Chapter 4

Molecular Mechanisms of Drug-Induced Plasticity

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Abstract

Substance-use disorders (SUDs) are a significant societal burden. Like many other conditions, SUDs are characterized by chronic relapse after periods without symptoms. Alterations in synaptic plasticity have been documented after acute and addiction-related behavioral exposures to drugs of abuse. These synaptic alterations are persistent and similar to the chronic relapse state of patients with SUDs, suggesting that reversing these synaptic alterations may prevent relapse. Additionally, many of these synaptic features of addiction mirror those found in other forms of learning and memory. These features suggest that the etiology of this disorder stems from persistent modifications in corticolimbic synaptic plasticity mediated by drug-induced alterations in addiction-related gene (ARG) expression. Understanding the regulation of addiction-related genes and their impact on synaptic plasticity and behavior may inform new pharmacological treatments that reverse these aberrant drug-evoked forms of plasticity in favor of remission.

Keywords: addiction, substance-use disorders, Fos, CREB, ADAR, BDNF, Mef2, miR-212, miR-9, FMRP, HuD, ELAVL

1. Introduction

Substance-use disorders (SUDs), or more colloquially known as drug addiction, are a significant societal burden both financially, incurring an estimated $193 billion in costs (www.justice.gov/ndic, 2011), and emotionally devastating to patients and their families. In opposition to more controlled, casual drug use, SUDs are characterized by uncontrollable bouts of drug consumption in spite of negative life consequences. Patients with this disorder appear to lose interest in normal prosocial activities, instead directing their energy toward the pursuit of these substances. Since addiction is a chronic, relapsing condition, this disorder has been notoriously difficult to manage. A complete review of pharmacological mechanisms of drugs of

abuse understanding of the molecular, physiological, and behavioral mechanisms involved in the disorder is necessary for the discovery and implementation of more effective treatments.

The mesolimbic dopamine system is the most well-studied and implicated circuit associated with the disorder. Naturally, this neurocircuit may have evolved as an information-processing center to direct behavior toward environmentally important stimuli predicting the presence of vital resources, for example, food and water. Synaptic plasticity within these regions is implicated in associative learning of these stimuli to guide behavior necessary to receive these rewarding resources. Depending on the frequency and accuracy that a particular stimulus may predict a natural reward, goal-directed behavior toward this stimulus with the intention of obtaining the reward may become habitual. Thus, if an exogenous substance were to recruit this same neurocircuitry, this may elicit similar goal-directed behavior toward obtaining these compounds.

Structurally, drugs of abuse are highly varied and have many specific protein targets within the body (for a review of pharmacological mechanisms of drugs of abuse, see [1]). However, all pharmacological mechanisms of drugs of abuse cause excessive dopamine release originating from the ventral tegmental area within the nucleus accumbens (VTA, NAc; [2, 3]). Not only are these regions involved in this disorder, they also appear to be crucial mediators of appropriate goal-directed behavior toward natural rewards. Dopaminergic projections from VTA neurons are important in regulating motivation to perform integral, evolutionarily conserved behaviors such as feeding and reproduction [4, 5]. Drug-elicited synaptic plasticity also occurs within this region, possibly through similar mechanisms as natural rewards. Mirroring a classical symptom of addiction, the synaptic alterations induced by drugs of abuse inhibit the ability of other non-drug-related experiences to elicit synaptic plasticity [6, 7]. As such, it has been hypothesized that drugs of abuse cause a heightened form of plasticity-dependent associative memory leading to habit formation and addiction-like behaviors [8].

Although drug use is required for the development of addiction, it is most certainly not sufficient to cause this disorder. For example, around 176.6 million Americans from the age of 12 and up drink alcohol but only 17 million are classified as having an alcohol-use disorder (SAMSHA, 2013). Drugs are metabolized and eventually cleared from the body, thus, the drug's pharmacological effect is not sufficient. In addition, SUDs are classically characterized by chronic relapse after periods without symptoms [9]. This may occur many years after a patient's last reported use of a drug, suggesting that some stable functional alteration has occurred within the brain. Repeated drug exposure is required for an accumulation of molecular events that alter plasticity within specific regions affecting the functioning of the entire circuit. These synaptic alterations are persistent and similar to the chronic relapse state of patients with SUDs, suggesting that reversing these synaptic alterations may prevent relapse [9, 10]. Additionally, they appear to be protein-synthesis-dependent forms of plasticity [11–13]. Thus, the molecular mechanisms regulating gene expression ending with the translation into functional protein may play a role in the etiology of this disorder and thus may stem from persistent modifications in region-specific synaptic plasticity mediated by drug-induced alterations in addiction-related gene (ARG) expression.

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Regulation of these molecules can occur at many different steps. The DNA in the genome is organized into small compact three-dimensional units assembled by histones into nucleosomes, which form the structure of chromatin. As such, basal transcription is necessarily stagnant in the absence of the regulation of gene accessibility. Modifications to the accessibility of genes, by regulation of these structures, are termed epigenetic regulation and have also been found to be an integral component in the development of addiction. Given that the epigenetic control of drug addiction has been elegantly reviewed in previous work [14–17], this chapter focuses on other aspects of gene expression control starting at the level of transcription.

2. Transcriptional regulation of addiction-related genes

Transcriptional regulation occurs through transcription factors, which are proteins that respond to intracellular changes leading to association with specific elements in target genes. Since the promoter region where the transcription factor binds to is outside of the coding region of that gene, these sequences are also termed cis-regulatory elements.

2.1. The Fos family transcription factors are differentially altered by drugs of abuse and contribute to addiction-related plasticity and behavior

Although altered transcription of various genes had been suggested by earlier work [18], it was not until the discovery that morphine caused increased striatal expression of a transcription factor, c-Fos, that it was shown that transcription factors may regulate this drug-induced gene expression [19]. Although first found to be regulated by acute morphine treatment, it was found that other drugs of abuse cause specific, dopamine-dependent, alterations in the expression of this transcription factor within addiction-related regions [20–22]. Important for the study of relapse, it was found that c-Fos was upregulated in mesolimbic structures following withdrawal, suggesting that it may play a role in the intense drug craving present in this disorder [23]. c-Fos is part of the Fos family of transcription factors, including FosB and ΔFosB, which all heterodimerize with Jun to form the AP-1 transcription factor complex [24]. This complex then associates its specific cyclic AMP response element (CRE), the AP-1 binding site, leading to increased transcription of genes downstream of these sequences.

Fos genes are considered immediate early genes (IEGs), or factors that are basally expressed at low levels but elevated rapidly by specific stimuli (first reviewed in the context of neuronal cells [25]). Since it was upregulated by other plasticity and memory-inducing events, it was hypothesized that c-Fos, and possibly other IEGs, may alter gene expression involved in memory formation [26]. As expected, the upregulation of c-Fos, FosB, ΔFosB, and Jun leads to increased AP-1-mediated transcription within addiction-related regions such as the NAc rapidly after acute drug administration [27]. Due to its regional specificity, it was hypothesized that alterations in these genes may provide a mechanism for reorganization of functional interactions between these brain regions in addiction [28]. Although c-Fos is rapidly upregulated and returns to basal levels quickly, AP-1 binding continues in the absence of elevated c-Fos mRNA or protein expression suggesting that other Fos proteins may replace

c-Fos and accumulate during chronic use of drugs. This may provide a molecular trace of chronic drug use in the absence of drug itself. This tolerance to initial c-Fos upregulation appears to be drug agnostic, as acute alcohol exposure blocked the previously observed acute cocaine upregulation of c-Fos, also suggesting that this molecular trace persists for the use of all different drugs [29].

To more specifically test the role of specific transcription factors in addiction, transgenic mice with specific mutations were engineered. The first experiment to utilize this approach used a transgenic mouse with a mutant *fosB* gene that prevented the production of ΔFosB. It is important to consider that this mutant *fosB* gene was not targeted to any specific cell type or even to the brain, but throughout the body. These mutant mice showed attenuated chronic induction of AP-1-binding activity, suggesting that the previously observed AP-1 binding without c-Fos upregulation was probably due to ΔFosB [30]. Additionally, this study was the first to link transcriptional regulation with altered addiction-like behavior. These researchers used a model of drug-seeking behavior termed conditioned place preference (CPP), where animals are trained to associate one environment with an experimenter-administered drug and a separate environment with saline [31]. Over time, animals will seek out the drug-paired cues associated with the environment where they received the drug. These fosB-mutant mice showed increased CPP compared to wild-type controls, suggesting that normal ΔFosB AP-1 binding might be involved in a compensatory or adaptive response to drugs. Fos family members have also been found to be upregulated after exposure to drug-paired cues in the absence of the drug itself, suggesting that this CPP effect may be due to the interaction between drug and cues soliciting the availability of the drug, an importance facet in addiction research [32].

Although certain molecular factors may cause increased addiction-like behavior or plasticity within one set of cells, it may cause an opposite effect on these measures in another. Cellular specificity is an important point that has been discussed in neuroscience for some time. In an experiment complimentary to this performed by Schroeder and colleagues, researchers developed an inducible system to specifically overexpress ΔFosB within D1 neurons in the striatum [33]. Neurons within the striatum are primarily GABAergic medium-spiny neurons that mostly express D1 or D2 dopamine receptors. Since D1 receptors are G_s GPCRs, they activate the neuron leading to increased GABA release, while D2 receptors are G_i and are inhibited by dopamine binding. Since drugs of abuse cause hyperdopaminergic conditions within the striatum, both D1 and D2 containing neurons play important but dissociable roles in the development of addiction. Targeted ΔFosB overexpression in D1 neurons showed a similar effect on increased CPP behavior at low doses (5 and 15 mg/kg), but normal CPP behavior at higher doses (20 mg/kg). This suggests that cocaine-induced ΔFosB expression within these cells is necessary and sufficient to promote addiction-like behaviors. Furthermore, GABAergic inhibition from these cells may play a role in CPP behavior. Finally, this is physiologically relevant, as drugs of abuse and to a lesser extent natural rewards cause upregulation of ΔFosB in this specific neuronal subtype [28, 34]. In a similar experiment, nonspecific deletion of ΔFosB throughout the body caused the same behavioral alteration, increased CPP behavior to lower doses of cocaine [30]. Although this finding may seem contradictory, when taken together with previous data, this points to the existence of other regions or possibly neuronal subtypes that act in opposition to D1 neurons. Following up on this, overexpression of ΔFosB within D2

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expressing neurons in the striatum produced no effects, illustrating the cellular specificity of these drug-induced alterations [35]. Thus, ΔFosB within these regions or cells may not play a role, or possibly inhibit, the plasticity required for the development of these behaviors.

Another behavioral model frequently used to study addiction is self-administration of drugs [36]. In this model, an intravenous catheter will infuse cocaine into the animal once it has completed a specific behavioral response, usually pressing an active lever in opposition to an inactive lever that produces no effect. This can be used to study motivation to consume drugs, as the requirement for lever pressing can be made harder by increasing the number of presses required to receive an infusion of drug. Animals with a similar inducible ΔFosB genotype as used by Kelz and colleagues showed increased motivation to self-administer cocaine [37]. This was also the first experiment to show that this alteration specifically affected motivation toward drugs and not naturally rewards such as a food pellet.

Transcription factors elicit changes in the expression of genes; thus this work suggests that there must be some downstream targets of Fos proteins that are mediating these effects on addiction-related behavior. Kelz and colleagues first described a downstream target that may alter plasticity involved in these behavioral alterations [33]. Striatal neurons are normally quiescent, even with dopamine input, and thus require glutamate which is an important neurotransmitter in addiction-like behaviors to alter their firing (reviewed in [38]). Kelz and colleagues found that ΔFosB overexpression caused an increase in a specific AMPAR subunit, GluR2 which could lead to altered plasticity [39]. Additionally, they could recapitulate their effects on behavior by viral-mediated overexpression of this subunit in the striatum. Overall, many ΔFosB targets are genes that appear to be previously linked to addiction-like behaviors such as CDK5 and NFkB.

2.2. CREB, a transcription factor well established in learning and memory associated plasticity, plays a role in addiction

Drugs of abuse can cause acute regulation of molecular-signaling cascades that can modify transcription factor activity. For example, many drugs of abuse can cause acute upregulation of the second messenger cAMP within many addiction-associated brain regions [40–46]. cAMP response element-binding protein (CREB) is phosphorylated in response to cAMP upregulation by a kinase sensitive to cAMP, protein kinase A (PKA; [47, 48]), calcium-calmodulin dependent kinases (CaMK) and other kinases [49]. The role of CREB in other forms of plasticity-associated memory has been well elucidated [48]. Once phosphorylated, CREB can enter the nucleus and bind to its response element, the cyclic AMP response element (CRE). CREB was first implicated in drug-induced alterations in response to acute and chronic morphine treatment within the locus coeruleus, another brain region associated with addiction [50]. Later, it was found that chronic, but not acute, morphine caused a decrease in CREB within the NAc [51]. Cocaine self-administration was found to be sensitive to PKA inhibition, an upstream regulator of CREB, by increasing lever pressing [52]. Following this experiment, it was later found that NAc overexpression of CREB caused a decrease in cocaine-CPP behavior [41]. Conversely, overexpression of a mutant CREB containing a single-point mutation, alanine for serine at residue 133, that prevents its phosphorylation and blocks its ability to

regulate transcription acting as a dominant negative form of CREB, caused an increase in cocaine-CPP behavior. Further correlating the role of this transcription factor in the association of drug cues, researchers found that re-exposure to the original drug-paired environment in CPP without drug caused increased phosphorylation of CREB [53]. Highlighting the differences of behavioral tasks, it was found that NAc overexpression of CREB caused an increase in self-administration behavior [54]. This gene has also been studied in human patients. Researchers found that opioid-dependent patients were more likely to have a polymorphism in a protein that associates with CREB, CREB-binding protein, within a region associated with its activation by phosphorylation [55]. Altogether, it appears that CREB expression is involved in many aspects of addiction-related behavior.

CREB is a nuclear transcription factor that binds to CRE upstream of target genes. CREB regulation has been found to cause upregulation of ARG mRNA such as *c-fos*, *Fosb*, brain-derived neurotropic factor (*BDNF)*, and *TrkB* (e.g., in methamphetamine self-administration [56]). BDNF and its receptor TrkB have a very long history in the study of addiction-related behaviors as well as general plasticity occurring within the brain [57]. Further implicating CREB as a regulator of plasticity, it has been found to be involved in late-phase forms of long-term potentiation (LTP [58]). As mentioned before, NAc neurons are normally quiescent and require glutamate activation with or without dopamine stimulation to fire. CREB has been associated with the regulation of this feature of NAc neuronal membrane excitability [59]. It was found that increased CREB activity leads to enhanced NMDAR-mediated currents, an important receptor for causing action potentials as well as for learning and memory. This regulation increases NAc neuronal-firing probability through enhancement of the membrane excitability. This may partially explain the effect of NAc CREB on behaviors such as self-administration. Thus, CREB regulates the expression of many genes associated with plasticity and addiction-related behaviors.

CREB and ΔFosB are very well-documented addiction-related transcription factors but, undoubtedly, there are many more transcriptional factors that alter addiction-related plasticity and ultimately behavior. Myocyte-enhancing factor 2 (MEF2) was found to be involved in cocaine-induced structural plasticity [60]. Interestingly, it was necessary and sufficient to increase the number of dendritic spines. Structural plasticity or the alteration of the physical synaptic shape has been associated with electrophysiological measurements of plasticity [61–63] specifically in addiction [63]. Additionally, it was found that MEF2 regulates a wide network of plasticity-associated genes opening up further exploration into its role in addiction-related plasticity and behavior [64]. Overall, transcriptional regulation of ARG expression can lead to modifications in drug-evoked synaptic plasticity and behavior [65, 66].

3. Posttranscriptional regulation of plasticity and addiction-related transcripts can promote addiction-like behaviors

Posttranscriptional regulation occurs after transcription until the mRNA is translated into a functional protein. Posttranscriptional regulation takes many forms such as mRNA processing, splicing, editing, stability, and translation. mRNA stability and translation have been

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the most well-characterized posttranscriptional mechanism in plasticity, especially in addiction. Additionally, it appears that mRNA stability may be especially important in the brain, as nearly 20% of brain-expressed genes have been predicted to be controlled through this mechanism [67].

3.1. miRNAs destabilize specific mRNAs which could lead to diminished expression of genes involved in addiction

Stability can be influenced by direct binding of factors to discrete recognition sites. One group of factors involved in this type of mRNA stability are small noncoding RNAs, termed microRNAs (miRNAs). miRNAs are ~20–22 oligonucleotide molecules that are encoded within the genome and make up nearly 2–3% of transcribed genes but are not translated into protein. miRNAs target specific mRNAs through binding of complementary sequences within the miRNA, termed seed regions, to the 3′ untranslated region (UTR) of the mRNA. Association of miRNAs with the 5′UTR of mRNA has also been discovered [68] leading to different cellular effects, but most studies within the brain have focused on the 3′UTR. Accordingly, the rest of this section focuses on this mechanism.

Although the miRNA may associate directly with the mRNA target, the aftereffects of this binding are mediated through a large, supporting protein complex, the RNA-induced-silencing complex or RISC. Through associating with the RISC, an miRNA can target specific mRNAs for degradation or translational repression [69]. This complex contains a multitude of auxiliary proteins, with the most important being Argonaute (Ago; [70]). Ago is the component most directly involved in regulating the mRNA. There are many Ago isoforms, but generally they are separated into those containing nuclease "slicer" activity and those without. Thus, Ago is important for the well-characterized miRNA-induced destruction of mRNA.

Although one miRNA has one specific seed region to bind to mRNAs, mRNAs may have numerous sites complementary for multiple miRNAs. This suggests that a single miRNA targets many mRNAs, affecting a myriad of cellular processes and pathways. This is reminiscent of transcriptional regulation, as one transcription factor may regulate a specific sequence that is upstream of various types of genes. This opens the possibility for an miRNA that may regulate a network of plasticity-associated genes. For example, miR-9-3p was found to diminish *Dmd* and *Sap97* mRNA [71]. These genes are negatively associated with LTP expression, thus miRNA-induced silencing of these mRNAs would reverse this effect. A hippocampal LTP-dependent behavior, the Morris water maze, was also found to be regulated by the expression of this miRNA.

Similar to a group of plasticity- and addiction-associated transcription factors, miRNA expression patterns appear to be similar to IEGs in their temporal- and activity-dependent regulation [72–74]. As demonstrated before, many of these IEGs play integral roles in general plasticity and addiction-related plasticity. Similar to IEGs, miRNAs have been associated with neural development, synaptic plasticity, and even behavior [73–79].

The role of miRNA-induced posttranscriptional regulation in addiction was first studied in the regulation of the large-conductance-calcium-and-voltage-activated potassium channel (BK). This channel is integral to plasticity by affecting excitability, firing, and transmitter release

from neurons [80]. It is also one of the many protein targets of alcohol within the brain, for the most part potentiating its conductance [81]. This channel has been well studied in its role in tolerance to alcohol in the striatum, requiring larger amounts to exert similar effects [82]. This seems to be mediated by decreased BK channel expression in the membrane. A single gene can produce multiple mRNAs with the same coding region but with different 3'UTRs through the inclusion or exclusion of different exons [83]. Research has shown that the alpha subunit of this BK channel is alternatively spliced both in the coding region and in the 3' UTR in response to neuronal activity [82, 84]. These researchers also found that alcohol caused a decrease in one specific BK mRNA that has an miR-9-binding site in its 3' UTR. Given that this isoform of the BK channel mRNA is the most abundant in the striatum and miR-9 expression is increased by alcohol exposure, alcohol tolerance seems to be mediated at least in part by this miRNA [82]. As mentioned before, miRNAs target many mRNAs that contain a complementary sequence in the 3'UTR. Thus, these authors also proposed that miR-9 targets many other mRNAs such as the beta subunit of the GABA receptor, GABRB2, and the D2 receptor. Overall, this suggests that alcohol-mediated upregulation of miR-9 leads to the development of an alcohol-specific regulation of mRNAs associated with plasticity and addiction.

When animals are given extended access to drugs of abuse in a self-administration model, they undergo a specific behavioral response termed escalation of drug use. Uncontrollable use of large amount of drugs is an important facet in the human condition. With this, researchers sought out an miRNA that may be increased by this behavior and found that miR-212, an activity-dependent miRNA regulated by CREB, was upregulated in the dorsal striatum of these animals after extended access [85]. One of the targets of miR-212 is Sprout-related, EVH1 domain containing 1 (SPRED1), a corepressor of serine-threonine protein kinase Raf1, which increases the activity of adenylate cyclase by promoting its phosphorylation. Thus, upregulation of miR-212 during escalated drug use diminishes SPRED1 levels, potentiating cAMP production and CREB activity leading to increased miR-212 expression. When miR-212 was overexpressed within the dorsal striatum, rats in extended access showed decreased levels of cocaine infusions. Oppositely, blocking of miR-212 by a locked nucleic acid (LNA) caused an increase in cocaine infusions. Thus, extended access to cocaine may recruit miR-212 leading to a positive feedback loop that effectively diminishes stereotypical escalation of drug intake. Overall, this suggests miR-212 acts on a pathway involving CREB to enhance its signaling, possibly in a compensatory, protective manner.

3.2. RNA-binding proteins bind to mRNAs and can bidirectionally regulate addiction-associated mRNA translation into protein

RNA-binding proteins (RBPs) are another group of regulators of mRNA stability and translation. Some RBPs recognize discrete sequences in the 3'UTR, such as the AU-rich instability conferring elements (AREs [86]). As with miRNAs, there is potential for a single RBP to affect multiple downstream processes leading to miRNAs and RBPs to be termed "master switches" of gene regulation [87, 88]. This is especially important in the brain, as around 15–20% of brain-specific transcripts contain AREs suggesting these genes are regulated by this type of posttranscriptional regulation [67]. Fragile x-mental retardation protein (FMRP)

is an RBP that regulates the translation of nearly 850 brain mRNAs, many associated with synaptic function [89]. One of its regulatory targets are the group I metabotropic glutamate receptors mGluR1 and mGluR5 [90–92]. These receptors have been associated with cocaine-evoked behaviors [93, 94]. Thus, Smith and colleagues tested the role of FMRP in addiction-related behaviors [95]. They found that *Fmr1* KO mice were deficient in cocaine locomotor sensitization and conditioned place preference. The effect on conditioned place preference was reversed by genetic reduction in mGluR5, suggesting that FMRPs effect on drug-evoked behaviors was due to mGluR5 activity. Finally, they found that FMRP caused a reduction in cocaine-induced structural plasticity suggesting that these behavioral deficits may be caused by this aberrant plasticity.

Although FMRP is the only RBP specifically studied in addiction-like behaviors, many more have been associated with these behaviors [96]. One such family of RBPs is the Hu, or embryonic lethal abnormal vision-like (ELAV-L) proteins. Hu proteins are brain and neuronal specific and are homologous to the *Drosophila* protein ELAV protein [97, 98]. HuD expression and function is activity dependent, suggesting it may regulate IEGs and other activity-dependent genes associated with plasticity [99–101]. In confirmation of this idea, our laboratory has shown that HuD is critical for stabilizing U-rich containing mRNAs during neuronal development and synaptic plasticity [101]; work from our laboratory reviewed in [102, 103]. HuD is a critical regulator of multiple plasticity-associated genes, thus suggesting that it may be involved in addiction-related altered gene expression, plasticity, and ultimately behavior. Overall, post-transcriptional regulation may emerge as an important player tying drug-evoked molecular alterations with behavior.

3.3. mRNA editing can alter the sequence or expression of an addiction-related mRNA leading to alterations in addiction-related plasticity and behavior

mRNA editing is another posttranscriptional regulatory mechanism. The most common mechanism for RNA editing is through covalent modifications of a specific nucleotide, without the alteration of the original DNA-encoded gene. This would generate multiple alternative forms of a protein which may be important in different cellular contexts.

The most common mRNA modification leading to editing is the removal of an amino group and its replacement with an oxygen, termed deamination. This occurs on the N6 position of adenosine nucleotides, converting this nucleotide into an inosine. This position directly contributes to conventional Watson-Crick base pairing, thus allowing inosine to pair with cytosine similar to guanosine. Translationally, this leads to the original adenosine to be read as a guanine, effectively causing an A→G site-directed mutagenesis. This modification is catalyzed by adenosine deaminase that acts on RNA (ADAR) enzymes [104–108].

Specific mRNA editing in a neurophysiological context was first described in the GluRA2 subunit of AMPAR [109]. As mentioned before, editing of mRNA is a rapid mechanism to generate multiple alternative forms of a protein depending on environmental circumstances. These receptors are integral to excitatory synaptic signaling, especially in plasticity. Thus, AMPAR editing generates channels that are impermeable to calcium and displays

faster recovery rates from desensitization. In terms of drug-induced plasticity, a recent study demonstrated that GluA2 editing by ADAR2 in the NAc of rats regulates cocaine seeking [110]. These researchers studied reinstatement, a specific stage of drug self-administration [36]. Animals first need to learn the required instrumental behavior to receive a reward in self-administration. When the animal reaches an experimenter-determined criterion, then the animal is said to have "acquired" self-administration behavior. If the animal is then presented with the same context and levers, but rewards are withdrawn, the animal will eventually override the previously learned reward-driven behavior. Eventually, the animal will no longer perform the task required for the reward, which is termed extinction. Finally, when an animal is exposed to cues associated with the reward or the reward itself, the animal will reinstate its behavior to receive the reward. Reinstatement is thought to be analogous to relapse in human-addiction patients. In this study, they found that abstinence from cocaine was associated with a decrease in NAc-edited calcium-impermeable AMPAR as well as ADAR2. Next, Schmidt and colleagues overexpressed ADAR2 within the NAc. They found that this diminished cocaine-primed reinstatement of self-administration behavior, suggesting that ADAR2 within the NAc is important for the regulation of relapse-like behavior. Overall, there are many avenues for mRNA editing in drug-induced plasticity and addiction-like behaviors [111].

Another posttranscriptional mRNA modification is the covalent modification of adenosine to N6-methyladenosine (m^6A). This modification is carried out by a methyltransferase complex, containing WTAP, METTL14, and KIAA1429. Hence, this complex is usually thought of as the "writers" of m^6A modifications. In opposition to the activity of this complex, enzymes have been discovered that promote the demethylation of mRNA, or the "erasers" of these modifications. These modifications have been studied for many years as a stable, unalterable modification. However, with the discovery of m^6A demethylases this shifted opinion to suggest that this modification is dynamic and thus could be regulated by physiological conditions (reviewed in [112]). For example, it was reported that regulation of m^6A was important to the normal functioning of the circadian rhythm in mammals [113]. Thus, m^6A is physiologically relevant in behavior.

The first m^6A demethylase to be discovered was the fat mass and obesity-associated protein (FTO). As the name suggests, it was identified as the strongest genetic variation to predispose patients to obesity [114–117]. At the opening of this chapter, evidence was presented to show that addiction-related neurocircuitry originally evolved to elicit goal-directed behavior toward food, suggesting this gene may also be involved in other forms of goal-directed behavior. The first study to link these findings was performed in alcoholic patients, finding that the genotype associated with obesity (rs9939609) was inversely correlated with general alcohol consumption, measures of alcohol dependence, as well as cigarette use [118].

Later work found that this gene is expressed in dopaminergic neurons within the midbrain and is increased by acute cocaine administration (20 mg/kg [119]). Cocaine, and to a lesser extent amphetamines, inhibits the dopamine transporter (DAT), leading to increased synaptic dopamine. This in turn leads to hyperactivation of dopamine receptors on both sides of the synapse. The presynaptic terminal contains D2 and D3 receptors, which are inhibitory GPCRs. Thus, the presynaptic dopaminergic neuron will show increased suppression of firing in response to cocaine. In the next set of experiments, these researchers found that Fto-deficient

dopaminergic neurons showed diminished cocaine-induced suppression of firing rate, suggesting that signaling through D2/D3 receptors is regulated by Fto. As expected, it was found that protein expression of these downstream targets (DRD3, GIRK2, and NMDAR1) was reduced by Fto deficiency. Functionally, Fto deficiency led to a reduction in GIRK currents, possibly detailing a mechanism for the diminished cocaine-induced suppression of firing rate in dopaminergic neurons. Finally, Fto-deficient mice showed attenuated acute cocaine-induced locomotor activity, suggesting that these genetic and electrophysiological measures translate into this behavioral modification.

4. Conclusion

As shown here, there are many avenues for regulation of ARGs at the transcriptional or the posttranscriptional level. These regulatory mechanisms all have been implicated in the development of this disorder and thus may be involved in the vulnerability of some individuals to substance-use disorders. Understanding the regulation of addiction-related genes and their impact on synaptic plasticity and behavior may inform new pharmacological treatments that reverse these aberrant drug-evoked forms of plasticity in favor of remission.

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