Genome Medicine

REVIEW

New insights into the roles of microRNAs in drug addiction and neuroplasticity

Jean-Luc Dreyer

Abstract

Drug addiction is a major public health issue. It is typically a multigenetic brain disorder, implying combined changes of expression of several hundred genes. Psychostimulants (such as cocaine, heroin and amphetamines) induce strong and persistent neuroadaptive changes through a surfeit of gene regulatory mechanisms leading to addiction. Activity-dependent synaptic plasticity of the mesolimbic dopaminergic system, known as the 'reward pathway', plays a crucial role in the development of drug dependence. miRNAs are small non-coding RNAs, particularly abundant in the nervous system, that play key roles as regulatory molecules in processes such as neurogenesis, synapse development and plasticity in the brain. They also act as key spatiotemporal regulators during dendritic morphogenesis, controlling the expression of hundreds of genes involved in neuroplasticity and in the function of synapses. Recent studies have identified changes of several specific miRNA expression profiles and polymorphisms affecting the interactions between miRNAs and their targets in various brain disorders, including addiction: miR-16 causes adaptive changes in production of the serotonin transporter; miR-133b is specifically expressed in midbrain dopaminergic neurons, and regulates the production of tyrosine hydroxylase and the dopamine transporter; miR-212 affects production of striatal brain-derived neurotrophic factor and synaptic plasticity upon cocaine. Clearly, specific miRNAs have emerged as key regulators leading to addiction, and could serve as valuable targets for more efficient therapies. In this review, the aim is to provide an overview of the emerging role of miRNAs in addiction.

Correspondence: jean-luc.dreyer@unifr.ch
Division of Biochemistry, Department of Medicine, University of Fribourg, Rue du Musée 5, CH-1700 Fribourg, Switzerland

Addiction, neuroplasticity and miRNAs

Drug addiction is a major public health issue. Drugs of abuse modulate gene expression, and produce their rewarding effects of euphoria or pleasure through an interaction with the mesolimbic dopaminergic system, leading to persistent alterations (neuroplastic, structural and functional) in the reward-related and memory-related brain centers. An overview of the pathways involved in miRNA regulation of gene expression in addiction is shown in Figure 1. Long-term intake of addictive substances such as cocaine, heroin and nicotine, for example, results in neurological adaptations that decrease the sensitivity of an individual to these drugs. Drugs induce persistent perturbation of activity-dependent synaptic plasticity, progressing towards high-risk, drug-seeking behavior and relapse [1], but the molecular mechanisms leading to addiction are poorly understood. Emerging evidence suggests that drug-induced neuroplasticity depends on epigenetic changes in gene expression and post-transcriptional regulation [2,3], because addiction is typically a multigenetic brain disorder, implying combined changes of expression of several hundreds of genes. Tight regulation of such a large array of genes in a very complex behavioral paradox is mediated by a variety of transcriptional and post-transcriptional events that control the expression of individual gene products. Recently, a novel class of highly potent post-transcriptional regulators of gene expression has been described that consist of small (19-25 nucleotides) non-coding RNAs. These miRNAs are considered to be 'master regulators' of gene expression, and they control the translation of target mRNAs, thereby regulating critical aspects of neuroplasticity and synapse consolidation. In the mammalian nervous system, the spatiotemporal control of mRNA translation has an important role in synaptic development and plasticity. Targeted mRNAs are selectively and reversibly suppressed translationally or subjected to degradation by miRNAs, possibly in a combinatorial fashion based on the complementarity in the 3'-untranslated region (3'UTR) of the mRNAs. Local translational control in dendritic spines is a powerful mechanism to regulate morphologic and functional plasticity [2], and recent

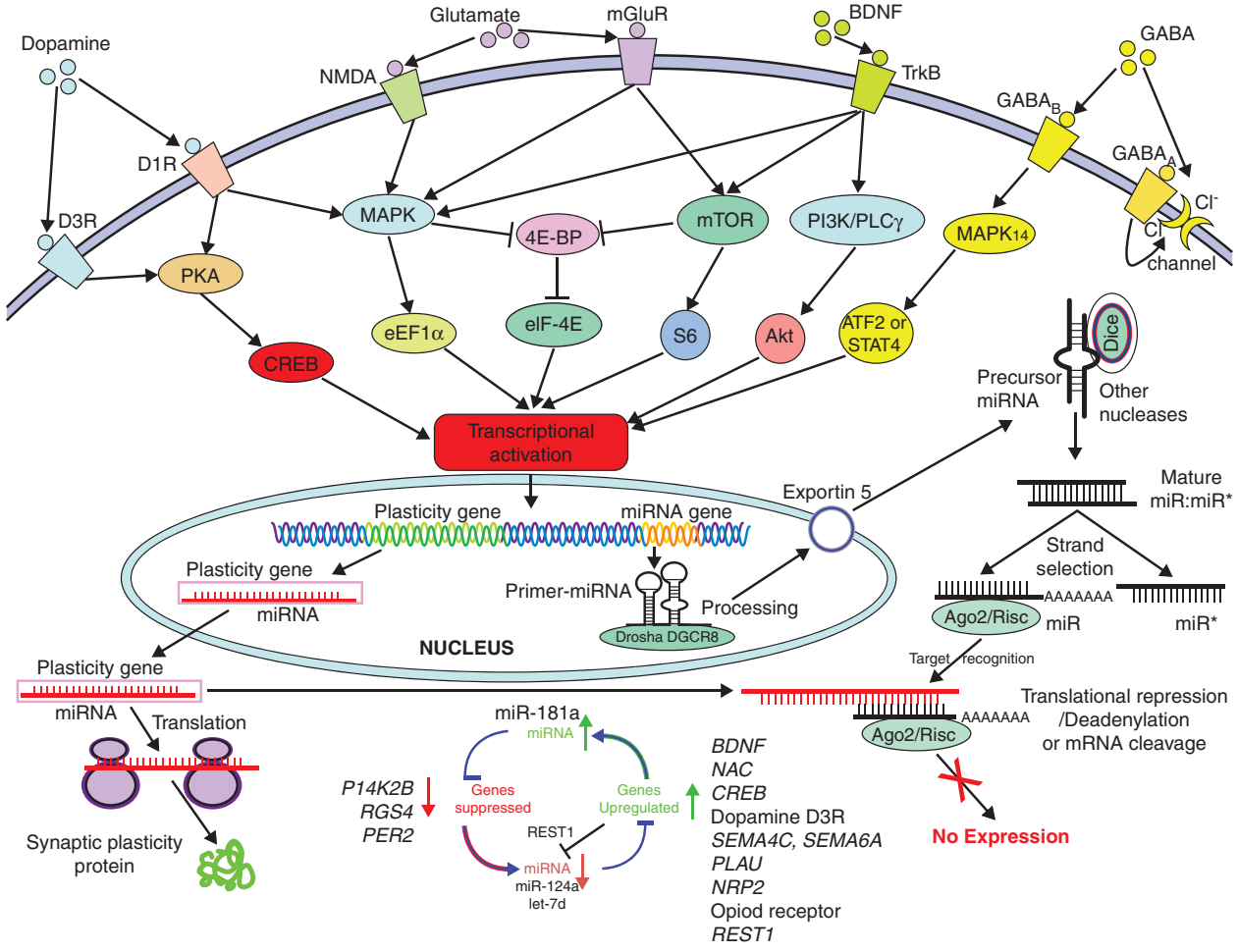

Figure 1. Simplified overview of the pathways involved in miRNA regulation of gene expression in addiction. Neurotransmitters activate intracellular signaling pathways through binding to their different receptors, leading to activation of transcription factors. Transcriptional activation induces transcription of a large program of plasticity-related genes – leading to synaptic adaptation and favoring the formation of the addictive phenotype – together with transcription of primer miRNAs. Primer miRNAs are processed by Drosha/DGCR8, and then exported by exportin 5 as precursor miRNAs to be converted to mature miRNA by Dicer and other nucleases. Upon strand selection, the selected strand of the mature miRNA binds with Ago2 and the Risc complex to interact with its specific target. Perfect match with the target mRNA induces deadenylation and mRNA cleavage, while imperfect match prevents binding to ribosomes and blocks translation: in both cases expression is silenced. In many cases, miRNAs regulate gene expression (including plasticity-related genes) in a dynamic double negative feedback loop, as exemplified here with miR-181a/miR-124/let-7d, involved in cocaine (adapted from [10,11]): the brain-enriched miR-124 is suppressed by chronic cocaine in the mesolimbic dopaminergic pathway (presumably by the induction of REST), which induces expression of genes encoding miR-124 targets (BDNF, integrin β1, NAC1, axon guidance molecules such as SEMA6A, and so on), while downregulation of let-7d by cocaine results in induction of the genes encoding its targets (μ-opioid receptor, dopamine receptor D3R, semaphorins SEMA6A and SEM4C, PLAU, and so on); these genes (upregulated by cocaine) markedly induce miR-181a, causing downregulation of its targets (RGS4, PI4K2B, Per2, and so on), which in turn regulate expression of miR-124a and let-7d. Abbreviations: Ago2, argonaute 2; ATF2, cAMP-dependent transcription factor 2; BDNF, brain-derived neurotrophic factor; CREB, cAMP-responsive element binding protein; DGCR8, DiGeorge syndrome critical region *protein* 8; Dicer, double-stranded RNA endoribonuclease III; 4E-BP, translational repressor protein; eEF1A, elongation factor 1A; eIF-4E, eukaryotic translation initiation factor 4E; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3 kinase; PKA, protein kinase A; PLCγ: phospholipase C-γ; Risc, RNA-induced silencing complex; STAT4, signal transducer and activator of transcription protein 4; S6, ribosomal *protein S6* kinase.

studies have shown involvement of several miRNAs (miR-212, miR-133b, miR-132, miR-181a, miR-140, miR-190, and so on [4-13]) in dendritic spine morphogenesis and the development of addiction [3-5,10,11,14-16]. Table 1 lists miRNAs that have been found to be involved in addiction, and the mechanisms that they affect. In this review, the aim is to present the recent advances in the field, highlighting the emerging role of miRNAs in addiction. These miRNAs have been implicated in the mechanisms of drug addiction, and further studies may be central for developing novel therapeutic targets of this major brain disorder.

Table 1. MiRNAs involved in addiction

Drug	miRNAs involved	Mechanisms affected	References
Cocaine	miR-212	Decreases activity of CREB and TORC1, and controls expression of gene encoding BDNF via interaction with MeCP2	[4,15]
	miR-181a	Upregulated by cocaine; affects expression of genes encoding BDNF, DAT, CREB, Homer1 and Drd3	[10,11]
	let-7d	Downregulated by cocaine; targets semaphorins, BDNF, neuropilins and mGluR5	[10,11]
	miR-124	Downregulated by cocaine; targets Drd3, DAT and FosB	[10,11]
	miR-324-5p	Induced by Arg2 in Drd2 neurons; regulates cdk5r1, FosB and Mef2d	[5,9]
	miR-369-3p	Induced by Arg2 in Drd2 neurons; regulates cdk5r1, FosB and Mef2d	[5,9]
Nicotine	miR-140	Induced by nicotine; regulates dynamin-1, regulates synaptic endocytosis	[12,16]
	miR-504	Upregulates gene encoding Drd1	[12,16]
Opiates	miR-23b	Induces mOR	[19]
	miR-190	Induced by mOR by upregulation of talin2	[13,19]
	miR-15b, miR-181b	Induced by morphine	[20,21]
		Induced by morphine	
	miR-133b	Decreased by morphine; this increases expression of gene encoding Pitx3 and induces TH and DAT	[6]
Antidepressants, alcohol and CYP3A4	miR-133b	Specifically expressed in dopaminergic neurons; downregulates expression of gene encoding Pitx3; Pitx3 induces production of TH and DAT and regulates maturation of midbrain dopaminergic neurons	[6,21]
	miR-16	Induced by SSRI in serotonergic neurons; reduces expression of gene encoding SERT	[23]
	miR-9	Induced by alcohol; downregulates BK channels	[4]
	miR-212	Induced by alcohol; decreases ZO-1, affects cell permeability	[22]
	miR-27b	Downregulates CYP3A4	[17]
	miR-298	Downregulates CYP3A4	[17,24]

Arg2, arginase, type II; cdk5r1, cyclin-dependent kinase 5, regulatory subunit 1; CREB, cAMP-responsive element binding protein; BDNF, brain-derived neurotrophic factor; CYP3A4, cytochrome P_{450} 3A4; DAT, dopamine transporter; Drd1, dopamine receptor D1R; Drd2, dopamine receptor D2R; Drd3, dopamine receptor D3R; FosB, FBJ murine osteosarcoma viral oncogene homolog B; MeCP2, methyl CpG binding protein 2; Mef2d, myocyte enhancer factor 2D; mGluR5, metabotropic glutamate receptor 5; SSRI, selective serotonin reuptake inhibitor; TH, tyrosine hydroxylase; TORC1, transducer of regulated CREB activity 1; ZO-1, tight junction protein.

Cocaine

Cocaine use is a common disorder of neuroplasticity that triggers cellular and molecular alterations in brain reward systems, mainly in the dorsal striatum. Compulsive cocaine use and cocaine relapse is due to drug-induced neuroadaptations in reward-related learning and memory processes, and these cause hypersensitivity to cocaine-associated cues, impulsive decision making and abnormal habit-like learned behaviors that are insensitive to adverse consequences [3]. Cocaine-induced neuroplasticity changes in the mesolimbic dopamine system mediate psychomotor sensitization and cocaine-seeking behaviors. Hollander *et al.* [4] demonstrated that cocaine-seeking behavior in rats is modulated by miR-212, which decreases the activity of a group of genes (*CREB*, *TORC1*, *Raf1* and *SPRED1)*, thus limiting the transition to an uncontrolled intake of cocaine in animals exposed to the drug over a long period of time. Interestingly, artificially increasing miR-212 expression leads to decreased cocaine intake under conditions of extended access, whereas blocking the expression of this regulatory miRNA increases cocaine intake. Furthermore, cocaine addiction, commonly viewed as a disorder of neuroplasticity, affects expression of *MeCP2*; MeCP2 regulates cocaine intake through homeostatic interactions with miR-212 to control the effects of cocaine on striatal brain-derived neurotrophic factor (BDNF) levels, leading to synaptic plasticity and thus regulating vulnerability to cocaine [15].

Cocaine also affects the expression of a number of other miRNAs: miR-124 and let-7d are suppressed, whereas miR-181a is induced after chronic cocaine use [10]. Cocaine causes a strong induction of miR-181a in different regions of the midbrain. The role of miR-181a in lineage modulation-determining ratio of cell types and as a positive modulator of B cell differentiation is well established, and miR-181a has putative target sites on several cocaine-suppressed genes: *BDNF*, *DAT*, *mGluR5*, *Homer1*, *Drd3* (dopamine receptor D3R), *Per2* and *CREB* [6]. Interestingly *Per2* is induced after cocaine exposure, but *mPer2* mutant mice exhibit a hypersensitized response to cocaine and show a strong cocaine-induced place preference. While chronic cocaine decreases surface production of mGluR5 and Homer 1 in the nucleus accumbens, and withdrawal increases their production in the dorsal prefrontal cortex, miR-181a

reveals a correlating inverse expression pattern with the expression pattern of *mGluR5* in these regions [10,11]. Chronic cocaine also mediates downregulation of miR-124a in the mesolimbic dopaminergic pathway, and this could have a greatest impact on the targeted gene expression (for example, *DAT*, *FosB*, *CREB* and *Drd3*) [10,11]. miR-124a is an exclusively neuronal miRNA, highly conserved between invertebrates and vertebrates, and accounts for 25-48% of total adult brain miRNA. Dysregulation of let-7 miRNA seems to play a crucial role in the etiology of neurological disorders. The CA1 pyramidal cells of the hippocampus have high levels of μ-opioid receptors and cocaine activation may differentially modulate memory processes, synaptic plasticity and the encoding of information. Chronic cocaine use suppresses let-7d [5,9], which has a putative binding site in the μ-opioid receptor in the CA1, suggesting that downregulation of let-7d is crucial in the development of drug dependence. miRNAs can indirectly regulate their own expression through double-negative feedback loops. It has been proposed [10,11] that these miRNAs (124, let-7d and 181a), together with their target transcription regulator genes (*CREB*, *NAC1* and *REST1*), along with various target plasticity-related genes (encoding semaphorins, BDNF and neuropilins) and neurotransmitter receptor genes (encoding dopamine receptor D3R, μ-opioid receptor, mGluR5 and AMPA-R) might act in such a feedback loop during the development of cocaine-induced neural plasticity. Therefore these miRNAs may play an important role in the development of addiction.

Finally, argonaute 2 (Ago2) plays an important role in miRNA generation and execution of miRNA-mediated gene silencing, and is involved in the regulation of cocaine addiction [5]. Deficiency of Ago2 in dopamine receptor D2R (*Drd2*)-expressing neurons greatly reduces the motivation to self-administered cocaine in mice. A distinct group of miRNAs is specifically regulated by Ago2 in the striatum [5]. Comparison of miRNAs affected by Ago2 deficiency with miRNAs that are enriched and/or upregulated in Drd2 neurons in response to cocaine identified a set of 23 Ago2-dependent, induced by cocaine and Drd2-enriched (ADICD) miRNAs that are likely to play a role in cocaine addiction [9]. These ADICD miRNAs (for example, miR-431, miR-212, miR-324-5p, miR-369-3p, and so on) contribute to cocaine addiction and to the regulation of genes important for the development of cocaine addiction; these genes include *Cdk5r1* and the transcription factors *FosB* and *Mef2d*. The contribution of individual ADICD miRNAs to various facets of addictive behavior in mice, and possibly humans, remains to be investigated further, but may provide useful paths to new therapies.

Nicotine

As a drug of abuse, nicotine, an agonist of nicotinic acetylcholine receptors, induces neural plasticity leading to addiction. Exposure to nicotine can disrupt this finely programmed coordination and alter gene expression of a diversity of genes in different brain regions, mainly genes encoding synaptic-vesicle-related proteins involved in endocytosis and exocytosis (dynamin-1, synapsin-1, syntaxin-7, and so on), neurotransmitter receptors, ion channels and transporters (dopamine Drd1 receptor, γ-amino butyrate $(GABA)_A$ receptor β-subunits, serotonin receptor 5A, and sodium and potassium channels), and kinases and phosphatases for signal transduction [12]. Nicotine selectively modulates expression of multiple miRNAs and increases expression of miR-140, coordinated with the nicotine-augmented expression of its host gene *WWP2*. miR-140 targets the 3'UTR of the gene encoding dynamin-1 by direct-base pairing [12,16]. Because dynamin-1 has an essential role in synaptic endocytosis in the central nervous system, nicotine-induced miRNA-mediated regulation may illustrate its importance in neural plasticity, which underlies a molecular mechanism of nicotine addiction. Furthermore, the dopamine receptor gene *DRD1* is associated with nicotine dependence, with two alleles (A and G) of polymorphism rs686 in the 3'UTR of *DRD1* being expressed differentially. It has been shown that miR-504 (not miR-296) upregulates reporter luciferase activity and increases Drd1 production by targeting the *DRD1* 3'UTR, whereas inhibition of miR-504, not miR-296, has the opposite effect [16]. The direct binding of miR-504 to the *DRD1* 3'UTR, verified by site-directed mutagenesis, causes a significant expression difference between the two alleles. This shows that miR-504 upregulates *DRD1* expression by direct binding to the 3'UTR, and this leads to differential allele-specific expression of *DRD1*. Interestingly, the variant is also associated with alcohol dependence and autism spectrum disorder, providing additional genetic evidence of *DRD1* and its importance in neuropsychiatric disorders [12,16]. This miRNA-mediated differential modulation of *DRD1* expression may alter the density of the DRD1 receptor in the brain. Because of the significant role of the DRD1 receptor in mediating dopamine action, the predisposition of *DRD1* expression may contribute to the molecular mechanisms underlying nicotine dependence. Furthermore, because miR-504 is chromosome X associated, the modulation of *DRD1* expression by miR-504 may play a role in the sex influences on nicotine dependence [12].

Opiates

Opiates affect multiple structures that provide major afferent input to the ventral tegmental area (that is, the

nucleus accumbens and the ventral pallidum) as primary sources of GABA input; the prefrontal cortex, the amygdala, and the mediodorsal thalamus as primary sources of glutamate input; and the pedunculopontine tegmental nucleus as a source of acetylcholine input. These structures are characterized by a high density of opiate receptors and dense reciprocal connections and are implicated in the mediation of goal-directed behavior and the rewarding effects of psychostimulants [17,18]. Opiate abuse may destabilize neuronal functions, and in HIV-1-infected individuals it may lead to an accelerated form of HIV-1-associated dementia. A strong relationship seems to exist between opiate usage and HIV-1 neuropathogenesis. Opiates promote HIV-1 propagation in immune cells, while suppressing immune functions. miRNA-based analysis identified a role of miR-23b in the regulation of the μ-opioid receptor [19]. In turn, the μ-opioid receptor regulates miR-190 in an agonist-dependent manner, via yingyang-1 phosphorylation; fentanyl, but not morphine, decreases the miR-190 level in rat primary hippocampal neuron cultures. miR-190 is conserved and located in the intronic regions of the *talin2* gene. Yinyang-1 regulates the activity of the *talin2* promoter and transcription regulation of *talin2* could modulate the overall miR-190 level within the hippocampal neurons [19]. Furthermore, in mouse hippocampi, miR-190 expression is differentially regulated by μ-opioid receptor agonists [13]. In addition, differentially expressed miRNAs, for example miR-15b (which is upregulated by morphine treatment) and miR-181b, have several targets in the pro-inflammatory pathways and may have a potential role for inducing inflammation and oxidative stress in human monocyte-derived macrophages, thereby contributing to HIV-1 central nervous system reservoir expansion and disease progression [20]. In addition to these effects on miR-190, morphine decreases miR-133b expression, and hence increases the production of its target, Pitx3, which is a transcription factor that activates tyrosine hydroxylase and the dopamine transporter [6]. Taking into consideration the implication of the dopaminergic system in addictive disorders, including addiction to opioid drugs, these results provide evidence that the miR-133b is a possible new target for the design of new treatments against addictive disorders.

Antidepressants and alcohol

Neuroplasticity of the midbrain-forebrain dopaminergic circuits regulate a diverse set of behaviors, from the control of movement to modulation of cognition and desire; this is because these circuits relate to mood, attention, reward and addiction. Defects in these pathways, including neurodegeneration, are implicated in a variety of psychiatric and neurological diseases, such as schizophrenia, attention-deficit/hyperactivity disorder and drug addiction. Recently, the roles of some miRNAs in mammalian midbrain dopaminergic neurons have been identified, and they have been found to relate to addictive behaviors. In particular, miR-133b is specifically expressed in midbrain dopaminergic neurons and is deficient in midbrain tissue from patients [6,21]. miR-133b is interesting because it regulates the maturation and function of midbrain dopaminergic neurons within a negative-feedback circuit that includes the paired-like homeodomain transcription factor Pitx3. miR-133b functions within such a feedback loop, as Pitx3 specifically induces transcription of miR-133b, and Pitx3 activity is downregulated by miR-133b post-transcriptionally [21]. Furthermore, deletion of the gene encoding Dicer leads to the progressive loss of midbrain dopaminergic neurons, suggesting that other miRNAs in addition to miR-133b function in these cells and are involved in the fine tuning of dopaminergic-related behaviors such as reward and addiction [21].

Other miRNAs may play a role in specific responses to drugs of neural circuits in this brain area, as illustrated in alcohol tolerance [4]. Addiction to drugs (and alcohol) is characterized by compulsive drug taking and seeking, and the dorsal striatum has been implicated in such maladaptive persistent habits. Recently miR-9 has been found to be involved in this process, and to destabilize the mRNA of the calcium-activated and voltage-activated potassium channel BK [4], which is a well-established alcohol target. This effect is restricted to a specific BK splice variant harboring a miR-9 recognition element in its 3'UTR. Furthermore, alcohol also increases miR-212 expression, which decreases ZO-1 protein levels, disrupts tight junctions, and increases cell permeability [22], providing a further example of the control of mRNA expression by miRNA in addiction.

In addition, addictive behaviors, and particularly relapse, are much related to mood disorders and depressive states, which are generally associated with a deficit of serotonin, a neurotransmitter particularly involved in eating and sexual behaviors, anxiety and mood problems, the sleep-wake cycle, and also with pain. A recent study showed that the miRNA *miR-16* controls synthesis of serotonin transporter (SERT), which clears away serotonin [23]. miR-16 is expressed at higher levels in noradrenergic than in serotonergic cells; its reduction in noradrenergic neurons causes *de novo* SERT production. In mice, chronic treatment with the selective serotonin reuptake inhibitor fluoxetine (Prozac) increases miR-16 levels in serotonergic raphe nuclei, and this reduces SERT production and releases the neurotrophic factor S100b, which acts on noradrenergic cells of the locus ceruleus. By decreasing miR-16, S100b turns on the expression of serotonergic functions in noradrenergic

neurons. miR-16 thus may contribute to the therapeutic action of selective serotonin reuptake inhibitor antidepressants in monoaminergic neurons [23].

miRNAs and CYP3A4

CYP3A4 is a member of the cytochrome P_{450} (CYP) mixed-function oxidase system, and is one of the most important enzymes involved in the metabolism of drugs in the body. CYP3A4 is involved in the oxidation of the largest range of substrates of all the cytochromes P_{450}, and it metabolizes most of the drugs on the market, particularly benzodiazepines and also HIV antivirals, macrolide antibiotics and statins. It is induced by many drugs of abuse and, as a methadone-metabolizing enzyme, it interacts with many drugs and substances used in therapies (antabuse, barbiturates, aldactone, cannabinoids, Prozac, and so on). As a result, CYP3A4 is the CYP present in the largest quantity. Although transcriptional regulation of CYP3A4 is tightly controlled by some nuclear receptors including the vitamin D receptor (VDR/NR1I1), post-transcriptional regulation of CYP3A4 remains elusive. CYP3A4 activity is significantly decreased by miR-27b and miR-298, but not by miR-122a or miR-328, indicating that gene expression may be regulated by specific miRNAs at the transcriptional level and the post-transcriptional level [17]. The decrease in CYP3A4 protein production is associated with significantly decreased *CYP3A4* mRNA levels. Also, interactions and downregulation of miR-27b or miR-298 with the vitamin D receptor 3'UTR have been observed [24]. These data show the role of miRNAs in the complex regulation of CYP3A4, which is a central drug metabolizing enzyme.

Future directions

From the studies described here it is clear that specific drugs affect specific pathways and implicate specific miRNAs as key regulators. Future studies will be required to identify the specific targets or genetic networks through which miRNAs selectively influence pathways underlying drug addiction. Collectively, these observations will reveal a new class of drug-related genes and, as such, provide new ways in our understanding of addiction. Thorough description of the intracellular pathways involved and the genes regulated by these drug-specific miRNAs is strongly needed and must be established. Further searches for specific miRNAs implicated in different types of drug addiction will then enable stronger and more specific therapies. Targeting these miRNAs may be a challenging but valuable approach that must be investigated, and it could prove useful for treating addiction. Future studies will also establish whether some miRNAs may affect common genes or pathways implicated in multidrug addiction.

Conclusions

These studies identify the correlation between miRNA regulation and addiction. Clearly a number of miRNAs may respond specifically to different drugs and thus regulate different pathways in response to a specific drug and differentially affect drug-induced neuroplasticity. The mechanistic reach of miRNAs extends well beyond suppression of gene expression and encompasses a complex system of post-transcriptional control. miRNAs have the ability to form autoregulatory loops and can attract a variety of activities to their targets – even stimulating translation [25]. The complex outcome for the mRNAs targeted by miRNAs suggests their involvement in homeostatic or switch-like events during various phases of synaptic plasticity. miRNAs may thus serve as potent spatiotemporal regulators of complex learning-related synaptic plasticity [26], fine-tuning the levels of hundreds of proteins simultaneously and in a bidirectional manner, to direct gene-silencing processes critical for maintenance of addiction phenotype. Therefore, therapeutic strategies based on modulation of miRNA activity hold great promise because of their ability to potently affect gene expression and gene regulation. Future studies will reveal the roles of miRNA as diagnostic biomarkers and as potential targets for therapeutic intervention for addiction and related brain disorders.

Abbreviations

ADICD, argonaute-2 dependent, induced by cocaine and Drd2-enriched; BDNF, brain-derived neurotrophic factor; CYP, cytochrome P_{450}; GABA, γ-amino butyrate; miRNA, microRNA; SERT, serotonin transporter; 3'UTR, 3'-untranslated region of mRNA.

Competing interests

The authors declare that they have no competing interests

Acknowledgements

The author is grateful to V Chandrasekar for useful discussions. This study was supported by Swiss National Foundation grants 3100-059350 and 3100AO-100686. The funders had no role in study design, decision to publish, or preparation of the manuscript.

Published: 23 December 2010

References

1. Russo SJ, Dietz DM, Dumitriu D, Morrison JH, Malenka RC, Nestler EJ: **The addicted synapse: mechanisms of synaptic and structural plasticity in nucleus accumbens.** *Trends Neurosci* 2010, **33:**267-276.
2. Schratt GM: **microRNAs at the synapse**. *Nat Rev Neurosci* 2009, **439:**283-289.
3. Thomas MJ, Kalivas PW, Shaham Y: **Neuroplasticity in the mesolimbic dopamine system and cocaine addiction**. *Br J Pharmacol* 2008, **154:**327-342.
4. Hollander JA, Im HI, Amelio AL, Kocerha J, Bali P, Lu Q, Willoughby D, Wahlestedt C, Conkright MD, Kenny PJ: **Striatal microRNA controls cocaine intake through CREB signaling.** *Nature* 2010, **466:**197-202.
5. Schaefer A, Im HI, Venø MT, Fowler CD, Min A, Intrator A, Kjems J, Kenny PJ, O'Carroll D, Greengard P: **Argonaute 2 in dopamine-2-receptor-expressing neurons regulates cocaine addiction.** *J Exp Med* 2010, **207:**1843-1851.
6. Sanchez-Simon FM, Zang XX, Loh HH, Law PY, Rodriguez RE: **Morphine regulates dopaminergic neuron differentiation via miR-133b.** *Mol Pharmacol* 2010, **78:**935-942.
7. Kuss AW, Chen W. **MicroRNAs in brain function and disease.** *Curr Neurol Neurosci Rep* 2008, **8:**190-197.

8. Impey S, Davare M, Lasiek A, Fortin D, Ando H, Varlamova O, Obrietan K, Soderling TR, Goodman RH, Wayman GA. **An activity-induced microRNA controls dendritic spine formation by regulating Rac1-PAK signaling.** *Mol Cell Neurosci* 2010, **43:**146-156.
9. Wayman GA, Davare M, Ando H, Fortin D, Varlamova O, Cheng HY, Marks D, Obrietan K, Soderling TR, Goodman RH, Impey S. **An activity-regulated microRNA controls dendritic plasticity by down-regulating p250GAP.** *Proc Natl Acad Sci USA* 2008, **105:**9093-9098.
10. Chandrasekar V, Dreyer JL: **microRNAs miR-124, let-7d and miR-181a regulate cocaine-induced plasticity**. *Mol Cell Neurosci* 2009, **42:**350-62.
11. Chandrasekar V, Dreyer JL: **Regulation of miR-124, let-7d and miR-181a in the accumbens affects the expression, extinction and reinstatement of cocaine-induced conditioned place preference.** *Neuropsychopharmacology*, in press.
12. Huang W, Li MD: **Nicotine modulates expression of miR-140, which targets the 3k-untranslated region of dynamin-1 gene (Dnm1)**. *Int J Neuropsychopharmacol* 2009, **12:**537-546.
13. Zheng H, Chu J, Zeng Y, H. Loh HH, Law PY: **Yin-Yang-1 phosphorylation contributes to the differential effects of μ-opioid receptor agonists on microRNA-190 expression.** *J Biol Chem* 2010, **285:**21994-22002.
14. Pietrzykowski AZ, Friesen RM, Martin GE, Puig SI, Nowak CL, Wynne PM, Siegelmann HT, Treistman SN: **Posttranscriptional regulation of BK channel splice variant stability by miR-9 underlies neuroadaptation to alcohol.** *Neuron* 2008, **59:**274-287.
15. Im HI, Hollander JA, Bali P, Kenny PJ: **MeCP2 controls BDNF expression and cocaine intake through homeostatic interactions with microRNA-212.** *Nat Neurosci* 2010, **13:**1120-1127.
16. Huang W, Li MD: **Differential allelic expression of dopamine D1 receptor gene (DRD1) is modulated by microRNA miR-504.** *Biol Psychiatry* 2009, **65:**702-705.
17. DeVries TJ, Shippenberg TS: **Neural systems underlying opiate addiction.** *J Neurosci* 2002, **22:**3321-3325.
18. Koob GF, Sanna PP, Bollm FE: **Neuroscience of addiction.** *Neuron* 1998, **21:**467-476.
19. Wu Q, Zhang L, Law PY, Wei LN, Loh HH: **Long-term morphine treatment decreases the association of μ-opioid receptor (MOR1) mRNA with polysomes through miRNA23b.** *Mol Pharmacol* 2009, **75:**744-750.
20. Dave RS, Khalili K: **Morphine treatment of human monocyte-derived macrophages induces differential miRNA and protein expression: impact on inflammation and oxidative stress in the central nervous system.** *J Cell Biochem* 2010, **110:**834-845.
21. Kim J, Inoue K, Ishii J, Vanti WB, Voronov SV, Murchison E, Hannon G, Abeliovich A: **A microRNA feedback circuit in midbrain dopamine neurons.** *Science* 2007, **317:**1220-1224.
22. Tang Y, Banan A, Forsyth CB, Fields JZ, Lau, Zhang LJ, Keshavarzian A: **Effect of alcohol on miR-212 expression in intestinal epithelial cells and its potential role in alcoholic liver disease.** *Alcohol Clin Exp Res* 2008 **32:**355-364.
23. Baudry A, Mouillet-Richard S, Schneider B, Launay JM, Kellermann O: **miR-16 targets the serotonin transporter: a new facet for adaptive responses to antidepressants.** *Science* 2010, **329:**1537-1541.
24. Pan YZ, Gao W, Yu AM: **MicroRNAs regulate CYP3A4 expression via direct and indirect targeting**. *Drug Metab Dispos* 2009, **37:**2112-2117.
25. Vasudevan S, Tong Y, Steitz JA: **Switching from repression to activation: microRNAs can up-regulate translation.** *Science* 2007, **318:**1931-1934.
26. Rajasethupathy P, Fiumara F, Sheridan R, Betel D, Puthanveettil SV, Russo JJ, Sander C, Tuschl T, Kandel E: **Characterization of small RNAs in Aplysia reveals a role for miR-124 in constraining synaptic plasticity through CREB.** *Neuron* 2009, **63:**803-817.

doi:10.1186/gm213
Cite this article as: Dreyer J-L: New insights into the roles of microRNAs in drug addiction and neuroplasticity. *Genome Medicine* 2010, **2:**92.