Long Noncoding RNAs in Substance Use Disorders

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Contents

Abstract Substance abuse (including illicit and prescription drugs) has become a significant public health and economic burden. Acute and chronic substance use often leads to a pathologic pattern of behaviors as well as physiologic manifestations, such as tolerance and withdrawal, collectively called substance use disorders (SUDs). Clinical and animal studies have demonstrated that SUDs are heritable in both humans and rodents. The exact molecular mechanism(s), however, is mostly unclear. Long noncoding RNAs (lncRNAs) have emerged as pivotal epigenetic regulators of gene expression in various human diseases, including SUDs. This chapter summarizes current findings and thoughts on the dysregulation as well as

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the role of lncRNAs in the context of the use of substances, such as morphine, cocaine, methamphetamine, alcohol, etc. The potential applications of lncRNAs in SUDs will also be discussed in this chapter.

Keywords Substance use disorders · Long noncoding RNAs · Opioids · Morphine · Fentanyl · Cocaine · Methamphetamine · Marijuana · Alcohol · Tobacco/nicotine

1 Introduction

Abused drugs are threatening human health, and many drugs can alter a person's thinking and judgment, leading to health risks including addiction, drugged driving, and infectious disease. The use of substance(s) causes significant clinical and functional impairments which is a medical condition called substance use disorder (SUD), also known as drug use disorder or substance dependence (Goplerud et al. 2017). In terms of information released from the National Institute on Drug Abuse, the commonly abused drugs include alcohol, ayahuasca, central nervous system depressants, cocaine, heroin, inhalants, ketamine, marijuana (cannabis), methamphetamine, prescription stimulants, prescription opioids, psilocybin, Rohypnol® (flunitrazepam), *Salvia*, steroids (anabolic), synthetic cannabinoids, synthetic cathinones ("bath salts"), and tobacco. Currently, SUDs are among the most common and costly health conditions affecting the population around the world, and rates of substance use disorders vary by nation and by substance, but the overall prevalence is high. On a global level, men and younger individuals are affected at a much higher rate than women and older adults, respectively (Kuerbis et al. 2014; Morisano et al. 2014). Strikingly, drug overdose is one of the leading causes of death of young people in the United States. According to the National Center for Health Statistics at the Centers for Disease Control and Prevention, national deaths from drug overdose have increased significantly from 16,849 in 1999 to over 70,237 in 2017.

The symptoms of SUDs include, but not limited to, behavioral changes, physical changes, and social changes characterized by a series of mental, physical, and behavioral signs and symptoms (Schulte and Hser 2014). SUDs impose an enormous medical, financial, and emotional burden on society in the form of overdose and health complications, family disintegration, loss of employment, and crime. The National Institute on Drug Abuse (NIDA) estimates that the total cost of drug abuse in the United States exceeds $600 billion annually. Additionally, a sharp increase in the abuse of prescription drugs and drug abuse by teenagers has also been observed. These data suggest the urgent need for research into the effects of drugs of abuse and the mechanisms of addiction, in the expectation of uncovering novel targets for treating and preventing SUDs.

Increasing evidence from clinical and animal studies has demonstrated that SUDs are heritable in both humans and rodents, which are a result of the interplay of

multiple genetic and environmental factors (Kendler et al. 2007; Mayfield et al. 2008; Wong and Schumann 2008; Zahr and Sullivan 2008; Agrawal et al. 2012; He and Wang 2012; Volkow and Muenke 2012; Verhulst et al. 2015). Indeed, genetic factors have demonstrated a major role in a person's risk of developing SUD (Prom-Wormley et al. 2017; Demontis et al. 2019; Palmer et al. 2019). Although the genetic contribution to the risk for substance abuse is 40–60% (He and Wang 2012), the fact that chronic exposure of drugs induces structural and functional changes of the brain suggests that dysregulation of gene expression could contribute to the addictive phenotype (Robison and Nestler 2011). Currently, many SUD-associated genes have been identified and shown to be dysregulated in the context of substance abuse. The expression of SUD-associated genes is regulated at various levels, including the epigenetic, transcriptional, and posttranscriptional levels (Robison and Nestler 2011; Nestler 2014). The epigenetic regulation of addiction is mainly through three different mechanisms such as posttranslational modifications of histone proteins (such as acetylation, ubiquitination, SUMOylation, methylation, phosphorylation, and ADP-ribosylation) and DNA methylation (Robison and Nestler 2011; Nestler 2014). Interestingly, the transcriptional mechanism is classically through the actions of transcription factors controlling gene expression in addiction. The transcription factors, including DeltaFosB (Hiroi et al. 1997; Nestler 2008; Perrotti et al. 2008), CREB (Carlezon et al. 1998; Barrot et al. 2002; Pluzarev and Pandey 2004; Edwards et al. 2007), NF-κB (Sullivan et al. 2004; Russo et al. 2009), and MEF2 (Pulipparacharuvil et al. 2008), have been directly linked to addiction-related behaviors, neuronal excitability, drug tolerance, and dependence. Recently, emerging evidence suggests that noncoding RNAs, especially long noncoding RNAs (lncRNAs), function as additional regulatory machinery of the genome controlling both transcriptional and posttranscriptional events in progression of SUDs.

2 Long Noncoding RNAs

It is well known that DNA sequences in the human genome corresponding to protein-coding exons and untranslated regions all together comprise only 1.5–2% (Alexander et al. 2010). Increasing evidence suggests that the non-protein-coding portion of the genome is not junk but has functional importance. With the development of advanced deep sequencing and other analysis technologies, the detection of ncRNAs has facilitated the in-depth research of different classes of ncRNAs. In terms of their length, localization, and function, these ncRNAs are divided into two groups: small ncRNAs (sncRNAs), such as microRNAs which have demonstrated predominating roles in different biological processes of higher eukaryotes, and numerous classes of long ncRNAs which have been broadly categorized as long intergenic ncRNAs, long intronic ncRNAs, telemetric ncRNAs transcribed from subtelomeric promoters, pseudogene transcripts, circular RNAs, enhancer RNAs, and transcribed ultraconserved regions (Kumarswamy and Thum 2013; Kung et al. 2013). lncRNAs are generally greater than 200 nucleotides in length, and numerous

studies have revealed a huge number of long noncoding RNAs (lncRNAs) coded by the genome (Quinn and Chang 2016; Chang et al. 2017), which have been recently discovered to mediate diverse biological processes such as in the central nervous system (CNS) during normal development and under various pathological conditions (DiStefano 2018; Cao et al. 2019a; Fernandes et al. 2019).

The biogenesis of lncRNAs shares similar features with that of mRNA, such as transcribed by RNA polymerase II, processed by RNA splicing, and polyadenylated (Brannan et al. 1990). Differently, the lncRNAs can be transcribed with or without polyadenylation, and alternative cleavage, polyadenylation, and splicing also lead to different isoforms from the same locus (Fernandes et al. 2019). In addition, similar to the regulation of coding genes, some of lncRNAs, such as large intervening noncoding RNAs (lincRNAs), can also be transcriptionally regulated by key transcription factors, such as p53, NF-κB, Sox2, Oct4, and Nanog, and these lncRNAs are functional, highly conserved, and implicated in diverse biological processes (Guttman et al. 2009). The first described and identified mammalian lncRNA was H19 which was found in 1990 during liver development and shares the common features with mRNAs. Up to now, bioinformatic studies have revealed that tens of thousands of lncRNAs do not code for proteins and can also be mapped to the genome (Rinn and Chang 2012; Engreitz et al. 2016; Lee et al. 2016; Quinn and Chang 2016; Ransohoff et al. 2018). Although lncRNAs have emerged as regulators of diverse biological processes, the functional relevance of most lncRNAs remains unknown. Currently, lncRNAs have been found to involve in diverse biological processes, including X-chromosome inactivation, such as Xist and Tsix (Brown et al. 1991; Lee et al. 1999); pluripotency and reprogramming (Guttman et al. 2011; Yan et al. 2017); maintenance of genomic stability, such as LINC00657 (NORAD) and ionizing radiation-inducible lncRNA (lnc-RI) (Arainga et al. 2016; Agrahari et al. 2019); imprinting, such as H19 and air (Sleutels et al. 2002); lineage commitment and apoptosis, such as HoxA-AS3 and lncRNA MEG3 (maternally expressed gene 3) (Zhu et al. 2016; Li et al. 2019b); mammalian cell differentiation, such as LncRNA HOTAIRM1 and LncKdm2b (Fu et al. 2019; Li et al. 2019a); and adult neurogenesis, such as RMST and Sox2OT (Ng et al. 2012; Tosetti et al. 2017). A recent breakthrough in identifying the roles of lncRNAs during the development of SUDs underscores the importance of lncRNAs in SUDs.

3 LncRNAs in SUDs

SUDs are a typical behavioral condition resulted from structural and functional alterations in various brain regions of drug abusers (Robinson and Kolb 2004; Zhu et al. 2012). Drugs involved in SUDs include alcohol, opioids, methamphetamine, cocaine, tobacco/nicotine, etc. Genome-wide computational analyses have revealed that lncRNA genes from the human genome are one of the most abundant classes of ncRNAs (Jia et al. 2010) and are involved in diverse biological processes as described above. Additionally, the analyses using a transcriptomic atlas of mouse

neocortical layers and in situ hybridization data from the Allen Brain Atlas have revealed that lncRNAs are highly abundant in the brain (Mercer et al. 2008; Belgard et al. 2011). Although the roles of lncRNAs, in addition, remain unclear, increasing evidence has suggested that lncRNAs play important roles in the development of SUDs. We here summarize the regulatory mechanisms of lncRNAs in SUDs.

3.1 LncRNAs in Alcohol Use Disorders

Alcohol addiction has become the second most impactful psychiatric disorder, which is characterized as compulsive alcohol seeking and taking despite adverse consequences (Hyman and Malenka 2001; Koob and Le Moal 2008; Collins et al. 2011). In addition, alcohol addiction can also cause various somatic diseases and is responsible for a mortality rate of about 6% worldwide (Friedmann 2013). Using human and animal models, the widespread alterations in brain gene expression have been observed during chronic alcohol exposure, and epigenetic regulations including histone methylation, histone acetylation, and ncRNA expression have been found to be involved in the expression of multiple genes in various types of brain cells contributing to the pathogenesis of brain related with alcohol abuse and dependence (Ponomarev 2013). Increasing evidence has suggested that lncRNAs play important roles in the synaptic plasticity alterations during drug abuse and dependence. Thus, the role of lncRNAs in the regulation of disease progression of alcohol use disorder (AUD) is gaining attention (Table 1). Although more than 130 differentially expressed lincRNAs have been observed with significant alterations in the postmortem alcoholic brain tissue across different brain regions (Mayfield 2017), the precise role and mechanism of these lincRNAs in alcohol abuse and dependence remain unclear. However, several lncRNAs have been identified with the dysregulation during chronic alcohol exposure. For example, nuclear-enriched abundant transcript 2 (NEAT2), also known as MALAT1, was significantly increased in specific regions including the cerebellum, hippocampus, and brain stem of the human alcoholic brain rather than in other regions, such as frontal or motor cortices. Differently, there was no significant increase of NEAT2 in cerebellum and cortex of alcohol-treated rats; however, NEAT2 was significantly upregulated in rat cortex following alcohol withdrawal (Kryger et al. 2012), suggesting that the dysregulation of lncRNAs induced by chronic alcohol exposure contributes to alcohol actions in the CNS. In addition, H19 as the first identified lncRNA is located at specific loci with normal hypermethylation and contributes to cell proliferation and imprinting. Increased demethylation in the offspring after prenatal exposure to alcohol has been demonstrated (Ouko et al. 2009; Stouder et al. 2011; Liang et al. 2014), suggesting that chronic alcohol use regulates some epigenetic modifications of genomic regions that are critical for embryonic development. Genome-wide association studies of alcohol dependence also revealed that another large antisense-overlapping lncRNA, called LOC100507053, was found to be located within an alcohol dehydrogenase (ADH) cluster and cover multiple loci for ADH genes and form a risk-genomic region for

Table 1 lncRNAs in alcohol use disorders (AUDs)

SUD	LncRNA	Research model	Regulation	Functions	Mechanism of action	Target	References
Alcohol	MALAT1 (NEAT2)	Human subjects	Upregulation	Epigenetic regulation; pro-angiogenesis	Alternative splicing; gene expression	VEGFR2, etc.	Mayfield (2017), Kryger et al. (2012), Lamichhane et al. (2017), Zhang et al. (2018) and Patel et al. (2019)
Alcohol	H19	Mice	Hypomethylation	Cell proliferation and imprinting	Interaction with the methyl-CpG-binding domain protein 1 MBD1	IGF2	Stouder et al. (2011), Liang et al. (2014) and Monnier et al. (2013)
Alcohol	MEG3	Mice	Upregulation	miRNA sponge contributing to EtOH-induced hepatic steatosis and apoptosis	A sponge for miR-let-7c-5p	NLRC5	Wang et al. (2018b)
Alcohol	HOTAIR	Endothelial cells	Upregulation	Pro-angiogenesis	Alternative splicing; gene expression	VEGFA and Ang2	Lamichhane et al. (2017)
Alcohol	BDNF-AS	Human subjects	Upregulation	Epigenetic regulator in the amygdala in early-onset AUD	Methylations at regulatory regions of BDNF	BDNF	Bohnsack et al. (2019) and Patel et al. (2019)
Alcohol	PSD4-1 and NETO-1	Human subjects	Upregulation	Alcohol-associated cancers	Epigenetic regulations	Unknown	Yu et al. (2016)

NLRC5 nucleotide-binding domain and leucine-rich repeat-containing receptor 5, *MEG3* maternally expressed gene 3, *MALAT1* metastasis-associated lung adenocarcinoma transcript 1, *NEAT2* nuclear-enriched abundant transcript 2, *HOTAIR* HOX transcript antisense RNA

alcohol dependence and has a significant impact on cellular responses to alcohol (Zuo et al. 2014; Xu et al. 2015).

The liver is the principal organ for the metabolism of alcohol. Alcohol-induced hepatic steatosis and apoptosis play a primary role in direct alcohol-related morbidity. Using a mouse model of chronic plus single binge ethanol gavage to mimic the chronic alcohol exposure, one study has demonstrated that lncRNA MEG3 was significantly increased in either mouse with alcohol exposure or alcohol-treated in vitro hepatocytes, and further mechanistic studies revealed that lncRNA MEG3 serves as a sponge for let-7c-5p which in turn enhances the expression of NLRC5, a target of let-7c-5p, and ultimately induces hepatic steatosis and apoptosis (Wang et al. 2018b).

In addition to liver, alcohol consumption also contributes to many other diseases related to extrahepatic tissues. Recent evidence suggests that alcohol-induced upregulation of lncRNAs-HOTAIR and MALAT1 in endothelial extracellular vesicles (EVs) plays a significant role in mediating pro-angiogenic effects of these vesicles (Lamichhane et al. 2017; Patel et al. 2019). In these studies, the authors demonstrated that ethanol conditioning upregulates the vascularization bioactivity of endothelial cell-derived EVs. Interestingly, both HOTAIR and MALAT1 were found to be significantly upregulated in EVs isolated from ethanol-exposed HUVECs (human umbilical vein endothelial cells) compared with control HUVECs (Lamichhane et al. 2017). To determine the specific roles of these lncRNAs, the authors transfected HUVECs with siRNAs targeting HOTAIR and MALAT1, or both HOTAIR and MALAT1, and then assessed the vascularization bioactivity of the EVs isolated from the transfected HUVECs using endothelial gap closure assays. The findings from this study demonstrated that downregulation of MALAT1 alone and MALAT1 and HOTAIR together significantly abrogated the ethanol-induced vascularization bioactivity in HUVEC EVs (Lamichhane et al. 2017), indicating that lncRNAs in endothelial EVs may contribute to the pathogenesis of remote organs during the chronic alcohol exposure.

Chronic alcohol exposure or alcohol abuse also contributed to the pathogenesis of cancers. Recent RNA-seq analysis of clinical data has identified another two alcohol-associated lncRNAs – lnc-PSD4-1 and lnc-NETO-1 (Yu et al. 2016). The dysregulation of these two lncRNAs has been implicated in the pathogenesis of head and neck squamous cell carcinoma. Specifically, the authors demonstrated that low expression of lnc-PSD4-1:14, an isoform of lnc-PSD4-1, showed a strong correlation with high survival rates in a Cox proportional hazards regression model (Yu et al. 2016). Increasing evidence has suggested that lncRNAs play critical roles in brain development and synaptic plasticity (Wu et al. 2013; Karpova et al. 2017; Wang et al. 2017). It was well known that neurotrophic factors (NTFs) play important roles not only in the neuronal survival of the peripheral nervous system but also in the synaptic plasticity of the brain. Brain-derived neurotrophic factor (BDNF), one of the most studied NTFs, is a central neurotrophin involved in many neuronal processes and has been linked to several psychiatric diseases as well as addictive disorders (Koskela et al. 2017). Increasing evidence from human subjects and experimental animal models suggested that the BDNF level is negatively

correlated with adverse phenotypes associated with harmful alcohol consumption. For example, the alcohol addiction or the mental illness and compulsive behavior resulting from alcohol dependency are associated with the low plasma levels of BDNF (Joe et al. 2007; Zanardini et al. 2011). Consistent with the clinical data, the low levels of BDNF in the prefrontal cortex of mice and in the nucleus of the stria terminalis and in the central extended and medial amygdale of rats also contribute to the development of alcohol dependence compared with animals without alcohol addiction (Prakash et al. 2008; Logrip et al. 2009).

Furthermore, the reduction of BDNF expression or inhibition of BDNF signaling pathway in mice will increase the consumption of alcohol (Hensler et al. 2003; Jeanblanc et al. 2006; Logrip et al. 2015), whereas the activation of BDNF signaling pathway will decrease the consumption of alcohol (Pandey et al. 2006; Jeanblanc et al. 2009, 2013; Warnault et al. 2016). These studies revealed that BDNF is a critical determinant of compulsive alcohol drinking. Interestingly, one lncRNA called BDNF-AS (BDNF antisense lncRNA) has recently been shown to inhibit BDNF expression via epigenetic modifications at regulatory regions in the BDNF gene in the early-onset alcohol use disorder (AUD) group rather than in late-onset AUD group. Further molecular mechanism studies revealed that alcohol drinking during adolescence increases the BDNF-AS expression in the amygdala of AUD group, which results in increased recruitment of EZH2 and subsequently the increase of repressive H3K27 trimethylation (H3K27me3) at regulatory regions in the BDNF gene contributing to a significant decrease in BDNF expression and signaling. On the other hand, adolescent alcohol drinking also decreases the expression of the activity-regulated cytoskeleton-associated protein (ARC) and signaling by increased EZH2 deposition of repressive H3K27me3 at the ARC synaptic activity response element. These BDNF-AS-mediated epigenetic mechanisms contribute to decreased synaptic plasticity, higher risk of developing alcohol use disorder in adulthood, and the increased comorbidity with other psychiatric disorders (Bohnsack et al. 2019).

3.2 LncRNAs in Opioid Use Disorders

Opioids are a class of drugs including illegal drug heroin, synthetic opioids such as fentanyl, and prescription pain relievers, such as oxycodone, hydrocodone, codeine, morphine, and many others. A computational and annotation pipeline has been developed to identify the alteration of lncRNA transcripts in the human nucleus accumbens (hNAcc) of heroin abusers (Michelhaugh et al. 2011). In this study, Michelhaugh et al. developed a computational and annotation pipeline to identify lncRNA transcripts represented on Affymetrix U133 arrays followed by assessing a previously published dataset derived from hNAcc of heroin abusers and controls. The authors demonstrated that the expression of five lncRNAs – MIAT, MEG3, NEAT1, NEAT2, and EMX2OS – was upregulated in heroin abusers compared to matched, drug-free controls (Table 2). Myocardial infarction-associated transcript (*MIAT*) is a lncRNA predominantly expressed in heart and fetal brain tissues.

Table 2 lncRNAs in opioid use disorders

SUD	LncRNA	Research model	Regulation	Functions	Mechanism of action	Target	References
Heroin	MIAT, MEG3, NEAT1, NEAT2	Human subjects	Upregulated in NAc of heroin abusers	Unknown	Unknown	Unknown	Michelhaugh et al. (2011)
Fentanyl	MIAT	Mice	Downregulation	Pro-apoptosis of cardiomyocytes	A miRNA sponge	miR-145	Zhang et al. (2016b) and Zhao et al. (2017)
Morphine	lncRNA-Cox2	Cell and mice	Upregulation	Microglial phagocytosis	Negative regulation of phagocytosis	Phagocytosis-related genes	Hu et al. (2018)
Opiate	BDNF-AS	Human subjects	Upregulation	Inhibition of BDNF expression	Epigenetic modifications at regulatory regions in the BDNF gene	BDNF	Palma-Alvarez et al. (2017)

MIAT myocardial infarction-associated transcript

Increasing evidence suggests that MIAT functions as a competing endogenous RNA (ceRNA) and also acts as a sponge for miRNAs in mediating microvascular dysfunction, diabetic cardiomyopathy, and advanced atherosclerosis (Yan et al. 2015; Zhou et al. 2017; Ye et al. 2019). Recently, MIAT has been found to play cardioprotective effects of fentanyl in myocardial ischemia-reperfusion injury by negatively regulating miRNA-145/Bnip3 pathway axis (Zhang et al. 2016b; Zhao et al. 2017). In addition, neuronal enriched lncRNA MEG3 is a maternally imprinted lncRNA and plays an essential role in GABA neuron neurogenesis. Studies have demonstrated that MEG3 regulates the formation of brain microvessels through controlling the expression of angiogenesis genes (McLaughlin et al. 2006; Gordon et al. 2010; Mercer et al. 2010), which in turn modulates the vulnerability to heroin addiction (Nielsen et al. 2008). Interestingly, Gao et al. demonstrated that MEG3 is upregulated in morphine-exposed mouse hippocampal neuronal HT22 cells compared with control cells (Gao et al. 2019). Furthermore, the authors demonstrated that knockdown of MEG3 reduced morphine-mediated upregulation of autophagy through inactivating ERK pathway in HT22 cells (Gao et al. 2019). Brain-enriched lncRNAs – NEAT1/2 and EMX2OS – play a pivotal role in controlling the expression of synaptic genes at transcriptional level as well as posttranslational level such as mRNA splicing, which subsequently regulates synaptic density (Hutchinson et al. 2007; Bond and Fox 2009; Bernard et al. 2010; Spigoni et al. 2010). Although these lncRNAs have been associated with heroin abusers, the mechanism of the action and targets in the brain remain, however, to be elucidated.

Opioids, such as morphine, are used extensively in the clinical setting for pain management owing to their beneficial effects. However, opioid use often leads to tolerance and dependence on the drug. Recently, two independent groups have identified differentially altered lncRNAs in the spinal cord using a rat morphine tolerance model. Shao et al. performed lncRNA microarray analysis and demonstrated that the expression of 136 lncRNAs was significantly altered in the spinal cord of morphine tolerance rats compared with saline controls (Shao et al. 2018). In another study, Qiu et al. demonstrated that the expression of five LncRNAs, XR_006440, XR_009493, AF196267, MRAK150340, and MRAK037188, was downregulated and the expression of five lncRNAs, MRAK046606, XR_005988, DQ266361, uc.167−, and uc.468+, was upregulated in the spinal cord of morphine tolerance rats compared with controls (Qiu et al. 2019). These results suggest that lncRNAs could play a pivotal role in the development of morphine tolerance, although the function and the underlying mechanisms of the lncRNAs remain largely unknown.

Opioid use also manifests deleterious side effects in the brain including, but not limited to, neuroinflammation. Recent studies suggest that the long intergenic noncoding RNA (lincRNA)-Cox2 (proximal to the Cox2 gene with no overlap) plays an important role in the pathogenesis of neuroinflammation-dependent diseases including auto-inflammatory and neurodegenerative diseases. Upon immune stimulation, lincRNA-Cox2 is upregulated via the NF-kB signaling pathway and is required for the transcription of inflammatory genes (Carpenter et al. 2013; Hu et al. 2016; Liao et al. 2019; Xue et al. 2019). In addition, microglial dysfunctions, such as

impaired phagocytosis and immune responses, also contribute to the pathogenesis of neurodegenerative diseases. Recently, lincRNA-Cox2 has been found to be involved in morphine-mediated neurodegeneration through regulating microglial phagocytosis activity (Agrahari et al. 2019). In response to morphine stimulation, astrocytes will release EVs that are taken up by microglial endosomes resulting in the upregulation of lincRNA-Cox2 in microglia by activating Toll-like receptor 7 (TLR7) and the impairment of microglial phagocytic activity, suggesting that lncRNA-Cox2 may indirectly contribute to the pathogenesis of SUDs.

As discussed above, BDNF is a critical determinant of compulsive alcohol drinking. Interestingly, clinical study also suggests that the decreased plasma level of BDNF is correlated with the increased risk of compulsive behavior and BDNF Val66Met polymorphism in heroin users which has been proved to contribute to the increased compulsive alcohol drinking in animals (Warnault et al. 2016; Rovis et al. 2018). Moreover, it has been reported that opiate-induced neurotoxicity in the CNS may be correlated with modifications in BDNF expression, and peripheral BDNF level may also be correlated with opiate use disorders in humans (Palma-Alvarez et al. 2017), suggesting that lncRNA BDNF-AS mediated the epigenetic regulation of BDNF that may also contribute to not only alcohol use disorder but also opiate addiction.

3.3 LncRNAs in Cocaine Use Disorders

Cocaine is a CNS stimulant that affects the brain by increasing the levels of dopamine, a brain chemical associated with pleasure and reward. Studies have demonstrated that cocaine negatively affects every part of the body along with many severe long-term effects. Cocaine use leads to alterations of gene expression in CNS cells, in addition to other permanent effects including talkativeness, excitement, alertness, anxiety, and overconfidence (Novikova et al. 2005; Repantis et al. 2010). Using cocaine-conditioned mice, a transcriptome analysis of lncRNAs of the nucleus accumbens (NAc) has been performed and revealed that cocaine administration results in genome-wide alterations of lncRNAs in the NAc, suggesting these RNA transcripts may play roles in cocaine-induced neural plasticity and addiction (Bu et al. 2012). Data analysis using Affymetrix arrays revealed that four brain-enriched lncRNAs – MIAT, MEG3, NEAT2, and EMX2OS – were significantly upregulated in the NAc of human cocaine abusers compared to matched drug-free control subjects (Sartor et al. 2012). Although upregulation of these lncRNAs has been observed in the NAc of human cocaine abusers, the potential targets and precise mechanisms remain unknown.

Increasing evidence suggests that these lncRNAs play important roles in the cardiovascular dysfunctions (Yan et al. 2015; Zhou et al. 2017; Ye et al. 2019), neurogenesis (McLaughlin et al. 2006), angiogenesis (Gordon et al. 2010), and synaptic density and gene transcription (Hutchinson et al. 2007; Bond and Fox 2009; Bernard et al. 2010; Spigoni et al. 2010); however, the mechanism of action

and targets in the brain of cocaine abusers remain largely unknown. Interestingly, similar aberrations in lncRNA expression in response to cocaine and heroin abuse have been observed in human abusers (Michelhaugh et al. 2011; Bannon et al. 2015). For example, Bannon et al. performed a custom lncRNA microarray analysis of postmortem human midbrain specimens from chronic cocaine abusers and control subjects (Bannon et al. 2015). This study demonstrated a group of lncRNAs dysregulated in chronic cocaine abusers. Importantly, using in situ hybridization histochemistry (ISHH), the researchers have demonstrated that the cocaine-associated lncRNAs exhibit dopamine cell-specific expression, different subcellular distributions, and covariance of expression with known cocaine-regulated protein-coding genes. Specifically, the expression of LINC00162 and TRAF3IP2-AS1 transcripts was visualized nearly exclusively in dopamine neurons. Furthermore, the results of qPCR and Pearson's correlation analysis suggest that TRAF3IP2-AS1 transcript abundance positively correlated with the levels of TRAF3IP2 protein-coding transcript, indicating a potential role of TRAF3IP2-AS1 in regulating the expression of its cognate protein-coding gene (Bannon et al. 2015). In addition to TRAF3IP2-AS1, the authors also demonstrated that the expression of 32 well-annotated lncRNAs was differentially expressed in the midbrains of human cocaine abusers, such as upregulated lncRNAs HOTAIRM1, RPPH1, and WDR11-AS1 as well as downregulated lncRNAs RNF219-AS1, PRKCQ-AS1, STX18-AS1, LINC00540, and LINC00403 (Bannon et al. 2015) (Table 3). These lncRNAs may mediate broader downstream changes in gene expression arising within the dopamine neurons of chronic cocaine abusers through epigenetic alterations of chromatin state at gene loci. For example, as discussed by Bannon et al. (2015), given that both TRAF3IP2 and PRKCQ proteins are master mediators in regulating the activity of the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), TRAF3IP2-AS1 and PRKCQ-AS1 lncRNAs could play a key role in NF-kB signaling in cocaine abuse.

BDNF is one of the neurotrophic factors and also plays a critical role in the growth, survival, and differentiation of developing neurons. It has been reported that cocaine exposure induced the synthesis and release of BDNF from NAc neurons that contributed to addictive phenotypes (Graham et al. 2007). Moreover, chronic cocaine use also induces upregulation of NAc TrkB, a high-affinity receptor of BDNF, which in turn leads to the transition to more addicted biological states (Graham et al. 2007, 2009). Both in vitro and in vivo studies have demonstrated that lncRNA BDNF-AS controls the expression of BDNF at both transcriptional and posttranscriptional levels (Modarresi et al. 2012), suggesting that lncRNA BDNF-AS could be a master regulator and controls drug-seeking behaviors in cocaine abusers.

Table 3 lncRNAs in cocaine use disorders

SUD	LncRNA	Research model	Regulation	Functions	Mechanism of action	Target	References
Cocaine	NEAT2, MIAT, MEG3, and EMX2OS	Human subjects	Upregulated in NAc of heroin abusers	Unknown	Unknown	Unknown	Michelhaugh et al. (2011)
Cocaine	BDNF-AS	Human subjects	Upregulation	Inhibition of BDNF expression	Epigenetic modifications at regulatory regions in the BDNF gene	BDNF	Palma-Alvarez et al. (2017)
Cocaine	TRAF3IP2-AS1	Human subjects	Upregulation	Inhibition of TRAF3IP2 expression	Epigenetic effects on gene expression through alterations of chromatic state	TRAF3IP2	Bannon et al. (2015)
Cocaine	PRKCQ-AS1	Human subjects	Downregulation	Inhibition of PRKCQ expression	Unknown	PRKCQ	Bannon et al. (2015)

MIAT myocardial infarction-associated transcript, *MEG3* maternally expressed 3, *NEAT2* nuclear paraspeckle assembly transcript 2, *EMX2OSE* MX2 opposite strand/antisense RNA, *PRKCQ-AS1* protein kinase C theta-antisense 1, *TRAF3IP2-AS1* tumor necrosis factor receptor-associated factor 3-interacting protein 2-antisense 1, *BDNF* brain-derived neurotrophic factor

3.4 LncRNAs in Other Drug Use Disorders

Repeated exposure to addictive drugs, including methamphetamine (METH), marijuana, or tobacco/nicotine, elicits long-lasting cellular and molecular changes. METH is a highly addictive psychostimulant (Sim et al. 2017). Zhu et al. have examined the lncRNA expression profile in the NAc of METH-sensitized mice using high-throughput strand-specific complementary RNA sequencing technology (ssRNA-seq) (Zhu et al. 2015), and demonstrated that the expression levels of 14,623 lncRNAs and 65 lncRNAs were significantly decreased and increased, respectively, in the NAc of METH-sensitized mice compared with saline controls. To further evaluate the potential functionality of these lncRNAs, the authors identified the cis- and trans-regulatory target genes of the lncRNAs followed by Gene Ontology (GO) and KEGG pathway enrichment analyses. The findings suggest that METH elicits global changes in lncRNA expression in the NAc of sensitized mice and the METH-induced alteration of the lncRNAs could play important roles in neuronal development, neuronal plasticity, learning and memory, and reward as well as addiction (Zhu et al. 2015). Indeed, five of METH-regulated lncRNAs, including Kcnq1ot1, Zfhx2as, Neat1, Neat2, and Miat, have been reported to interact with targeted loci in either *cis* or *trans* manner (Komine et al. 2006; Lewis et al. 2006; Hutchinson et al. 2007; Bernard et al. 2010) (Table 4). In addition, studies have also demonstrated that these lncRNAs modulate the LTP of hippocampus and behavioral abnormalities through various mechanisms, such as regulating the expressions of their sense partners (Komine et al. 2006; Lewis et al. 2006), function as cofactors for pre-mRNA splicing by interacting with the splicing factors (Hutchinson et al. 2007; Tollervey et al. 2011; Tsuiji et al. 2011), or regulate neuronal plasticity by modulating the expressions of multiple synaptic genes (Bernard et al. 2010). Although the precise regulatory mechanism remains largely unknown, these studies suggest that lncRNA-related nuclear modifications could play a role in METH addiction through rapid posttranscriptional changes of gene expression.

METH can also damage neurons in the brain. To understand the role of METH in the expression of lncRNAs in neurons, Xiong et al. performed microarray analysis in METH-exposed primary rat prefrontal cortical neurons (Xiong et al. 2017). This study revealed that 280 lncRNAs were upregulated, and 393 lncRNAs were downregulated in the METH-exposed neurons compared with control neurons. Results from the gene ontology (GO) and pathway analysis suggested that METH-mediated lncRNA alteration could play a role in ER stress and p53-mediated apoptosis in neurons. Furthermore, the upregulation of three lncRNAs, NR_110713, NR_027943, and growth arrest-specific transcript 5 (GAS5) in METH-stimulated neurons, was validated using qPCR analysis (Xiong et al. 2017). Moreover, GSA5 has been reported to regulate cell apoptosis through p53 signaling pathway by posttranscriptional regulation (Shi et al. 2015), which thus suggests a regulatory role of GAS5 on the p53 signaling pathway in METH-induced neurotoxicity.

Table 4 lncRNAs in other drug use disorders

SUD	LncRNA	Research model	Regulation	Functions	Mechanism of action	Target	References
METH	Kcnq1ot1, Zfhx2as, Neat1, Neat2, and Miat	Mice	Down (Neat1/2, Miat); up (Kcnq1ots and Zfhx2as)	Gene expression involved in the neuronal plasticity, learning, and memory	Interaction with targeted foci in cis or trans manner	Kcnq1ots and Zfhx2as partners; splicing factors; synaptic genes	Zhu et al. (2015)
METH	GAS5	Rat neurons	Upregulation	Neurotoxicity	Posttranscriptional regulation	P53 signaling pathway	Xiong et al. (2017)
METH	lncRNA NR_110713 and NR_027943	Rat neurons	Upregulation	Unknown	Unknown	Unknown	Xiong et al. (2017)
Nicotine	lncRNA H19	Human subjects and cells	Upregulation	Unknown	Unknown	Unknown	Kaplan et al. (2003)
Nicotine	LINC00599, LINC01362, LINC00824, LINC01624, RP11-563D10.1, RP11-98G13.1, AC004791.2	Human subjects	Six upregulation and one downregulation (underlined)	Unknown	Unknown	Unknown	Parker et al. (2017)

METH methamphetamine, Kcnq1ot1 potassium voltage-gated channel subfamily Q member 1 overlapping transcript 1, *Zfhx2as* zinc finger homeobox 2 antisense, *GAS5* growth arrest-specific 5

Nicotine dependence (ND) is a type of psychiatric disorder. In 2010, Silva et al. analyzed the transcription across the entire genome in normal human bronchial epithelial cells (NHBE) with exposure to the tobacco carcinogen NNK (nicotine-derived nitrosamine ketone), utilizing whole-genome tiling arrays (Silva et al. 2010). This study identified 12 lncRNAs that were upregulated in NNK-stimulated NHBE cells (Silva et al. 2010). Northern blot and qPCR analyses further demonstrated that these lncRNAs are upregulated in NNK-exposed NHBE as well as in a number of lung cancer cell lines and breast cancer cell lines (Silva et al. 2010). The roles of these lncRNAs in cellular stress and in cancer development, however, are still under investigation.

Kaplan et al. investigated the expression of the paternally imprinted gene, lncRNA H19, in the airway epithelium of individuals with a history of mild to moderate cigarette smokers, and demonstrated that lncRNA H19 was significantly upregulated in the airway epithelium compared with that of nonsmokers (Kaplan et al. 2003). The authors further demonstrated that the smoking-induced upregulation of H19 does not result from an alteration of the normal imprinting pattern (Kaplan et al. 2003). Previous studies have demonstrated that frequent loss of imprinting of H19 is associated with lung cancer (Kondo et al. 1995), indicating an important role of H19, and the assessment of its expression, and/or loss of imprinting could serve as early a biomarker in the progression of airway epithelium toward lung cancer (Kaplan et al. 2003).

Recently, Parker et al. performed whole-blood RNA sequencing in 229 current and 286 former smokers, and identified seven smoking-associated lncRNAs, LINC00599, LINC01362, LINC00824, LINC01624, RP11-563D10.1, RP11-98G13.1, AC004791.2, which were significantly altered (Parker et al. 2017). Among them, LINC01624 was downregulated, and the left lncRNAs were significantly upregulated in current smokers compared with former smokers (Table 4). Although the mechanism of action and targets of these lncRNAs remain to be further investigated, these findings imply a role for smoking-associated lncRNAs in nicotine-mediated pathological effects.

4 The Action Mechanisms of LncRNAs in Various SUDs

Despite noncoding molecules, lncRNAs are multifunctional. Increasing evidence has demonstrated numerous functions for lncRNAs in many cellular processes, including gene imprinting (Kanduri 2016), stress response (Valadkhan and Valencia-Hipolito 2016), differentiation and development (Fatica and Bozzoni 2014), speciation and species-specific development, and vernalization in plants (Heo and Sung 2011). The addictive phenotype involving in brain structure and function was attributed to the alterations of gene regulation caused by chronic exposure to drugs of abuse. lncRNAs may function by regulating gene expression through multidimensional mechanisms, including transcriptional and epigenetic mechanisms (Kanduri 2016; Cao et al. 2019b). Recently, lncRNAs have been

shown to play a crucial role in the regulation of alternative splicing in response to several stimuli or during disease (summarized in Romero-Barrios et al. 2018). Moreover, increasing evidence now indicates that chromatin-modifying complexes are directed to their sites of action by lncRNAs. Therefore, it is possible that lncRNAs play an important role in SUDs by regulating epigenetic processes. The epigenome consists of DNA methylation and histone modifications including acetylation, methylation, and phosphorylation. It has been reported that specific enzymes responsible for histone acetylation, methylation, and DNA methylation in reward-related brain areas are critically involved in cocaine addiction (LaPlant et al. 2010; Maze et al. 2010). For example, two lncRNAs – Air and Kcnq1ot1 antisense – have been found to play a role in histone methylation by interacting with histone methyltransferase G9a which is downregulated in the NAc following cocaine exposure and is important in cocaine-related behaviors (Nagano et al. 2008; Pandey et al. 2008; Maze et al. 2010). In addition, lncRNA-mediated regulation of histone acetylation, methylation, and DNA methylation, as well as other important cocaine-mediated modifications, has been reviewed (Maze and Nestler 2011). Collectively, lncRNAs exert their function at multidimensional levels in various SUDs.

5 The Potential Applications of LncRNAs in SUDs

Currently, lncRNAs have garnered attention as another species of regulatory RNA with key roles in development, epigenetics, regulation of transcription, and other essential biological processes. Aberrant expressions of lncRNAs play critical roles in the progression and development of various SUDs, some of which may be further evaluated as highly sensitive biomarkers as well as potential therapeutic targets. It has been reported that BDNF-AS lncRNA is associated with malignant status and shows the potential as a prognostic biomarker and therapeutic target for some cancers (Huang et al. 2018; Shang et al. 2018). Interestingly, BDNF-AS has also been found to be dysregulated in response to chronic cocaine, alcohol, and opiate addiction (Modarresi et al. 2012; Palma-Alvarez et al. 2017; Bohnsack et al. 2019). Moreover, BDNF-AS as a conserved noncoding antisense RNA transcript regulates the expression of BDNF at both transcriptional and posttranscriptional levels, which in turn is involved in many neuronal processes including the synaptic plasticity in the amygdala of AUD (Bohnsack et al. 2019), drug-seeking behaviors in chronic cocaine use (Graham et al. 2007), and neurotoxicity in the CNS during opiate abuse (Angelucci et al. 2007), suggesting BDNF-AS has the potential as a therapeutic target of these SUDs.

Chronic exposure to drugs of abuse in vulnerable populations causes long-term behavioral abnormalities, which involve a complex interplay between gene expression and environmental factors (Walker and Nestler 2018). Increasing evidence suggests that the alterations of gene expression in the reward circuitry of the brain, particularly in the mesolimbic dopaminergic systems, contribute to the persistent behavioral abnormalities (Alcaro et al. 2007; Walker and Nestler 2018). It has been

reported that TRAF3IP2-AS1 lncRNA was upregulated, whereas PRKCQ-AS1 was downregulated in the midbrain of cocaine abusers (Table 3), which were involved in broader downstream gene alterations in dopamine neurons through epigenetic alterations of chromatin state at gene loci (Bannon et al. 2015). These studies suggest that lncRNAs are master regulators in SUDs and thus could be potential targets for therapy. Intriguingly, recent study has demonstrated that lincRNA-Cox2 contributes to morphine-mediated neurodegeneration through impairing microglial phagocytosis, and intranasal delivery of lincRNA-Cox2 small interfering RNA (siRNA) can restore microglial phagocytic activity in morphine-administered mice (Hu et al. 2018), suggesting that EV-loaded lincRNA-Cox2 siRNA can be used as therapeutic strategy for a multitude of neurodegenerative disorders associated with opiate abuse. Recently, the following study has been carried out to investigate the effects of EV-loaded lincRNA-Cox2 siRNA on the LPS-induced microglial proliferation which has been implicated in the pathogenesis of various neurodegenerative disorders, such as Alzheimer's disease (AD) (Spangenberg et al. 2016; Liao et al. 2019). The results demonstrated that intranasal delivery of EV-loaded lincRNA-Cox2 siRNA can efficiently pass through the blood-brain barrier (BBB) to target activated microglia in the brain where lincRNA-Cox2 siRNA significantly decreases the expression of lincRNA-Cox2 in the microglia contributing to the inhibition of LPS-induced microglial proliferation by controlling the expression of a set of cell cycle genes (Liao et al. 2019). These findings indicate that the EV-based delivery strategy targeting specific lncRNAs could be used to develop the therapeutics for the treatment of CNS disorders, such as SUDs.

Moreover, lncRNAs (or lncRNA fragments) can also be packaged into EVs and released into body fluids such as blood (Wang et al. 2018a; Kitagawa et al. 2019). These findings thus raise the possibility that abnormal levels of lncRNAs in EVs could serve as biomarkers for the prognosis of human diseases (Vausort et al. 2014; Zhang et al. 2016a, 2019; Dai et al. 2017; Yuan et al. 2017; Jiang et al. 2018). Recently, lncRNAs have also been found to be dysregulated and incorporated into EVs in the context of drug abuse, for example, alcohol-induced upregulation of lncRNAs HOTAIR and MALAT1 in endothelial EVs (Lamichhane et al. 2017), which may contribute to the transfer of pathophysiological phenotypes in the remote organs through the lncRNA-enriched circulating EVs. While more reliable EV lncRNAs for SUD biomarkers are to be determined, efforts aimed at deciphering the correlation between the expression levels of the EV lncRNAs and disease severity warrant investigation.

6 Conclusions and Perspectives

Although a growing number of lncRNAs have been identified in addiction-related neuroadaptations, their function and the underlying mechanism(s) in SUDs, however, remain to be investigated. Recently, many new methodologies and technologies have been proposed for the discovery and functional analysis of lncRNAs

(reviewed in Kashi et al. 2016). The development and application of new tools will enhance our understanding of the roles of lncRNAs in SUDs. Additionally, a novel method has recently been developed to identify potential lncRNA-disease associations by Integrating Diverse Heterogeneous Information sources with positive pointwise Mutual Information and Random Walk with restart algorithm (named IDHI-MIRW) (Fan et al. 2019), which will be very useful for studying the relationship between lncRNAs and drug addiction. Thus, the identification of lncRNA-SUD associations will also gain insights into SUD-related lncRNAs and benefit SUD diagnoses and treatment. Furthermore, given the fact that lncRNAs often serve as master regulators in various biological processes, they could be ideal therapeutic targets for preventing and treating SUDs. Moreover, many gender-associated lncRNAs have also been identified and could contribute to the gender differences in SUDs, which indicates that it could be crucial to develop lncRNA-based gender-specific therapeutic strategies.

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