studies has been on the initial chromatin-localized events that occur on a timescale of minutes to regulate neuronal gene expression. Neuronal activity signals can be transmitted to the nucleus through the engagement of G protein-coupled receptors that stimulates cAMP signaling to set off a signaling cascade via the PKA pathway and members of the mitogen-activated protein kinases (MAPKs), which can directly phosphorylate histones to prompt further changes in chromatin structure, including transcriptionally activating histone acetylation (Gräff and Tsai, 2013a; Nestler, 2016). Additionally, signals of neural activity are transmitted to chromatin via the calcium/calmodulin-dependent kinase II (CaMKII), which becomes activated upon cellular depolarization and influx of calcium. CamKII stimulates transcription of BDNF, a well-known neurotrophin involved in neuroplasticity, by phosphorylating and thus releasing the DNA methylation “reader” methyl CpG-binding protein 2 (MeCP2), a highly abundant chromosomal protein within the brain, from its promoter (Im et al., 2010; Nott et al., 2016; Zhou et al., 2006).

This process is important in both drug addiction and reinforcement learning, and interestingly these changes have been linked to both chromatin modifications and changes in cellular morphology. MeCP2 in the dorsal striatum was shown to control escalated cocaine consumption, a process thought to mimic the uncontrolled use seen in human addicts. A critical aspect of this study is that MeCP2 only regulated escalated cocaine consumption, not consumption on restricted access schedules, suggesting that it plays a role in drug-induced plasticity, rather than the rewarding effects of cocaine in general. Further, the actions of MeCP2 in this specific context were found to be via alterations in BDNF (Im et al., 2010). Similarly, striatal BDNF transmission is known to increase the motivation to self-administer cocaine (Graham et al., 2007, 2009; Grimm et al., 2003; Hall et al., 2003; Horger et al., 1999; Im et al., 2010; Lu et al., 2004; Schoenbaum et al., 2007), and increases have been linked to the increased spine changes that are characteristic of cocaine exposure (Zhou et al., 2006). BDNF activates the enzyme nitric oxide synthase, leading to nitrosylation and dismissal of chromatin-bound HDAC2, thus ultimately increasing histone acetylation at genes involved in neural plasticity for LTP and learning (Nott et al., 2008). Notably, whereas inhibition of HDAC2 and HDAC3 enhances histone acetylation and synaptic plasticity, deficit of other HDACs, namely HDAC4, has the opposite effect (Gräff and Tsai, 2013a). These data indicate that histone acetylation is a highly specific epigenetic mark that is controlled by different regulatory processes in a time-sensitive window with gene-specific transcriptional outcomes.

Whereas activity-induced gene expression and protein synthesis is transient, the circuit rewiring linked to associative learning and memory storage is long-lasting (Tonegawa et al., 2015). Notably, histone acetylation is known as a highly dynamic modification that rapidly turns over. Equally, even the extended half-life of channel proteins such as AMPA and NMDA receptors—whose expression is manipulated by drugs of abuse—is transitory when compared to timescales of pathological states of addiction, as drug relapse can occur even

after years of abstinence and clinical intervention. Therefore, persistent changes in transcriptional regulation caused by drugs of abuse are likely maintained by the complex interplay of short lived epigenetic marks—e.g., transient histone acetylation with dramatic effects on gene expression—that regulate synaptic and circuit strengths and permanent epigenetic aberrations that preserve transcriptional dysregulation in concert with alterations at the synapse and cell signaling.

7.2 TRANSIENT CHANGES AS A SCAFFOLD FOR LONG-TERM EPIGENETIC CHANGES

All of the aforementioned mechanisms rely on acute changes that are transient in nature and are likely involved in quick and adaptive responses of cellular circuits to environmental information. But the question is how these precisely timed processes ultimately lead to permanently altered epigenetic landscapes that underlie dysregulated transcription in addiction.

Results support an emerging view that rapid changes in DNA methylation—traditionally viewed as a permanent and immutable mark in postmitotic cells—are involved in activity-dependent regulation of neuronal gene transcription. The maintenance DNA methyltransferase, DNMT1, is highly expressed across the brain, and transient increases in DNMT1 expression are not only seen with Pavlovian learning, but have been reported after administration of drugs of abuse, specifically methamphetamine (Goto et al., 1994; Numachi et al., 2007). In fact, following chronic exposure to drug, increases in DNA methylation in the striatum are persistent and evident even after extended periods of withdrawal (Mychasiuk et al., 2013). Notably, in the case of Pavlovian learning, DNMT inhibition in the mPFC blocked memory recall even when applied acutely 1 month after training (Miller and Sweatt, 2007). Furthermore, upon synaptic activity, DNA demethylation is initiated by Tet family proteins that oxidize 5-methylcytosine and activate the base-excision repair pathway, dysregulation of which has been found to prevent homeostatic synaptic plasticity (Yu et al., 2015). These findings highlight the dynamic nature of the neuronal DNA methylome and suggests an important role for DNA methylation in the stabilization of epigenetic change that is instigated by drugs of abuse (Feng et al., 2015). In fact, both acute and chronic cocaine has been shown to cause hypomethylation of the FosB promoter in the striatum, linked to decreased binding of MeCP2 and upregulation of FosB expression (Anier et al., 2010). Intriguingly, repeated drug exposure causes accumulation of its splicing variant

FosB in D1 MSNs due to its increased stability (Nestler et al., 2001). This provides a partial window into how neuronal activity patterns can be integrated over time to license permanent changes in chromatin structure and gene regulation, and endure even after FosB protein expression is reduced following prolonged withdrawal.

As outlined earlier, the aforementioned changes in chromatin structure produce plasticity at the synaptic and circuit level, including alterations of the AMPA and NMDA receptor levels and their subunit composition. Just like with dendritic spines where the thin spines serve as a scaffold to create more mature spines, transient epigenetic marks can set a series of events in place that help to consolidate information permanently only if the stimulus is incredibly salient or encountered repeatedly over long periods of time. This would provide gating so that the long-term changes would only happen after repeated exposure.

7.3 PERMANENT EPIGENETIC CHANGES AS MEDIATORS OF GENE PRIMING

Evidence from rodent addiction models supports the view that permanent epigenetic adaptations underlie persistent anomalies in transcription regulation induced by drugs of abuse across the brain. While these permanent marks could change basal levels of gene expression, it is important to understand how they would alter stimulus-induced gene expression. Specifically, repeated cocaine exposure alters the inducibility of key genes, referred to as gene priming and desensitization. Such latent transcriptional dysregulation has been linked to epigenetic priming in the context of immunology, but is unexplored in neuropsychiatric disorders. Notably, most of these changes are not manifested in altered steady-state levels of mRNA, but rather, are latent and reflected in dysregulated expression of genes upon challenge with drug at a later time point. A similar phenomenon is notably seen with AMPA receptor trafficking where the insertion into the membrane is faster after withdrawal from cocaine exposure (Lee et al., 2013; MacAskill et al., 2014), and it is possible that this is driven by epigenetic changes at the gene level.

Mounting evidence suggests that aberrations in the epigenetic landscape are responsible for these persistent changes in gene expression. In this view, alterations in chromatin architecture “scar” gene regulatory regions to permanently prime specific gene sets for rapid induction or repression in response to future stimuli. Accordingly, drug-induced changes in the epigenetic landscape persist and distinctly prime neuronal populations that participate in the reward circuit for aberrant transcriptional responses in the future. The extant literature supports this assertion but has been insufficiently mechanistic. DNA methylation, which, as discussed earlier, is permanently altered by the epigenetic processes set off by drugs of abuse, and could underlie this process. The methylation state of genes acts to control both transcription and splicing events in plasticity and surface receptor genes. Thus, deepening our knowledge of the causal roles epigenetic mechanisms play in long-lasting transcription dysregulation will spur development of novel treatments to manipulate chromatin pathways in neuropsychiatric disorders.

8 BIDIRECTIONAL CROSS-TALK BETWEEN THE EPIGENOME AND CELLULAR ACTIVITY

Together, a large body of work has shown the critical role of epigenetic modifications in drug addiction (Walker et al., 2015). Similarly, many studies have defined the specific neural adaptations at the circuit level that underlie these same maladaptive behaviors (Dumitriu et al., 2012; Robinson, 1999; Robinson et al., 2001). Thus, understanding the basic process by which activity-dependent changes in the epigenome can feed back and alter cellular excitability in specific populations will lead to a better understanding of how certain neurons are recruited to respond to specific stimuli in health and disease. The ability to strengthen some synapses while weakening others is a critical mediator of learning and helps to guide appropriate behaviors. This process relies on precise temporal activity in both the pre- and postsynaptic cell, which through activity-dependent calcium signaling, leads to the maturation and stability of that particular synapse.

Changes in the resting membrane potential, gene priming, and stable receptor expression levels can all alter the probability that a specific cell will fire, and thus can increase the incorporation of these neurons into memory ensembles and strengthen synaptic connections. Work has shown that increasing CREB levels within neurons are sufficient to increase their incorporation into ensembles that encode specific memories, highlighting a role of activity-dependent molecular signaling in the process (Hsiang et al., 2014). Maintenance of these tonic levels of neurotransmitter, changes in transporter function, and postsynaptic receptor content have been shown to be regulated by epigenetic modifications at the chromatin level. Specific methyl and acetyl marks can act to change stable expression levels of proteins involved in this process, such as AMPA and NMDA receptors, which can change the speed and efficiency with which new synapses can be formed and destabilized. This can also change the response magnitude of these cells and circuits to salient stimuli in the environment, thus driving maladaptive behaviors. These specific processes have been shown to be dysregulated in both human addicts and rodent models of drug-addiction (Breiter et al., 1997; Calipari et al., 2016; Dackis and O'Brien, 2005; Volkow et al., 2005). Thus, basal epigenetic regulation of membrane-associated proteins can alter the excitability of neurons and concomitant behavioral processes associated with addiction.

Conversely, repeated stimulation of strengthened synapses can result in activity-dependent epigenetic remodeling via calcium-dependent signaling via effectors like CREB (Nestler, 2013). This increase in the activity level of neurons can lead to the activation of immediate early genes and concomitant wide scale changes in the accessibility of DNA and transcriptional processes. In addition, these changes can lead to a feedforward loop in which activity-dependent epigenetic changes lead to enhanced sensitivity to subsequent inputs. If these inputs are in pathways driving reinforcement learning this can act to increase self-administration and drug seeking.

Thus, it is the communication between the nuclear changes in DNA conformation/transcription and the precise changes in membrane excitability that allow for the refinement of information at the level of each individual neuron. A lack of plasticity in this process is what underlies drug addiction in a way that results in the strong and stable storage and expression of drug-associated memories over all others (Fig. 4).

9 FOCUSING TO THE FUTURE

9.1 GOALS OF TREATMENT

The goal of drug addiction treatment has historically focused on two main problems: (1) Helping individuals stop consuming drugs once they have started and (2) Preventing relapse in abstinent individuals. Both of these processes involve learning and updating information on a rapid timescale. Consumption relies on learning about response-contingency outcomes and drug seeking and relapse on learning about predictive cues. Together, the goal of all of these treatment strategies is to increase the probability of individuals learn new contingencies, allocate behavior away from drug seeking and taking, and instead toward more adaptive responses. Thus, in the case of both consummatory and appetitive processes increasing the metaplasticity of neural circuits so that they can weaken associations between

drugs and associated cues and replace them with more adaptive information about natural rewards will be important.

Applying pharmacological approaches to correcting behavioral disorders has been largely ineffective, likely because addiction is characterized by dysregulated learning, which is controlled by complex interconnected networks, not just the reward circuit, of neural signaling in a specific context. The neural circuit changes induced by drug exposure trigger a molecular cascade that can act to alter subsequent transcription through epigenetic remodeling. This remodeling can feed forward then act to change the connectivity and excitability of the circuit. Thus, to come up with effective therapies we need to understand the interplay between the molecular targets and the circuit disruption that controls discrete aspects of behavior. Altering either in isolation will likely not be sufficient to reverse the problem.

9.2 COMPLEX INTERPLAY BETWEEN CIRCUITS AND TRANSCRIPTION

While it is interesting to speculate which factor is more important in regulating addiction, and thus which to target for treatment, both epigenetic and circuit factors play critical roles, possibly in different temporal aspects of the behavior. For example, transcription happens on the time scale on minutes, however, the high perceived by drugs of abuse occur within seconds. Within 5s, and intravenous cocaine injection has sufficiently to elevated dopamine levels in reward-related brain regions in rodents (Yorgason et al., 2011). In fact, it is the speed at which the drug does this that predicts the euphoric effects of the drug in humans, and the reinforcing effects of the drug in animal models (Balster and Schuster, 1973; Volkow et al., 1995). Therefore, responding and updating information in real-time requires neural connections across the brain.

Further, drug-induced learning processes can be manipulated by altering circuit excitability. Optogenetic studies have shown that maladaptive drug seeking can be blocked by reversing activity deficits in PFC projections into the NAc (Chen et al., 2013). Further, the expression of cocaine-associated memories can be inhibited by blocking hippocampal or cortical projections to the NAc (Pascoli et al., 2014). Inhibiting the BLA to NAc projection is capable of inhibiting cocaine-induced locomotor sensitization (MacAskill et al., 2014). Finally, associative learning about drug rewards and predictive cues can be abolished by inhibiting D1 MSN activity during cue-cocaine pairing (Calipari et al., 2016). These are selected examples of many studies defining circuit activity as a critical regulator of these behavioral learning processes.

Similarly, epigenetic factors are also involved in learning about cocaine and associated stimuli. For example, blocking protein synthesis following a learning task can prevent memory consolidation, thus the ability to acutely upregulate specific proteins is critical (Bourtchouladze et al., 1998). Similar results have been seen with small molecules that inhibit epigenetic writers and erasers. HDACs have been shown to bidirectionally control associative learning for cocaine and predictive cues (Kumar et al., 2005). HDAC inhibitors enhanced associative learning for cocaine and predictive cues. Conversely, reducing histone acetylation in the NAc by virally expressed HDACs decreases the ability of animals to make

associations between cocaine and predictive cues (Renthal et al., 2007). Thus, epigenetic modifications are critical in the stabilization and expression of these learned behaviors.

Therefore, circuit activity is necessary for the expression of behavior and the ability to update information in real-time, while epigenetic information is necessary to maintain this information for the long-term. As a result, treatments that target the circuit dynamic changes, without normalizing the molecular basis for this change will likely only be transiently effective. However, targeting epigenetic writers and erasers, without activating the circuits in the appropriate context to allow for plasticity, will likely not lead to appropriate circuit remodeling to reduce drug craving.

9.3 WHAT TO TARGET AND HOW

On an epigenetic level, insight into the kinetic mechanisms of writers, readers, and erasers of chromatin modifications is anticipated to provide novel clinically relevant diagnostic, prognostic, and therapeutic avenues in the treatment of psychiatric disorders. Discussed earlier, different learning paradigms can result in different types of epigenetic modifications, that can feed back and influence neural circuit stability, making understanding the discrete aspects of learning and memory that underlie these changes critical moving forward. For example, targeting epigenetic marks that are responsible for stabilizing synaptic connections in specific pathways or cell types could be effective as treatments. As new tools develop to tackle these complex problems, we will get a more comprehensive view of how different marks are altered by drug exposure across the brain.

Epigenetic avenues of treatment are particularly appealing as epigenetic mechanisms are not only implicated in the molecular pathophysiology of drug addiction, but function as the principle regulators that are common to different neuropsychiatric disorders. Highly informative to current efforts in developing novel therapeutic approaches to drug addiction are recent insights from epigenetic treatments in posttraumatic stress disorder (PTSD). In PTSD, histone acetylation facilitates memory formation and long-term consolidation of fear. The learning process and mechanisms governing this process are similar in the case of drug abuse, where long-term associations between predictive cues and drugs can precipitate relapse (O'Brien et al., 1998).

Dynamic histone acetylation is further involved in the reconsolidation of memories following retrieval, which allows for memory updating and new associative learning linked to disease progression (Torregrossa and Taylor, 2013). Pharmacological agents that target these processes to manipulate traumatic memories are anticipated to be extremely useful in prevention and treatment of PTSD and other psychiatric disorders, including drug addiction (Kwapis and Wood, 2014). However, in order to use this as a treatment, we need to first understand what makes these memories accessible and renders the affected circuits plastic. Because drug addiction activates a brain wide network of circuits, it is important to understand how, when, and which neurons undergo plasticity in order to target them effectively.

Because cue learning is the factor that plays the largest role in relapse, treatment could potentially be aimed at delivering epigenetic drugs during cue exposure to facilitate

extinction learning. Once these neural ensembles are activated, they can be targeted with epigenetic modifying drugs such as HDAC inhibitors (HDACi). In the case of PTSD, HDACi are being used in clinical trials to enhance extinction learning in combination with cognitive behavioral therapy. Whereas the original trauma memory is not erased, such epigenetic pharmacotherapy enhances activity-induced histone acetylation and new learning that has shown preliminary success. Similarly, drug addiction may be treated by pairing cognitive behavioral therapy with epigenetic interventions, for instance, HDACi to facilitate extinction learning. The power of this approach is that epigenetic pathways that function in an activity-dependent manner, are targeted across different brain regions.

Thus, we propose a novel two-pronged approach to treat pathological states of addiction: combining cognitive behavioral therapy with pharmacological targeting of epigenetic plasticity mechanisms in a clinical setting to reverse permanent alterations in neural and circuit function caused by drugs of abuse.

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FIG. 1.

Bidirectional cross-talk between neuronal activity and the epigenome. The brain is a complex computational machine that must respond to information on a subsecond timescale and then store this information for long periods of time. This occurs via a complex interplay between neuronal activity and DNA modifications. Upon the presentation of a salient environmental stimulus, neurons are activated in various regions of the brain. In the case of drugs of abuse, these regions are often the reward pathway containing the ventral tegmental area and its projections to mid- and forebrain structures. This activation triggers activity-dependent molecular signaling cascades that can act to modify the DNA (*blue*) and the histone proteins that it is wrapped around (*green*). These modifications make DNA more accessible and can alter the expression of genes involved in synaptic function (*inset*). These epigenetic changes to chromatin (comprised of DNA and associated histone proteins) can change basal gene expression which can alter the composition of membrane receptors or increase regulatory proteins that can phosphorylate other effectors downstream. Epigenetic mechanisms allow for the initial activity-dependent changes to be solidified and outlast the life of any individual protein.

FIG. 2.

Neural circuits implicated in drug addiction. A complex network of brain regions participates in the encoding of information associated with drug addiction. (*left*) Network diagram of interconnected brain regions involved in drug addiction. *Orange*, GABAergic populations; *red*, glutamatergic projections; *purple*, dopaminergic projections. (*right*) The integration of signaling in the nucleus accumbens (NAc). The NAc is comprised of two major populations of projection neurons: D1 and D2 receptor containing medium spiny neurons. In basic reward processing, these neurons integrate information from glutamatergic inputs from the prefrontal cortex (PFC), hippocampus (Hip), and amygdala (Amyg.) with dopaminergic projections originating in the ventral tegmental area (VTA). While in dorsal regions of the striatum D1 and D2 MSNs signal through direct and indirect motor pathways, in ventral regions of the striatum populations project to the ventral pallidum (VP). Amyg., amygdala; BNST, bed nucleus of the stria terminalis; CPU, caudate putamen; Hip, hippocampus; LHb, lateral habenula; OFC, orbitofrontal cortex; RMTg, rostromedial tegmental nucleus; Thal, thalamus.

FIG. 3.

D1 and D2 medium spiny neurons in the NAc. (*left*) D1 and D2 medium spiny neurons in the NAc receive overlapping projections from cortical and sensory areas. These overlapping inputs allow these populations to balance information about internal state with other environmental factors to execute goal-oriented behaviors. These populations have been shown to be activated during self-administration for food and drug rewards. (*right*) Cocaine exposure changes the balance of inputs onto each of these populations differentially. Work from a number of groups has outlined the projection and cell type-specific effects of cocaine in the NAc (discussed in Section 4.3.1). Cocaine exposure leads to increased activity in D1 MSNs. This is likely driven by an enhancement of activity from hippocampal (Hip) and basolateral amygdala (BLA) projections. Further dopaminergic inputs from the ventral tegmental area (VTA) and glutamatergic inputs from the prefrontal cortex (PFC) are weakened. This reorganization of connectivity leads to greater signaling of D1 MSNs relative to D2 via downstream regions such as the ventral pallidum (VP) to drive enhanced behavioral responses to cocaine and associated stimuli. AC—anterior cingulate; M1, M2—motor cortices; S1, S2—sensory cortices; SNc—substantia nigra pars compacta; Thal—thalamus; V1, V2—visual cortices.

FIG. 4.

Epigenetic modifications to solidify neuronal ensembles. Drug-induced neuronal activation causes rapid changes in chromatin structure. Epigenetic signatures in neurons of the reward circuit gate intracellular signaling to regulate the temporally sensitive transcription of genes involved in synaptic plasticity. Upon initial activation, transient changes in chromatin modifications, like phosphorylation and acetylation, alter transcription in the short-term. Over time, epigenetic changes become more permanent, such as DNA methylation that can alter the ability of genes to be induced by neuronal activation. Such gene priming or desensitization can modify the ability of neurons to rapidly and efficiently respond to drug-associated cues. Thus, repeated exposure to drugs causes permanent changes in the epigenetic landscape that alter the inducibility of key genes, which solidifies which neurons will be activated and act to drive drug seeking.