



# MicroRNAs in Methamphetamine-Induced Neurotoxicity and Addiction

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Methamphetamine (METH) abuse remains a significant public health concern globally owing to its strong addictive properties. Prolonged abuse of the drug causes irreversible damage to the central nervous system. To date, no efficient pharmacological interventions are available, primarily due to the unclear mechanisms underlying METH action in the brain. Recently, microRNAs (miRNAs) have been identified to play critical roles in various cellular processes. The expression levels of some miRNAs are altered after METH administration, which may influence the transcription of target genes to regulate METH toxicity or addiction. This review summarizes the miRNAs in the context of METH use, discussing their role in the reward effect and neurotoxic sequelae. Better understanding of the molecular mechanisms involved in METH would be helpful for the development of new therapeutic strategies in reducing the harm of the drug.

**Keywords:** microRNAs, methamphetamine, neurotoxicity, addiction, treatment

## 1 INTRODUCTION

Methamphetamine (METH), also known as “ice,” is an amphetamine-type central nervous system (CNS) stimulant and a highly addictive psychostimulant (Monica et al., 2017). Given its easy synthesis and multiple ingestion pathways, METH is widely abused globally (Shaerzadeh et al., 2018). However, long-term use of METH inevitably causes damage to the CNS, resulting in psychosis, cognitive impairment, and neurodegenerative disease, which carries a severe global public health burden. Mounting evidence has been provided regarding METH action inside the body (Moratalla et al., 2017; Sambo et al., 2018; Chen et al., 2021a; Zhang et al., 2021). However, the cellular and molecular bases in response to the substance remain largely elusive. MicroRNAs (miRNAs) are eukaryotic non-coding RNA molecules about 19–25 nucleotides long (Lu and Rothenberg, 2018). They are believed to play a vital role in the morphology, neuronal development, and neuronal plasticity of the brain (Cao et al., 2016; Marangon et al., 2019). Many studies have found the function of miRNAs in regulating degenerative neural diseases, depression, schizophrenia, and drug addiction (Cao et al., 2016; Gu et al., 2020; Ma et al., 2020; Gowen et al., 2021). METH can induce the change of miRNA expression levels in several brain subregions, and some miRNAs have been shown to function in METH-related brain effects (Chavoshi et al., 2020; Sandau et al., 2020; Yang et al., 2020). In this review, we discuss the role of miRNA in METH-induced neurotoxicity and addiction, hoping to shed new light on the clinical application regarding its adverse consequences.

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## 2 MIRNAS IN THE NEUROTOXICITY OF METH

Neurotoxicity is defined as physical damage to the neurons. In a broader sense, it refers to the permanent or reversible adverse effects of substances on the structure and function of neurons, which results in the destruction of neuronal components and the anomaly of histological signs or behaviors (Moszczynska and Callan, 2017). METH is a highly neurotoxic substance and causes dopamine (DA) neuron damage through neuroinflammation (Dang et al., 2021), oxidative stress (McDonnell-Dowling and Kelly, 2017), hyperthermia (Matsumoto et al., 2014; Liao et al., 2021), and mitochondrial dysfunction (Shin et al., 2018). Despite the fact that important advances have been made in recent decades, the mechanism underlying the neurobiology of METH-induced neurotoxicity is not fully elucidated. The findings achieved so far have not led to the development of effective pharmacological treatments (Yang et al., 2018). In spite of the paucity of literature regarding miRNAs in METH-induced neurotoxicity, several studies have found that miRNAs participate in METH-related neuroinflammation (Bai et al., 2016; Yu et al., 2019). MiRNAs may also play a role in METH-induced oxidative stress and neuronal apoptosis (Du et al., 2016). Herein, we discuss the involvement of miRNAs in these processes. Although evidences that support a role for miRNAs in neurotoxicity are weak as compared with those in addiction, these early findings open a window for uncovering METH-induced toxic effects within the brain.

### 2.1 MiRNAs in Neuroinflammation

Reactive glial cell proliferation is considered a typical response to CNS damage and a sensitive marker of neuronal injury (Ares-Santos et al., 2013). The neuroinflammation, such as activation of microglia and release of proinflammatory molecules, has been extensively reported in METH-elicited neurotoxicity. METH-induced neuroinflammation mainly occur in dopaminergic related areas, including the striatum, substantia nigra pars compacta, etc. (Granado et al., 2011; Ares-Santos et al., 2012; Ares-Santos et al., 2013). The molecular mechanisms underlying the inflammatory processes mainly include activation of glial fibrillary acidic protein (GFAP), Nod-like Receptor Protein 3 (NLRP3), Toll-like receptors 4 (TLR4), and tumor necrosis factor (TNF) receptors, as well as release of interleukins (IL-1, IL-6) and TNF- $\alpha$  (Fernandes et al., 2016; Frank et al., 2016; Park et al., 2017).

Recently, in a neurotoxic mouse model, METH down-regulated the expression of miR-155-5p, which can bind to the 3'-UTR of Pellion1 (Peli1). Decrease of miR-155-5p facilitated the upregulation of Peli1 level and promoted the production and secretion of inflammatory factors (Yu et al., 2019). The evidence of miR-155-5p in modulating brain inflammation can also be found in chronic neuroinflammation studies, of which the level of miR-155-5p was positively correlated with the cytokines interferon (IFN)- $\gamma$ , TNF- $\alpha$ , IL-1, and IL-6 (Cardoso et al., 2012; Butovsky et al., 2015; Al-Ghezi et al., 2019).

MiR-143 can regulate NLRP3 by targeting the p53-up-regulated modulator of apoptosis (PUMA) to affect microglia

activation in METH exposure. The expression of miR-143 was down-regulated in BV2 cells after METH administration, which attenuated the inhibitory effect of miR-143 on PUMA expression, thereby activating NLRP3 inflammasomes and microglia (Zhang et al., 2016b; Du et al., 2019). In comparison, up-regulation of miR-143 was found in isolated human brain microvessels and several brain regions, such as the cortex, striatum, and midbrain. Increased miR-143 inhibited the expression of PUMA resulting in increased endothelial permeability and blood-brain barrier (BBB) damage after METH treatment (Bai et al., 2016). The inconsistent change trend of miR-143 may be due to the distinct models employed between studies. Therefore, we should consider the different responses of various cell types when studying the miRNAs in METH. Overall, these results offer novel evidence of miRNAs regarding METH-induced neuroinflammation. The strategy of pharmacotherapy based on the miR-143/PUMA axis may have translational potential.

### 2.2 MiRNAs in Oxidative Stress

Oxidative stress refers to the imbalance of reactive oxygen species (ROS) and endogenous antioxidants. Low concentrations of ROS are required in cell homeostasis, while excess ROS results in DNA damage, lipid peroxidation, and eventually cell death (van der Pol et al., 2019; Li et al., 2021a; Li et al., 2021b). METH leads to the oxidation of DA and produces a large number of ROS and lipid peroxides in the mitochondria, such as hydroxyl (OH), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), and superoxide ions (O<sup>2-</sup>), resulting in mitochondrial dysfunction and irreversible cell damage (Yang et al., 2018; Kim et al., 2020). In fact, there is an interaction between miRNA and oxidative stress such that miRNA regulates oxidative stress, and oxidative stress contributes to the alteration of miRNA expression level (Engedal et al., 2018).

Nuclear factor erythroid 2-related factor-2 (Nrf2) is an endogenous antioxidant protein that maintains the balance of oxidation reactions (Kurinna and Werner, 2015), which has a substantial protective effect on METH-induced neurotoxicity (Ramkissoon and Wells, 2015; Meng et al., 2020). The lack of Nrf2 results in severe consequences *via* promoting oxidative stress and inflammation (Granado et al., 2011). There is no direct evidence that a specific miRNA regulates METH neurotoxicity through Nrf2. However, miR-181 and miR-495, which showed an up-regulation trend after METH administration, have been correlated with Nrf2 in other models (Sim et al., 2017). For example, miR-181 promoted chlorpyrifos-induced oxidative stress through Nrf2 and led to the occurrence and progress of Parkinson's disease (Zhao et al., 2019). In the model of epileptic brain injury, upregulation of miR-495 negatively regulated Nrf2 to aggravate oxidative stress and neuronal apoptosis (Geng et al., 2018). Given the possible interaction between miRNA and Nrf2, miR-181, and miR-495 may regulate oxidative stress through Nrf2-related pathways in METH-induced brain insults (Kurinna and Werner, 2015; Ashrafzadeh et al., 2020). Further study was needed to clarify the role of these miRNAs in oxidative modulation.

## 2.3 MiRNAs in Neuronal Apoptosis

Specifically, METH triggers excessive DA release from synaptic terminals and affects the expression of multiple genes, which is of considerable significance in toxicity and relapse (Eskandarian Boroujeni et al., 2020; Fan et al., 2021). Excessive ROS generated from DA oxidation inhibits complexes I, II, III, and IV of the electron transport chain (ETC), resulting in mitochondrial dysfunction. Inhibition of ETC components enhances  $O_2^-$  production due to electron leakage, which leads to disturbance of mitochondrial energy metabolism (Yang et al., 2018). Mitochondrial damage can thus result in a decrease in the expression of anti-apoptotic proteins B-cell lymphoma-2 (Bcl-2) and Bcl-xL, and an increase in pro-apoptotic proteins Bcl2-associated X protein (Bax) and p53 protein, which triggers the cell death cascade (Jayanthi et al., 2001; Yu et al., 2015). It is worth mentioning as well that METH not only kills DA terminals but neurons in the PFC and substantia nigra pars compacta (Ares-Santos et al., 2014; Tehrani et al., 2019). Studies have found that altered levels of miR-222, miR-24, and miR-195 are related to the p53 and mitogen-activated protein kinase (MAPK) signaling pathway in METH treatment. It is speculated that these miRNAs may regulate METH-dependent neuronal apoptosis (Du et al., 2016). MiR-222 and miR-24, which are upregulated after METH exposure, may directly bind to Bcl2 to inhibit its expression and promote neuronal apoptosis, and down-regulated miR-195 after METH administration may relieve the suppression of miR-195 to Bcl2, thereby attenuating neuronal apoptosis (Srivastava et al., 2011; Puerta-Gil et al., 2012; Singh and Saini, 2012; Du et al., 2016).

## 3 MIRNAS IN METH ADDICTION

METH is known to transiently facilitate DA-mediated neurotransmission in specific brain circuits, notably the reward pathways. The canonical reward pathways extend from the ventral tegmental area (VTA) to the nucleus accumbens (Nac), dorsal striatum, hippocampus, and prefrontal cortex (PFC) through dopaminergic projections (Godino et al., 2015). Drug consumption in the addicted person is usually associated with an attenuated DA increase in these reward regions (Volkow et al., 2019; Chen et al., 2021a), which may be accompanied by a vicious circle of binge, sensitization, abstinence, and relapse (Volkow and Morales, 2015; Mizoguchi and Yamada, 2019). The essence of METH dependence and relapse is pathologically based on drug-induced gene expression and synaptic plasticity changes (Li et al., 2018; Chen et al., 2021b). In recent investigations, the expression level of miRNAs was associated with molecular events at the transcriptional and post-transcriptional levels in METH addiction.

### 3.1 METH-Induced miRNAs Changes in Brain Sub-Regions

#### 3.1.1 Nac

The Nac is one of the primary areas involved in regulating reward pathways. In a METH conditioned place preference (CPP) model,

the levels of some miRNAs were highly changed, such as miR-124, miR-134, miR-496-3p, miR-194-5p, miR-200b-3p, miR-181a-5p, and miR-9. Because these miRNAs are mainly located in the synapto-dendritic compartment of synaptic plasticity and neuronal function, their expression changes may be closely related to METH addiction phenotypes (Sim et al., 2017).

The regulatory role of miR-124 has been reported in the study of cocaine. Chandrasekar et al. found down-regulated expression of miR-124 in the Nac after cocaine administration. The targets of miR-124 are comprised of brain-derived neurotrophic factor (BDNF), integrin  $\beta$ 1, nucleus accumbens-associated protein 1 (NAC1), and axon-guidance molecules like semaphorin 6A (SEMA6A). These molecules were demonstrated conducive to the development of drug reward and addiction. Alteration of miR-124 level resulted in the change of BDNF expression to regulate the size of the spine, which was critical in cocaine-induced plastic reward and memory (Chandrasekar and Dreyer, 2009). Moreover, behavioral studies have demonstrated that overexpression of miR-124 in the Nac reduced cocaine-induced CPP, which can be reversed by down-regulated miR-124 after cocaine administration (Chandrasekar and Dreyer, 2011).

MiR-124 was also involved in argonaute2 (Ago2)-miRNAs-Dicer1 net, which may negatively influence METH addiction. Ago2 regulated miR-124 biogenesis through RNA-induced silencing complex (RISC) formation. When treated by METH, Ago2 was inhibited, resulting in the low expression of miR-124. Then the level of Dicer1 in the Nac was upregulated as the target of miR-124, which may be significant as the expression of Dicer1 in several brain regions is related to the response to abused drugs (Mulligan et al., 2013; Liu et al., 2019). Although the expression of miR-124 in Nac shares a similar descending trend between METH and cocaine, the underlying mechanisms may be distinct as the target genes vary between the investigations. More studies focusing on miR-124 would be of significance due to its activity across drug modalities. However, findings must be interpreted with caution because these studies did not determine miRNAs in the Nac core or shell. This is of critical importance because the functions between the two areas differ.

Repeated exposure to METH changes the cell morphology and synaptic function, which exhibits hyperresponsiveness to METH, termed psychomotor sensitization. In the METH sensitization model, some researchers have demonstrated that several miRNAs are significantly altered in Nac (Ni et al., 2019; Su et al., 2019; Li et al., 2021c; Liu et al., 2021). For example, decrease of miR-29c resulted in inhibition of DNA methyltransferase 3 (Dnmt3)a and Dnmt3b, which contributed to attenuation of METH-induced locomotor sensitization (Su et al., 2019). Besides, knockdown of miR-3068-5p, an Ago2-dependent miRNA, resulted in increased locomotor activity in mice, indicating a functional role of Ago2/miR-3068-5p cascade during the development of METH sensitization (Liu et al., 2021). In line with this finding, Liu et al. proposed that the downregulation of miRNAs in locomotor sensitization was likely owing to a reduction in Ago2-mediated splicing. Considering the essential role of Ago2 in miRNA biogenesis, we should realize that Ago2 may be an

**TABLE 1** | MiRNAs in METH-induced neurotoxicity.

MicroRNAs	Drugs	Species	METH dosing regimen	MicroRNA alteration	Downstream molecules	References
miR-143	METH	C57BL/6N mice	escalated doses of 1.5, 4.5, 7.5, 10 mg/kg i.p. for 8 days	Up	PUMA	Bai et al. (2016)
miR-143	METH	C57BL/6J mice	30 mg/kg i.p. $\times 4$ , at 2 h intervals	Down	PUMA, NLRP3	Du et al. (2019)
miR-155-5p	METH	C57BL/6J mice	10 mg/kg i.p. twice daily for 7 days	Down	Pel1	Yu et al. (2019)
miR-181	METH	Wistar rats	escalated doses of 0.25, 0.5, 1, 2, 3, 4, 5 mg/kg i.p. for 15 days	Up	Nrf2?	Sim et al. (2017), Zhao et al. (2019)
miR-495	METH	Wistar rats	escalated doses of 0.25, 0.5, 1, 2, 3, 4, 5 mg/kg i.p. for 15 days	Up	Nrf2?	Sim et al. (2017), Geng et al. (2018)
miR-124	cocaine	BV-2 cells, rPMs	10 $\mu$ M for 6, 12, 24 h	Down	MyD 88, IRAK 1, TRAF 6, KLF 4, TLR 4	Periyasamy et al. (2018)
miR-138	morphine	C57BL/6N mice	10 mg/kg, i.p. three times daily, with an increment of 5 mg/kg for 6 days	Up	TLR 7	Liao et al. (2020)

upstream regulator in METH sensitization, which needs further evidence to identify.

### 3.1.2 Dorsolateral Striatum

The dorsolateral striatum plays an essential role in the transition from controlled or recreational drug use to addiction despite largely unknown mechanisms (Giuliano et al., 2019; Lipton et al., 2019). It reported that the expression of miR-134 in the dorsolateral striatum was upregulated after excessive or uncontrolled intake of METH (Shi et al., 2019). MiR-134 was a brain-specific miRNA regulating memory formation and synaptic plasticity (Gao et al., 2010). In a self-administration (SA) model, miR-134 inhibited the expression and activity of LIM kinase 1 (LIMK1) to increase METH intake. Decrease of miR-134 in the dorsolateral striatum reduced excessive drug intake and addictive behavior, confirming a role of miR-134 contributing to uncontrolled METH consumption (Shi et al., 2019). It is worth noting that the expression level of miR-134 in Nac is also upregulated. We know that initial or limited exposure to substances like METH, cocaine, and alcohol, will cause changes in the function of the Nac before spreading to the back area (Shi et al., 2019). Thus, miR-134 may play a role in the Nac and dorsolateral striatum. However, LIMK1 does not show any changes in Nac, implying that miR-134 may participate in METH action by other targets instead of LIMK1.

Other studies in this area have focused on miR-181a, a miRNA with decreased level in METH-induced CPP rats. MiR-181a has been shown to directly regulate the expression of  $\gamma$ -aminobutyric acid receptor subunit alpha 1 (GABAA $\alpha$ 1) (Sengupta et al., 2013; Wang et al., 2021). However, in METH-addicted rats, both miR-181a and GABAA $\alpha$ 1 are concurrently downregulated in the dorsal striatum. The authors claimed that endoplasmic reticulum-associated protein degradation (ERAD) mediated ubiquitin protein degradation of GABAA $\alpha$ 1 (Jiao et al., 2017), and 36 target genes of miR-181a were cooperatively involved in endoplasmic reticulum-associated GABAA $\alpha$ 1 protein degradation. So they suggested that miR-181a induced the

ubiquitination of GABAA $\alpha$ 1 by ERAD rather than directly participating in METH addiction (Wang et al., 2021).

### 3.1.3 Hippocampus

The hippocampus remains a crucial site supporting learning and memory (Preston and Eichenbaum, 2013; Castilla-Ortega et al., 2016). It plays a vital role in regulating motor activity, exercise capacity, and the spatial memory of METH addiction (Yan et al., 2019). Changes to miRNAs in the hippocampus were revealed in METH-induced addiction phenotypes. For example, the expression of miR-31-3p was upregulated after METH administration. MiR-31-3p inhibited the expression of Ras Homolog Family Member A (RhoA), a small GTPase, to regulate neuronal morphology and synaptic plasticity, enhancing METH-induced CPP in mice (Qian et al., 2021). To our knowledge, miR-31-3p was mainly identified as a biomarker or regulator in tumor research (Hawryluck and Brindley, 2018; Oshima et al., 2021), whereas rarely reported in neurological disorders. Moreover, in a CPP model, miR-183-5p was significantly upregulated in the hippocampus. The expression level of neuregulin-1 (NRG1) was downregulated as a target of miR-183-5p, which is an indicator of METH dependence (Itzhak et al., 2015; Zhou et al., 2021). These results provide initial evidence that miR-31-3p and miR-183-5p may exert their function in the hippocampus to develop METH addiction. However, CPP is an experimental and controlled animal model; hence, verifying the results by using the self-administration (SA) model would be of great significance as it can better mimic METH ingestion in abusers.

### 3.1.4 The VTA and PFC

VTA is the primary source of DA to the Nac and hippocampus (Hyman et al., 2006; Volkow et al., 2019). Microarray analysis of miRNAs in the VTA region after METH administration showed that the expression of 78 miRNAs was altered, and only seven miRNAs showed up-regulation. In this study, miR-30b-5p was significantly downregulated (Bosch et al., 2015). Although it is not sure whether miR-30b-5p participates in METH addiction, it has the most connection with target genes

**TABLE 2** | MiRNAs in METH addiction.

Brain sub-regions	MicroRNAs	Drugs	Species	METH dosing regimen	MicroRNA alteration	Downstream molecules	References	
Nac	miR-124	METH	C57BL/6 mice	2 mg/kg i.p. for 7 days, abstinence 2 days	Down	Dicer1	Liu et al. (2019)	
		Cocaine	Wistar rats	15 mg/kg i.p. for 15 days	Down	BDNF, integrin $\beta$ 1, NAC1, SEMA6A	Chandrasekar and Dreyer (2009)	
	miR-128	METH	C57BL/6 J mice	2 mg/kg i.p. for 5 days, injection-free for 2 days, 2 mg/kg i.p. on 8th day	Up	Arf6, Cpeb3, Nlgn1	Li et al. (2021c)	
	miR-29c	METH	C57BL/6 mice	0.9% saline 10 ml/kg ip. for 2 days, 2 mg/kg i.p. for 5 days, injection-free for 2 days, 2 mg/kg i.p. on 10th day	Down	Dnmt3a, Dnmt3b	Su et al. (2019)	
	miR-204-3p	METH	C57BL/6 mice	0.9% saline 10 ml/kg i.p. for 2 days, 2 mg/kg i.p. for 5 days, injection-free for 2 days, 2 mg/kg i.p. on 10th day	Up	Sema3A, Plxna4	Ni et al. (2019)	
	miR-3068-5p	METH	C57BL/6 J mice	0.9% saline ip. for 2 days, 2 mg/kg i.p. for 5 days, injection-free for 2 days, 2 mg/kg i.p. on 10th day	Down	Grin1	(Liu et al., 2021)	
VTA	miR-30b	METH nicotine and/or alcohol	SD rats	continuous alternated doses of 0.25, 0.5, 1, 2, 3, 4, 5 mg/kg i.p. for 15 days	Up	BDNF	Sim et al. (2017)	
			SD rats	0.1 mg/kg infusion in SA	Down	? unknown	Bosch et al. (2015)	
	miR-145 miR-129 miR-29	METH	SD rats	SD rats	6 mg/kg nicotine, blood alcohol concentrations between 80 and 180 mg/dl, for 4 w	Down	GNAI2, COTL1	Kazemi et al. (2020)
				SD rats	0.1 mg/kg infusion in SA	Down	HDAC2	Bosch et al. (2015)
				SD rats	0.1 mg/kg infusion in SA	Down	HDAC2	Bosch et al. (2015)
				SD rats	0.1 mg/kg infusion in SA	Down	HDAC4	Bosch et al. (2015)
PFC	miR-195	METH	SD rats	0.05 mg/kg infusion in SA for 12–13 days, 1 h daily for 14 days	Down	BDNF	Du et al. (2016)	
			SD rats	0.05 mg/kg infusion in SA for 12–13 days, 6 h daily for 14 days	Up	LIMK2	Du et al. (2016)	
Dorsolateral striatum	miR-134 miR-181a	METH	SD rats	0.05 mg/kg infusion in SA for 12–13 days, 6 h daily for 14 days	Up	LIMK2	Du et al. (2016)	
			SD rats	0.05 mg/kg infusion in SA 2 h for 5 days, 6 h daily for 13–15 days	Up	LIMK1	Shi et al. (2019)	
Hippocampus	miR-31-3p miR-183-5p	METH	SD rats	1 mg/kg i.p. for 1 day $\times$ 4, 1 mg/kg saline for 1 day $\times$ 4 within 8 days	Down	GABAA $\alpha$ 1	Wang et al. (2021)	
			C57BL/6J mice Kunming mice	1 mg/kg i.p. $\times$ 4 within 8 days 2 mg/kg s.c., 0.9% physiological saline, 10 ml/kg, s.c. for 6 days	Up	RhoA NRG1	Qian et al. (2021) Zhou et al. (2021)	

METH, methamphetamine; i.p., intraperitoneal injections; i.v., intravenous; s.c., subcutaneous injection; SA, self-administration; SD, sprague-dawley; Nac, nucleus accumbens; VTA, ventral tegmental area; PFC, prefrontal cortex; rPMs, rat primary microglial cells.

following alcohol and nicotine-alcohol exposure (Kazemi et al., 2020). In a study of the genetic changes of nicotine in the VTA, miR-30b-5p had a significant probability of participating in DAergic synaptic pathways, and the enrichment of this pathway supported the hypothesis that the mesocorticolimbic DA pathway was involved in the reinforcing effects of nicotine abuse (Keller et al., 2018). Given that METH shares a similar mechanism with nicotine regarding DA release, the role of miR-30b-5p in reinforcement and neuroplasticity of METH-abused models is worth exploring.

The microsequence analysis of miRNAs in response to METH was also studied in the PFC. The authors found 28 miRNAs differentially expressed dose-dependently in the SA model. After a low dose of METH administration, the expression of miR-195 was down-regulated, while the expression of miR-24 and miR-127 was upregulated with increased drug doses (Du et al., 2016). The functions of the three miRNAs are related to neurotrophic

signaling pathways and axon guidance. miR-195 is one of the post-transcriptional inhibitors of BDNF. In the low-dose group, down-regulated miR-195 increased BDNF protein expression to regulate synaptic plasticity and maintain METH intake (Mellios et al., 2008). In comparison, the up-regulation of miR-24 and miR-127 after high-dose METH exposure may reduce the LIMK2 activity, so as to change the morphology of dendritic spines and affect drug addiction (Meng et al., 2003; Zhou et al., 2014; Du et al., 2016). The differential expression of miRNAs under low- and high-dose of METH may indicate different regulatory mechanisms in PFC. Nonetheless, it should be borne in mind that diverse factors, such as different technological platforms of sequencing, distinct criteria for determining miRNA up- or down-regulation, region-dependent repositories in the brain, and different postmortem intervals of sample materials might all introduce bias into the data. All of these factors should be considered when evaluating the role of the candidate miRNAs proposed by informatics.

## 4 CONCLUSION AND PERSPECTIVES

MiRNAs have great potential to target genes and gene products currently unavailable for drugs (Nunomura and Perry, 2020). The small size of miRNA is convenient for synthesis and manipulation (Cao et al., 2016). Moreover, miRNAs are considered attractive therapeutic tools for the low toxicity of their endogenous expression (Braoudaki and Lambrou, 2015). Both miRNA-mimics and antagomirs are used to regulate intracellular miRNA (Leggio et al., 2017). These facilitate the application of miRNAs as a new therapeutic target and biomarker in many diseases (Leggio et al., 2017; Saliminejad et al., 2019). MiRNAs are widely enriched in the CNS to regulate the growth and development of neurons. They play a key role in the pathogenesis of neurodegeneration, including Alzheimer's disease, Parkinson's disease, ataxia, and drug-induced neurotoxicity (Cao et al., 2016) (Table 1). In drug addiction, miRNAs regulate synaptic plasticity through interactions with transcription factors to generate more persistent neuroplastic changes at the cellular level (Li and van der Vaart, 2011; Gowen et al., 2021) (Table 2).

The studies so far provide a rationale that miRNA can be utilized as a therapeutic tool in METH abuse. However, there are some limitations to be addressed. For years, the delivery of miRNA to the brain mainly relies on recombinant adeno-associated viruses. Now, it has been found that non-viral vectors may significantly increase the delivery efficiency of miRNAs in the brain (Zhang et al., 2013; Lee et al., 2019). Additionally, it is necessary to consider the miRNA crossing BBB to reach the specific parts of the brain and avoid activation of immune cells to produce toxicity (Almutairi et al., 2016; Leggio et al., 2017; Goh et al., 2019). In general, miRNAs are delivered across BBB by exosomes, nanoparticles, and the carrier system which binds to nicotinic acetylcholine receptors (Lee et al., 2019; Xia et al., 2019). However, whether miRNAs that cross the BBB are affected by METH-induced BBB damage is unknown. Further, as mentioned above, miRNAs play a role in multiple regions of the brain with distinct mechanisms to inhibit the expression of all the targeted genes at the same time. This may lead to contradictory effects in developing addiction, as well as protection in one area while promoting damage in another. Moreover, the inaccurate targeted delivery results from miRNAs binding to multiple target genes will cause

unnecessary side effects and toxicity, also called off-target effects (Braoudaki and Lambrou, 2015; Cao et al., 2016).

It is sometimes difficult to determine whether a specific miRNA contributes to neurotoxicity or addiction. Generally speaking, miRNAs involved in the model of SA, CPP and locomotor sensitization are considered related to addiction. The establishment of the model was based on repeated-intermittent low dosing treatment of METH (no more than 2 mg/kg/day). By contrast, miRNAs may function in oxidative stress, apoptosis, and neuroinflammation models of METH, in which a relatively high dose of METH (over 2 mg/kg/day *in vivo*) was used. Besides, *in vitro* studies are commonly used to evaluate the toxicity of METH. It seems arbitrary for the classification just according to the criterion of dose regimen. Even at the low dose, METH may generate toxic effects in rodent brains, and drug users.

Overall, the study of miRNA in this field is still in its infancy. Although large bodies of data concerning METH-related miRNAs have been generated in recent years, the relationship between miRNA and METH is largely obscure. Translation of these observations into clinical practice is facing enormous challenges. More aggressive efforts remain to be made before reaching a clear understanding of miRNAs in METH action.

## AUTHOR CONTRIBUTIONS

BD and JY wrote the manuscript. ZZ, HZ, XZ, SN and XY completed the tables and provided advice. All authors reviewed the manuscript.

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