Epigenetics, microRNA, and addiction

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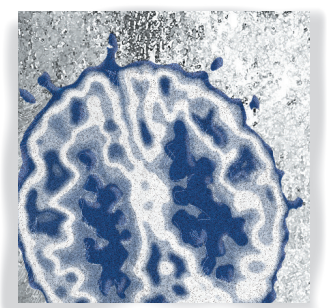

Introduction

Over 34 million Americans aged 12 or over report lifetime use of cocaine, with an estimated 1 million new users of cocaine each year.[1] The negative health and economic consequences of cocaine use on society are considerable, with cocaine use associated with potentially fatal cardiovascular events such as arrhythmias, myocardial infarction, and cerebral hemorrhage. In common with other substance-use disorders, cocaine addiction is characterized by a compul-

Drug addiction is characterized by uncontrolled drug consumption and high rates of relapse to drug taking during periods of attempted abstinence. Addiction is now largely considered a disorder of experience-dependent neuroplasticity, driven by remodeling of synapses in reward and motivation relevant brain circuits in response to a history of prolonged drug intake. Alterations in gene expression play a central role in addiction-relevant neuroplasticity, but the mechanisms by which additive drugs remodel brain motivation circuits remains unclear. MicroRNAs (miRNAs) are a class of noncoding RNA that can regulate the expression of large numbers of protein-coding mRNA transcripts by binding to the 3′ untranslated region (3′ UTR) of target transcripts and blocking their translation into the encoded protein or triggering their destabilization and degradation. Emerging evidence has implicated miRNAs in regulating addiction-relevant neuroplasticity in the brain, and in controlling the motivational properties of cocaine and other drugs of abuse. Here, the role for miRNAs in regulating basic aspects of neuronal function is reviewed. The involvement of miRNAs in controlling the motivational properties of addictive drugs is also summarized. Finally, mechanisms by which miRNAs exert their actions on drug intake, when known, are considered.

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sive need to seek and take the drug, a loss of control over the amount of drug consumed, and by periods of attempted abstinence closely followed by relapse to drug-taking behavior.[2] The mechanisms by which cocaine comes to dominate the behavioral repertoire in this manner remain unclear. Emerging evidence suggests that cocaine and other addictive drugs modify the transcriptional landscape of neurons in brain reinforcement circuits and drive the increasing control over behavior exerted by the drug. Cocaine can modify gene expression, and hence neuronal function, at the transcriptional and translational level. Much current work is focused on understanding the chromatin-modifying actions of cocaine that influence gene expression levels.[3] However, far less is known about the mechanisms by which cocaine impacts gene translation. As described below, microRNAs (miRNAs) are small noncoding regulatory RNAs that play key roles in regulating protein translation and that have been recently implicated in regulating the addiction-relevant behavioral effects of cocaine in rodents.

Modeling compulsive drug intake in rodents

In order to investigate the underlying neurobiology of compulsive cocaine intake, it is necessary to employ an animal model that accurately recapitulates many aspects of the compulsive cocaine seeking seen in human addicts. Loss of control over the amount of drug consumed marks the transition from controlled drug use to the compulsive drug intake that is a central feature of addiction. Periods of extended drug availability and resultant excessive drug consumption are likely a critical factor triggering the development of compulsive drug seeking in humans and a loss of control over intake.[4-8] Indeed, in human drug users a sudden increase in drug availability can precipitate the transition from low to high (and increasingly uncontrolled) levels of drug use.[9-11] Such "escalating" levels of drug consumption by human drug users in response to increased drug availability can be observed for most drugs of abuse.[9,12,13] Animal studies utilizing the intravenous cocaine self-administration procedure have shown that periods of extended daily access to cocaine and other addictive drugs can trigger escalating cocaine intake in rats similar to that observed in human drug users.[7,11,14,15] Rodents also show escalating levels of intake during extended daily access to self-administered heroin,[16] nicotine,[17] or methamphetamine.[18] Prolonged access to cocaine also results in the development of drug-seeking responses (lever presses) that become progressively less sensitive to the suppressant effects of a noxious stimulus (cue that predicts the onset of aversive footshocks).[14] This compulsive-like responding for cocaine in rats is similar to the drug seeking observed in human addicts that persists even in the face of negative social, economic, and/or health consequences associated with their drug habit.[2] Prolonged cocaine intake (>3 months) can trigger cocaine responding that persists even when drug delivery is directly paired with punishing electric shock.[15] Thus, a history of extended drug access can induce an addiction-like state in rats, characterized by a loss of control over the amounts of drug consumed (reflected in escalating daily intake),[7,11,14,15] and drug seeking that is impervious to negative outcome.[5,8,19] Understanding the underlying neurobiological mechanisms of these processes in rats may reveal novel insights into the addiction state in humans.

Role of the striatum in cocaine addiction

The psychomotor stimulant effects of cocaine and other drugs of abuse are related to increases in dopamine levels in the corpus striatum.[20-22] Ventral domains of the striatum, particularly the shell region of the nucleus acumbens and the olfactory turbercle, play an important role in the rewarding effects of cocaine in rodents upon initial exposure to the drug.[23,24] The core region of the nucleus accumbens appears to be important for the satiating effects of cocaine,[25,26] and may also regulate the enhancement of drug seeking that is observed in the presence of response-contingent pavlovian cues.[27,28] By contrast, the dorsal striatum does not appear to play a role in the motivational properties of cocaine or other addictive drugs, although cocaine and other drugs increase extracellular dopamine levels in this brain region.[23,29] Instead, it seems that the dorsal striatum is "recruited" by repeated drug intake and contributes to the enhancement of drug-seeking induced response-contingent pavlovian cues after overtraining.[30] Similarly, the dorsal striatum regulates habitual[31] and punishment-resistant[32] drug-seeking behaviors that emerge after extensive exposure to the drug. This suggests that ventral portions of the striatum control the acute reinforcing properties of addictive drugs, whereas dorsal striatum regulates the habit-like consumption that defines ad-

diction. Understanding these mechanisms by which cocaine rewires the striatum to drive compulsive-like drug-seeking responses may reveal novel treatment strategies for drug addiction.

Mechanisms of drug addiction

Susceptibility to substance abuse disorders aggregates in families, with rates of drug abuse higher among relatives of drug-dependent individuals than in the general population.[33,34] There is approximately a 4- to 8-fold increase in risk of substance abuse disorders in individuals with an affected first-degree family member across a wide range of abused substances, including cocaine, alcohol, nicotine, opiates, and cannabis.[34-36] The transmission of vulnerability to substance abuse is largely independent of familial aggregation of other psychiatric disorders.[35-38] Adoption studies have shown far greater similarities between substance abuse phenotypes with biological relatives than with adoptive family members.[39,40] Further, heritability of substance-abuse disorders is significantly higher in monozygotic compared with dizygotic twins.[41] Indeed, data from twins suggest that approximately 50% of vulnerability to addiction is heritable.[40] Genetic transmission of substance-abuse disorders does not appear to follow simple Mendelian inheritance. In common with other complex diseases, substance-abuse disorders instead appear to depend on the contribution of multiple susceptibility genes that act in concert with epigenetic and environmental factors to increase vulnerability to addiction.[39,41-44] Taken together, these observations support a strong genetic component to addiction vulnerability.

Although there is a strong genetic component to vulnerability, at its root addiction to cocaine and other drugs of abuse is considered a drug-induced disorder of neuroplasticity.[43,45-55] Indeed, cocaine addiction can be conceptualized as a disorder in which excessive cocaine consumption, in conjunction with genetic and environmental influences, manifests enduring neuroplasticity in brain circuitries that regulate reward and cognitive and emotional processing, and it is this plasticity that drives compulsive drug seeking. With the emerging appreciation that maladaptive neuroplasticity mechanisms drive addiction, much emphasis has been placed on such adaptations in addiction-related brain areas. In particular, considering that cocaine and all other major drugs of abuse increase dopamine transmission in the mesocorticolimbic system,[56] dopamine-dependent plasticity in mesocorticolimbic neurons has been a major focus of investigation. Nestler and colleagues have shown that cocaine engages "epigenetic" machinery in brain reward circuitries, and that this action influences gene expression in response to cocaine and thereby controls behavioral responses to the drug. Indeed, chromatin immunoprecipitation (ChIP) assays from mouse striatal tissues have revealed that chronic cocaine treatment induced marked increases in acetylation state of core histones in the promoter regions of the *FosB, brain-derived neurotropic factor (BDNF),* and *Cdk5* genes,[44] which have all been implicated in regulating the motivational properties of cocaine. Histone acetylation is catalyzed by histone acetyltransferases (HATs) and deacetylation is catalyzed by histone deacetylases (HDACs). HDACs catalyze the removal of acetyl groups from histone tails, resulting in more tightly compacted DNA-histone complexes, decreased access of transcription factors to gene promoter regions, and reductions in gene expression. Importantly, chronic but not acute cocaine treatment decreased the function of histone deacetylase 5 (HDAC5) in the nucleus accumbens (NAcc) of mice,[57] an action of cocaine that may explain the observed increase in acetylation of core histones in the promoter regions of *FosB, BDNF,* and *Cdk5* genes and the well-characterized increase in the expression of their associated proteins after chronic cocaine exposure.[58-62] Further, viral-mediated overexpression of HDACs in striatal tissues decreased,[44,57] whereas genetic or pharmacological knockout of striatal HDACs increased sensitivity to the rewarding effects of cocaine, as measured in a place conditioning procedure.[44,57] These data demonstrate that cocaine-induced modifications in histone acetylation state play a critical role in regulating the effects of cocaine in mice. More recently, histone methylation and other chromatin modifications, and even DNA methylation status, have all been implicated in regulating cocaine-induced changes in gene expression in brain reward systems.[3,63-67]

MicroRNAs: role in the central nervous system

In addition to regulating gene expression, cocaine may also influence neuroplastic responses in brain reward systems by influencing gene translation. One recently implicated mechanism of post-transcriptional gene reg-

ulation through which cocaine may act is through the miRNAs. The miRNAs are a class of small ncRNAs[68-70] that regulate gene expression through direct binding to the 3' UTR of gene targets and blocking their translation into encoded protein or triggering their destabilization and degradation.[71] Many hundreds of miRNA species have been identified in plants and animals.[72-76] In animals, miRNAs bind to the 3'UTR of target transcripts by incomplete complementary base-pairing, particularly at a portion of the 5' end of the miRNA termed the miRNA "seed" region. This imprecise complementary base-pairing means that potentially many hundreds of mammalian gene transcripts can be regulated by a single miRNA.

Expression profiling has shown that the expression levels of many miRNAs is dynamically regulated during development,[77,78] consistent with an emerging understanding for their important role in the development of brain structure and function.[77,78] Dicer-deficient zebrafish, which lack all mature miRNAs, displayed marked defects in neural development.[79,80] In *Drosophila,* dicer null mutation results in accumulation of pathogenic polyglutamine protein, a potent neurodegenerative agent.[81] Further, deletion of miR-8 in flies can directly drive neurodegeneration.[82] In mice, it was recently shown that miR-124 plays a critical role in differentiation of progenitor cells to mature neurons,[83] similar to its role in zebrafish described above.[80] Further, conditioned deletion of Dicer in Purkinje cells of mice resulted in cell-specific death of these cells, degradation of the cerebellum (within which Purkinje cells are located), and concomitant development of ataxia.[84] These findings demonstrate that miRNAs play a central role in neuronal development and survival.

In addition to their role in brain development, miRNAs also play a key role in adult brain function. By combining laser capture with multiplex real-time PCR, hundreds of miRNAs have been shown to demonstrate somatodendritic localization within mature neurons.[85] Based on this spatial pattern of expression, it is likely that miRNAs also play a role in the later stages of neuronal maturation and synapse formation.[77,78] Indeed, miRNAs can be transported away from their site of formation in the cell body of neurons to points of synaptic contact, implying a role for such miRNAs in synaptic development and plasticity.[86] Memory formation in *Drosophila* can drive degradation of the RISC-associated protein Armitage that is localized to the synapse.[87] This action results in the release of mRNAs (eg, CaMKII mRNA) that had been targeted for degradation in a RISC-dependent manner[87] and induction of memory-dependent protein synthesis.[87] In addition to Armitage, and its mammalian equivalent, Moloney leukemia virus 10 MOV10, several other important components of the miRNA biosynthesis cascade, such as Fragile X mental retardation protein (FMRP),[88-90] are also localized to sites of synaptic contacts and regulate synaptic function. Indeed, FMRP has been shown to regulate the actions of many CNS-enriched miRNAs on neuronal morphology and dendritic spine development.[91-95] Considering their enrichment at the synapse, it was proposed that miRNAs may play an important role in the induction and stabilization of long-term memories.[87,96] Indeed, there is now overwhelming evidence that miRNAs regulate almost all aspects of memory-associated structural and functional plasticity in brain; for recent references see refs 97-103.

Role for miRNAs in the rewarding effects of cocaine

To determine if miRNAs may play a role in regulating the motivational effects of addictive drugs, we recently examined the effects of conditionally deleting Argonaut 2 (Ago2) in D2 receptor-expressing medium spiny neurons (MSNs) in striatum. These neurons, also known as striatopallidal or "indirect" neurons, are thought to play a key role in response inhibition, with deficits in their function perhaps contributing to the development of compulsive drug use.[104] Ago2 is a core component of the RNA-induced silencing complex (RISC), which regulates the maturation and function of miRNAs. Deletion of Ago2 broadly in striatopallidal neurons was achieved by breeding $Ago^{fl/fl}$ mice with mice expressing Cre recombinase under the control of the D2 receptor promoter. It was found that brain anatomy and striatal integrity were not impacted but, as expected, miRNA expression and function was disrupted by deletion of Ago2 in these neurons.[105] Importantly, this genetic manipulation abolished the rewarding effects of cocaine, measured using a conditioned place preference (CPP) procedure.[105] Processes independent of drug reinforcement, such as spatial learning deficits, can confound CPP. Therefore, to more rigorously investigate the involvement of striatal miRNAs in the motivational properties of cocaine we assessed intravenous cocaine

self-administration in the Ago2-D2-ablated mice. Mutant animals self-administered far less cocaine than control mice across the entire cocaine dose-response curve when tested under a 1-h session on a fixed ratio 5 time-out 20 sec schedule of reinforcement use.[104] Responding for food was not impacted in the mutant mice responding under the same reinforcement schedule,[104] suggesting that decreased cocaine intake was not secondary to deficits in behavioral performance.

The above findings support a role for miRNAs in striatum in regulating drug reward, but which miRNAs are involved? Many laboratories have identified specific miRNAs whose expression is altered by exposure to drugs of abuse and that may play a role in regulating their motivational properties. Indeed, expression of various miRNAs is altered in the prefrontal cortex, striatum and other addiction-relevant brain sites in response to exposure to drugs of abuse. As detailed lists describing which miRNAs are altered in response to particular drugs are presented elsewhere, these effects won't be considered here.[106-112] Instead, the impact of altering expression of specific miRNAs on the motivational properties of addictive drugs will be considered. Chandresekar and Dreyer have shown that the miRNAs, miRNA-124a and let-7d, were downregulated in striatum in response to cocaine treatment.[113] Moreover, virus-mediated overexpression of these miRNAs in striatum decreased expression of BDNF and the dopamine D3 receptor, two key regulators of drug-seeking behaviors.[113] This suggests that miRNA-124a and let-7d may regulate cocaine-induced remodeling of the striatum and thereby influence the motivational properties of the drug. Consistent with this possibility, overexpression of these miRNAs in striatum, specifically in the nucleus accumbens region, decreased the conditioned rewarding effects of cocaine, whereas their inhibition increased these effects, as measured using a CPP procedure.[114]

Role for miRNAs in regulating cocaine intake

As noted above, rats permitted to self-administer cocaine during extended (≥6 h) but not restricted (1 h) daily session demonstrate the emergence of compulsive-like cocaine intake, including escalation of daily cocaine intake reminiscent of the increasingly uncontrolled intake seen in human addicts bingeing on the drug. Our laboratory has used miRNA gene expression arrays to characterize miRNA expression profiles in striatum of cocaine-naïve rats and in rats with restricted or extended daily access to cocaine. We also assessed miRNA expression in "yoked" rats that received cocaine infusions noncontingently when rats in the extended access group volitionally consumed the drug. We found that two miRNAs, miR-212 and miR-132, were upregulated in the striatum of the extended access rats 24 hours after the last cocaine self-administration session relative to the yoked, restricted access and cocaine-naïve control groups.[115] We verified these findings using Taqman assay.[115] These two miRNAs are arrayed in tandem in the miR-212/132 cluster located on chromosome 17 in humans and chromosome 10 in rats.[116] As such, both miRNAs are thought to function similarly. Next, to investigate the potential role for the miR-212/132 cluster in regulating cocaine intake we used a lentivirus to overexpress miR-212 in striatum of rats (Lenti-miR-212 rats) and assess the impact on self-administration behavior. We found that miR-212 overexpression did not impact cocaine intake in rats with restricted access.[115] By contrast, striatal miR-212 overexpression strikingly reduced the motivation to consume cocaine in rats with extended access to the drug, reflected in progressively decreasing levels of cocaine intake across sessions.[115] This progressively increasing inhibitory effect of miR-212 on cocaine intake is opposite to the escalating rates of cocaine consumption typically observed in extended access rats. Conversely, disruption of miR-212 signaling in striatum, achieved through local infusion of an antisense oligonucleotide against miR-212, accelerated the emergence of escalated cocaine intake in extended access rats.[115] These data suggest that miRNAs can regulate cocaine intake and potentially impact the development of compulsive consumption of the drug.

The mechanisms by which miR-212 influences cocaine intake has also been explored. The miR-212/132 gene cluster is highly responsive to the cAMP signaling cascade, with both miRNAs upregulated by cAMP response element binding protein (CREB).[116,117] We found that levels of phosphorylated (activated) CREB are increased in striatum of rats with extended but not restricted cocaine access[115]—those that show upregulated miR-212 levels. An emerging theme in the miRNA field is the observation that miRNAs often feedback onto the signaling cascade that triggered alterations in their expression to amplify or curtail activity of these same signaling cascades.[118] As CREB activity is known

to regulate the motivational properties of cocaine,[119-121] we investigated the possibility that miR-212 may regulate CREB activity. We found that miR-212 dramatically boosts CREB signaling in cultured cells and in the striatum of rats.[115] We used a hypothesis-driven approach to identify the gene targets for miR-212 that may explain its actions on CREB. It is known that Raf1 kinase can phosphorylate adenylyl cyclases to sensitize their activity, thereby increasing cAMP production and CREB activation, eg ref 123. Interestingly, SPRED1 is a known inhibitor of Raf1 activity and also a predicted target of miR-212 (www.targetscan.com). We found that miR-212 can repress SPRED1 expression in cultured cells and in striatum[115]), and thereby activates Raf1, which stimulates CREB activity. Moreover, we showed that enhancing CREB activity in striatum (accomplished by overexpressing the CREB coactivator CRTC1) decreased cocaine intake in rats with extended access to the drug. These findings show that mir-212 plays a key role in regulating cocaine intake and highlight an emerging signaling "motif" in which miRNAs play central roles in regulating signaling strength in neurons by controlling the activity of signaling cascades that modify their expression.

Role for miRNAs in regulating alcohol intake

In addition to cocaine and other psychomotor stimulants, miRNAs have also been shown to regulate the motivational properties of alcohol. Volitional alcohol intake decreased miR-124a expression in the dorsolateral portion of the striatum of rats,[123] and virus-mediated overexpression of miR-124a in striatum decreased alcohol-induced CPP and reduced alcohol drinking in rats.[123] Li and coworkers have shown that alcohol consumption by rats decreased expression of miR-382 in accumbens in rats.[124] It was also shown that miR-382 negatively regulates dopamine D1 receptor expression, and thereby attenuates alcohol-induced increases in the transcription factor ΔFosB,[124] known to play an important role in the rewarding effects of alcohol and other addictive drugs.[125] Importantly, virus-mediated overexpression of miR-382 in accumbens attenuated alcohol-induced increases in ΔFosB expression and reduced alcohol intake in rats.[124] Most recently, Tapocik and colleagues have shown that escalating levels of alcohol intake in alcohol-dependent rats increased expression of miR-206 in prefrontal cortex,[126] a miRNA thought to play an important role in cellular responses to stress but also shown to play a key role in muscle development and cancer.[127] Expression of miR-206 was unaltered by alcohol in accumbens or amygdala.[127] It is established that miR-206 negatively regulates expression of brain-derived neurotropic factor (BDNF),[128-131] which is known to play a key role in the motivational effects of alcohol and other addictive drugs.[132] Accordingly, it was found that alcohol-induced upregulation of miR-206 in prefrontal cortex was associated with a decrease in BDNF expression.[127] Moreover, virus-mediated miR-206 overexpression also decreased BDNF expression and accelerated the development of escalating levels of alcohol intake in rats.[127]

Transcription factor-miRNA interactions control sensitivity to drug reward

As noted above, an emerging theme in miRNA biology is the fact that miRNAs will often feed back onto the same signaling cascades that regulate their expression. The repressive effect of miRNAs on translation make them ideally suited to fulfill such feedback roles in moderating signaling cascades,[118] which may serve to stabilize signaling cascades by protecting against random fluctuations and facilitate stable cellular states.[133] Considering the pronounced effects of miR-212, and other miRNAs described above, in regulating the motivation to self-administer addictive drugs, our laboratory has investigated the transcriptional mechanisms by which miR-212 (and other miRNAs) expression is controlled. Loss-of-function mutations or duplications of the methyl CpG binding protein 2 (MeCP2) gene cause Rett syndrome (RTT) in humans,[134,135] a neurodevelopmental disorder associated with severe mental retardation. MeCP2 is an epigenetic factor that binds to methylated cytosine residues of CpG dinucleotides in DNA and can recruit HDACs and other transcriptional repressors to inactivate target gene expression.[136] Interestingly, MeCP2 expression is known to be negatively regulated by miR-212.[137] We found that MeCP2 levels were increased in the striatum of rats with extended but not restricted daily access to cocaine,[137] and that virus-mediated knockdown of MeCP2 in striatum enhanced the effects of cocaine on miR-212 expression.[138] We also found that MecP2 knockdown in striatum dramatically decreased cocaine intake in rats. This effect was reversed by antisense oligonucleotide-mediated inhibi-

tion of miR-212 signaling expression.[137] These findings suggest that MecP2 attenuates cocaine-induced increases in miR-212 activity and increases the motivation to consume cocaine and that, in turn, miR-212 negatively regulates MeCP2 expression. Hence, homeostatic interactions between miR-212 and MeCP2 are likely to play an important role in regulating sensitivity to the motivational effects of cocaine.

Conclusions and future directions

The above findings demonstrate that miRNAs, including miR-212, regulate the motivational properties of drugs of abuse. miRNAs regulate drug intake by impacting a wide range of downstream signaling cascades known to influence the rewarding properties of addictive drugs. This highlights the pleiotropic nature of miRNAs and how well-positioned they are to orchestrate intracellular signaling events in order to control the motivational properties of drugs. Important areas of future research will include achieving a more in-depth understanding of the intracellular signaling cascades, and broader understanding of impacted biological functions, impacted by addiction-relevant miRNAs. Also important will be understanding the mechanisms by which miRNAs activities are regulated, from miRNA transcription to the protein complexes that direct their activities. ❑

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Epigenética, micro ARNs y adicciones

La adicción a drogas se caracteriza por el consumo no controlado de éstas y una alta frecuencia de recaídas de consumo durante los períodos en que se intenta mantener la abstinencia. Actualmente la adicción se considera en gran medida un trastorno de la neuroplasticidad dependiente de la experiencia, que se produce por la remodelación de las sinapsis en importantes circuitos cerebrales de recompensa y motivación en respuesta a una prolongada historia de ingesta de drogas. Aunque las alteraciones en la expresión génica juegan un papel central en la neuroplasticidad de las adicciones, los mecanismos a través de los cuales las drogas adictivas remodelan los circuitos cerebrales de la motivación aun no están aclarados. Los microARNs (miARNs) son un tipo de ARN no codificante que pueden regular la expresión de un gran número de transcriptores de ARNm que codifican proteínas al unirse a la región 3' no transcrita (3' UTR) de los transcriptores blanco y bloquean su transcripción a la proteína codificada o gatillan su desestabilización y degradación. Existe una evidencia creciente que ha vinculado a los miARNs con la regulación de la neuroplasticidad de las adicciones en el cerebro, y con el control de las propiedades de motivación de la cocaína y otras drogas de abuso. En este artículo se revisa el papel de los miARNs en los aspectos básicos de la regulación de la función neuronal. También se resume la participación de los miARNs en el control de las propiedades motivacionales de las drogas adictivas y se revisan los mecanismos que se conocen a través de los cuales los miARNs ejercen sus acciones en la ingesta de drogas.

Épigénétique, microARN et addiction

L'addiction aux drogues se caractérise par une consommation incontrôlée de drogues et un taux élevé de rechute pendant les périodes d'essai d'abstinence. L'addiction est maintenant considérée en grande partie comme un trouble de la neuroplasticité dépendant de l'expérience, dominé par le remodelage des synapses des circuits cérébraux se rapportant à la motivation et à la récompense en réponse à des antécédents de prise prolongée de drogues. Les modifications de l'expression génique jouent un rôle central dans la neuroplasticité liée à l'addiction mais les mécanismes du remodelage des circuits cérébraux de motivation par les drogues addictives sont mal connus. Les microARN (ARNmi), classe d'ARN non codants, régulent l'expression de nombreux brins transcrits d'ARN codant les protéines, en se liant à la région 3'non traduite (3'UTR) des transcrits cibles et en bloquant leur traduction en protéine encodée ou en provoquant leur déstabilisation et leur dégradation. D'après des données récentes, les ARNmi sont impliqués dans la régulation de la neuroplasticité cérébrale liée à l'addiction et dans le contrôle des propriétés de la cocaïne et d'autres drogues illégales liées à la motivation. Le rôle des ARNmi dans la régulation des aspects fondamentaux de la fonction neuronale est analysé ici, et leur participation dans le contrôle des propriétés motivationnelles des drogues addictives est aussi résumée. Enfin, les mécanismes d'action des ARNmi sur la prise de drogue sont examinés, quand ils sont connus.

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