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RESEARCH ARTICLE

Brain microRNA profiles after exposure to heroin in rats

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Abstract

Heroin addiction is one of the neuropsychiatric burdens that affects many genetic and epigenetic systems. While it is known that heroin may change the expressions of some genes in the brain during dependence, there is no detailed study related to which gene are mostly affected. Therefore, in the current study, we aimed to determine alterations in the miRNA profiles of rats' brains for providing a detailed analysis of molecular mechanisms in heroin addiction-related toxicology. Next generation global miRNA sequencing was used to predict potential miRNAs in prefrontal cortex (PC), hippocampus, ventral tegmental area (VTA), striatum, and Nucleus accumbens (NA) of rats that exposed to heroin by intravenous injections. The total daily dose was started with 2 mg/kg and ended with 10 mg/kg on the 10^{th} day. In the striatum, miR-18a, miR-17-5p, miR-20a-5p, miR-106a, miR-301a-3p, miR872-5p, miR-15a-5p, miR-500-3p, and miR-339-5p expressions were upregulated by nearly 2-to-4 times with heroin. The expressions of hippocampal miR-153-3p, miR-130a-3p, miR-204-5p, miR-15b-5p, and miR-137-3p and the expressions of miR-872, miR-183-5p, miR-20a-5p, miR-325-5p, miR-379-5p, and miR-340-5p in the VTA were 2-times higher in the heroin-addicted rats. While there was nearly 2-times increase in the miR-129-1-3p and miR-3068-3p expressions in the NA, no change was noted in the PC due to heroin. The only heroin-dependent downregulation was observed in the expressions of striatal miR-450b-3p and miR-103-1-5p of VTA. These results suggested that heroin addiction might give harm to brain by altering cytokine balance and increasing neuroinflammation and apoptosis. In addition, neurons also try to compensate these abnormalities by enhancing neurogenesis and angiogenesis through several miRNAs in the different brain regions. In conclusion, the present study may provide a more integrated view of the molecular mechanism and a potential biomarker that will aid in clinical diagnosis and treatment of heroin-dependence.

Keywords Bioinformatics · Heroin addiction · microRNA · Next generation sequencing · Rat brain

Introduction

Addiction is a chronic and recurrent brain disease that begins with voluntary substance use and continues with compulsive substance seeking (Wise et al. 2014). According to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, the term substance use disorders is defined as a process that begins with reinforced responses to the substance that lead to repeated intakes of it and continues with the pleasurable emotions experienced with the ingestion as positive reinforcement, and negative sensations experienced when the substance is not taken as a negative reinforcer.

Heroin abuse is one of the typical representative drugs in addiction and has a huge effect on the plasticity of the central nervous system by developing encephalopathy (Cadet et al. 2016). There are three important aspects of addiction

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development after heroin use. These are genetic factors, substance-induced factors which produce neurobiological changes, and the environmental effects on the individual (Kendler et al. 2003; Kreek et al. 2005; Tsuang et al. 1996). In addition, low socioeconomic status and education level, absence of parents in childhood, close social contact with people using heroin, depression, anxiety disorders and mental illnesses such as attention deficit hyperactivity disorder have been associated with heroin addiction (Brown 2004).

Due to heroin abusers still experience poor health outcomes and high rates of potentially life-threatening disease, there is an urgent need to find new effective treatment solutions. Therefore, to improve the treatment solutions for heroin addiction, new biomarkers should be identified to understand the molecular mechanisms of heroin addiction. The molecules related to the epigenetic changes which can directly alter gene expressions have good potentials as a biomarker for drug addiction as previously mentioned (Pizzimenti and Lattal 2015; Feng and Nestler 2013). Among these epigenetic regulators, microRNAs (miRNAs) which are synthesized endogenously as a short single-stranded non-coding RNA are crucial for regulating negative post-transcriptional repression of gene expression (Doura and Unterwald 2016). While miRNAs are among the most popular topics in cancer research recently, there are studies demonstrating the involvement of miRNAs in the regulation of addiction (McQuown and Wood 2010). However, there is a few study related to the microRNA alterations in the heroin addiction (Liu et al. 2021a, b; Yan et al. 2017).

Although numerous altered proteins and metabolites related to heroin abuse have been identified, it is still difficult to identify a specific molecule as a potential biomarker. Therefore, in the present study, we aimed to determine alterations in the miRNA profile of different brain regions of rat for providing a more integrated view of the molecular background of heroin addiction and ultimately finding a potential biomarker that will aid in clinical diagnosis and treatment of heroin addiction related-toxicity.

Materials and methods

Animals

Adult, male, and sensitive to addiction, *Wistar* rats weighing 300 to 350 g ($n=30$) were supplied from Istanbul Medipol University, Turkey. The experimental procedures were applied according to the NIH guidelines (NIH publication No. 85 – 23, revised 1996) regarding the care and use of the experimental animals' standards (12 h light / dark cycles, 22 °C, and 60% humidity) with *ad libitum* food and water. All experimental procedures were approved by the Committee for Animal Research Ethics in Istanbul Medipol University (30.09.2015/73) and had been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments to minimize suffering in accordance with ARRIVE guidelines.

Addiction model

The heroin addiction model was applied to the addiction group ($n=15$) according to the previous studies (Lych et al., 2010). Heroin was obtained from The Forensic Medicine Institution in Turkey, ensuring all necessary legal permissions were secured (14103701/2015 – 427). After purification, heroin was dissolved in saline to a concentration of 3 mg/ml to enable precise intravenous administration.

To ensure controlled and consistent drug delivery, a jugular catheter was surgically implanted in each rat. Rats were anesthesized using intraperitoneal injection of ketamine/xylazine mixture (66 mg/kg ketamine hydrochloride and 1.33 mg/kg xylazine) to achieve effective anesthesia. Under sterile conditions, the catheter tip was inserted into the right external jugular vein and secured with sutures. The catheter was routed subcutaneously and exited on the rat's back, posterior to the scapula, to minimize discomfort and reduce the risk of infection.

In the days following the surgical procedure, the catheters were rinsed once a day with a cefazolin antibiotic solution in heparinized saline (Banna et al. 2010). The rats were cared for in quiet, humidity, and temperature-controlled environments, and each rat was kept in cages alone.

Following catheter implantation, heroin was administered intravenously twice daily for 10 days to replicate the escalation of drug intake observed in natural addiction processes (Doherty et al. 2013; Ammon et al. 2003). The dosing regimen started at 2 mg/kg per day and increased by 2 mg/kg every other day, reaching a total of 10 mg/kg on the tenth day. Doses were adjusted daily based on each rat's weight to ensure accurate dosing. The control group ($n=15$) received saline injections following the same catheter implantation procedure. No mortality occurred during the experimental period.

At the end of the heroin administration period, rats were euthanized. For subsequent analysis, brain tissues including the prefrontal cortex, hippocampus, ventral tegmental area (VTA), striatum and nucleus accumbens from both heroin-addicted and control rats were dissected as an overall structure by an experienced researcher using the same techniques for each animal and well-defined anatomical landmarks based on Paxinos and Watson Rat Brain Atlas (Paxinos and Watson 2007).

RNA and microRNA isolation from tissues

To ensure the acquisition of high-quality genetic material for analysis, total RNA was extracted from brain tissue samples. Approximately 50 mg of brain tissue from both addicted and control groups was homogenized in a sterile environment using RNAzol®RT and a homogenizer. This homogenization step facilitates effective cell lysis and RNA release. Following homogenization, the samples underwent centrifugation at 12,000 *g* for 15 min to eliminate cellular debris. RNA precipitation was then carried out according to the manufacturer's instructions to concentrate the RNA.

The yield and purity of the isolated RNA were evaluated using spectrophotometry (NanoDrop ND-2000c, Thermo Fisher Scientific, England) to ensure it met the quality standards required for downstream applications. Subsequently, microRNA's were isolated from the total RNA using a miRNA isolation kit targeting specific small non-coding RNA molecules essential for the study. Complementary DNA (cDNA) was synthesized from the isolated microRNAs using appropriate kits, following the manufacturer's protocols, to facilitate sequencing.

All cDNA samples were stored at -80ºC until analysis to preserve their integrity. Upon confirmation of RNA quality, the microRNA profiles of control and addicted rats were examined using an Illumina HiSeq™ 2500 sequencing system (Illumina, San Diego, CA, USA).

Next generation global miRNA sequencing and bioinformatics analysis

To investigate miRNA expression, we utilized a standardized sequencing approach to ensure accurate and reliable results. We began by constructing the miRNA library using the SMARTer smRNA-Sequence Library Prep Kit, which efficiently prepares small RNA samples for high-throughput sequencing. Sequencing was conducted on the Illumina NovaSeq 6000 platform, achieving a reading depth of 5 million reads per sample to enhance the detection and quantification of miRNAs.

Raw sequencing data were obtained in FASTA format and underwent quality assessment using the FASTQ Quality Trimmer, which employs a sliding window algorithm (Blankenberg et al. 2010). Removing adapter sequences specific to the SMARTer smRNA-Seq kit was essential to prevent interference with downstream analyses. Adapter trimming was performed using Cutadapt and Reaper software, followed by filtering reads based on quality scores to eliminate missing data and duplicates.

Cleaned and filtered reads were aligned to the reference rat genome using Bowtie1 alignment software, ensuring accurate matching to previously identified miRNAs. We employed miRDeep2 software for comprehensive data analysis. The MiRDeep2 Mapper module was used with default settings to map the cleaned miRNA reads to the reference genome, a critical step for identifying both known and novel miRNAs (Friedländer et al. 2012). The MiRDeep2 Quantifier module the reads mapped to known miRBase precursors, providing precise read counts for each miRNA (Fig. 1).

Further analysis involved aligning the mapped miRNA reads to miRNA precursors using SHiMPS alignment software to identify precursor regions involved in miRNA biogenesis. We analyzed changes in miRNA expression levels between control and addicted samples across different tissue region using DESeq2 and edgeR software. These tools allowed us to detect statistically significant differences by evaluating *p*-values and *p*-values (padj). Additionally, we assessed the 3P/5P ratios of miRNAs with altered expression using the RankProd statistic, offering insights into miRNA processing and functionality.

For library normalization and accurate interpretation of sequence reads, we utilized miRNA sequences from mirbase version 21.0, which includes data from current model organisms. This resource facilitated the prediction of precursor and mature miRNAs, ensuring robust and reliable results.

Statistical analysis

SPSS 22 package program was used for statistical analysis. First of all, the distribution of the data set was analyzed by Skewness-Kurtosis (data outside ± 1.5 were considered not normally distributed) and Shapiro-Wilk ($p<0.05$ data were considered not normally distributed) to determine whether the expression levels of the addicted and control groups were normally distributed. The 'Wilcoxon rank sum test' was used for the analysis of the data that were determined not to show normal distribution. Data were expressed as mean ± standard deviation and $p<0.05$ was considered significant.

Results

Differential expression analyses of striatum

In the striatum of addicted rats compared to the control rats, the expression levels of 6 miRNAs decreased and those of 59 miRNAs increased (Fig. 2). Of these altered miRNAs, eleven up-regulated and only one down-regulated miRNAs by heroin addiction were found with quantitative information according to the criteria of p value < 0.05 and log2 (fold change) > 1.5 in comparison with the control group.

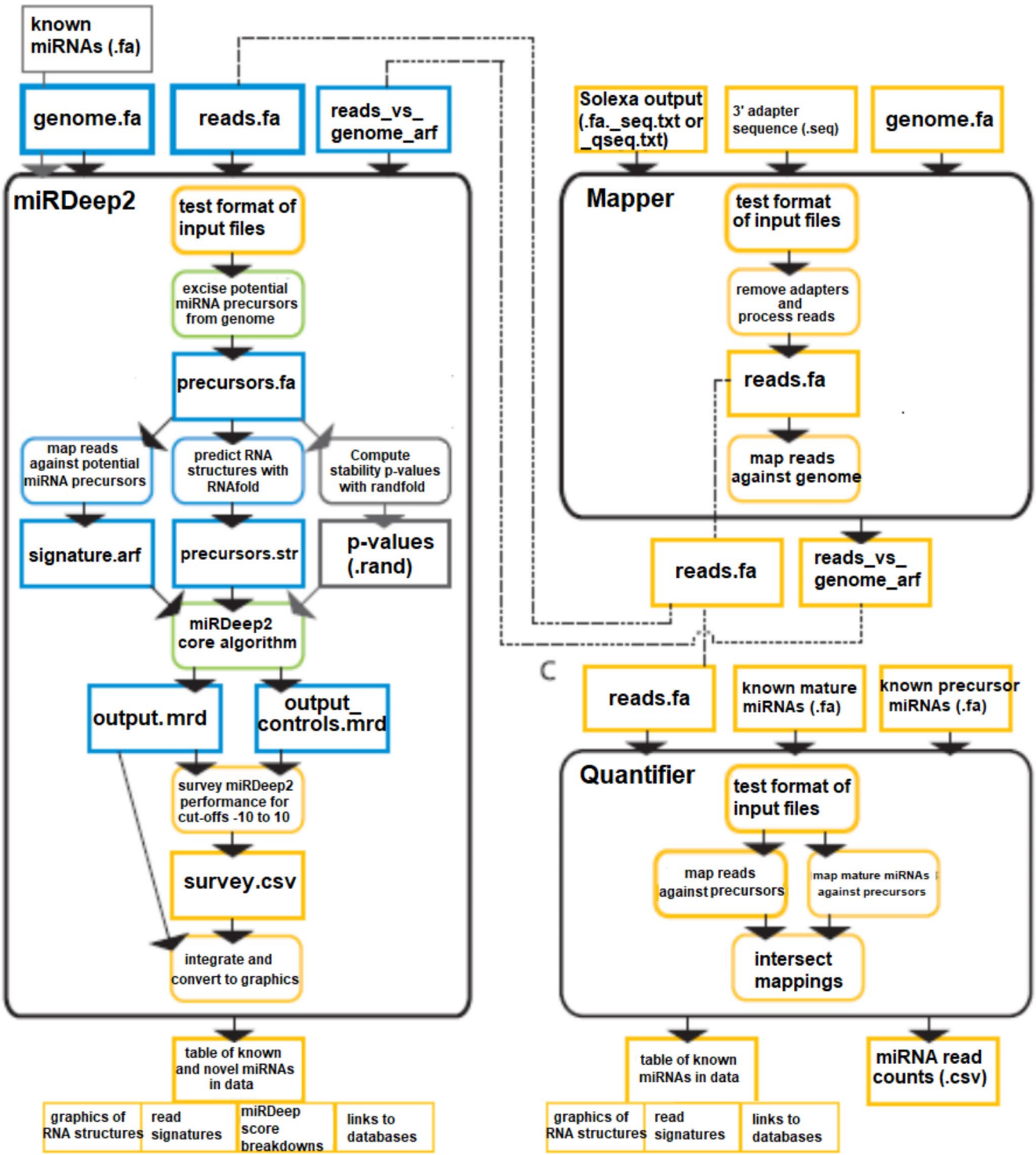


Fig. 1 The schematic diagram for microRNA analysis

Detailed information regarding the characteristics of these altered miRNAs can be found in Table 1; Fig. 2.

According to the fold change data of altered striatal miRNA's, the highest level (3.85 fold) was obtained in the mir-18a-5p expression of heroin-addicted rats compared to the control rats ($p = 0.0007$). In addition, the levels of mir-17-5p, mir-18a-3p, and mir-20a-5p in the heroin-addicted rats' striatum were above 3-fold higher than that of the control rats ($p = 0.003$, $p = 0.003$, and $p = 0.008$, respectively). On the other hand, in the striatum of the heroin-addicted rats, the expression of mir-450b-3p were significantly decreased

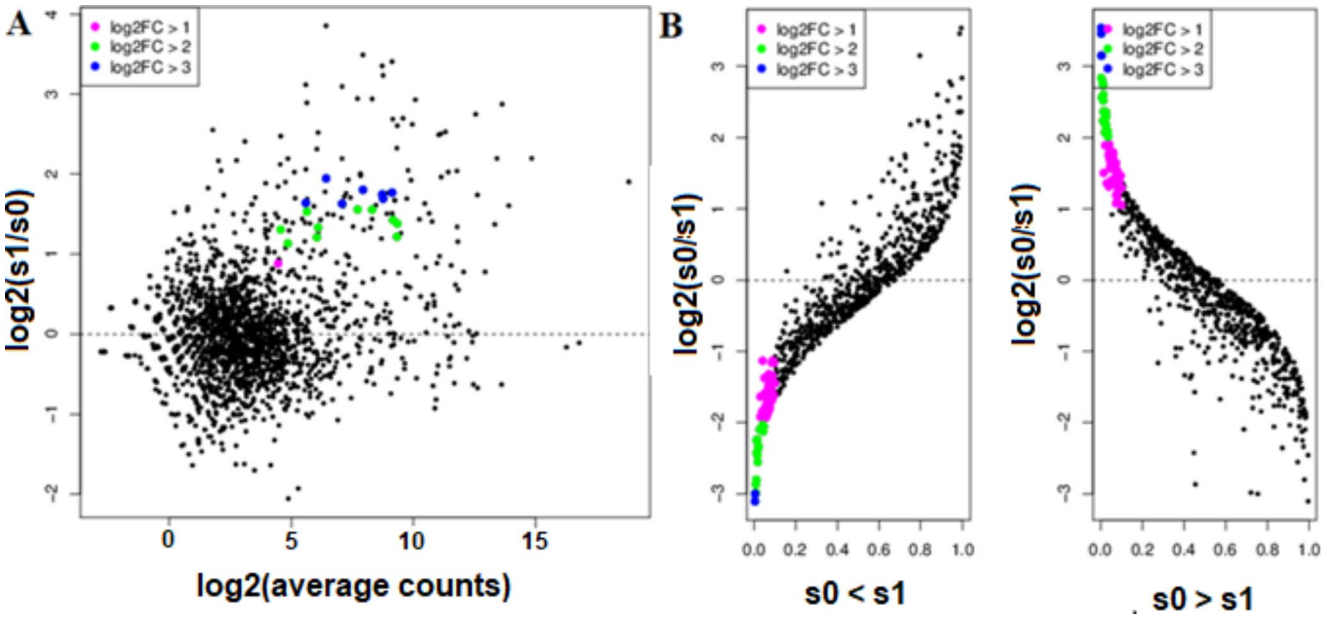


Fig. 2 Graph showing differentially expressed miRNAs in striatum tissue between S1 (addicted group) and S0 (control group) (**A**). Graph showing the variation in the proportions of mature 3p and 5p miRNAs derived from the same precursor miRNA in the striatum tissue S1 (treatment group) and S0 (control group) (**B**). Log_2Fold Change > 1, 2 or 3 are shown in pink, green, and blue, respectively

(1.64 fold) compared to that of the control rats ($p = 0.041$) (Table 1).

Differential expression analyses of hippocampus

In the hippocampus of addicted rats, significant alterations in miRNA expression levels were observed compared to control rats, with five miRNAs down-regulated, and 139 miRNAs up-regulated (Fig. 3).

Among these miRNAs, 41 up-regulated and no down-regulated miRNAs by heroin addiction were found with quantitative information according to the criteria of p value < 0.05 and log2 (fold change) > 1.5 in comparison with the control group. Detailed information regarding the characteristics of these altered miRNAs can be found in Table 1; Fig. 3.

As shown in Table 1, mir-153-3p had the highest expression level in the heroin addicted rats compared to the control rats ($p = 0.0002$). The 2-fold increased miRNA's of hippocampal tissue of the heroin-addicted rats were mir-130a-3p ($p = 0.0002$), mir-204-5p ($p = 0.0002$), mir-15b-5p ($p = 0.0002$), and mir-137-3p ($p = 0.0009$) (Table 1).

Differential expression analyses of nucleus accumbens

In the nucleus accumbens, 38 miRNAs were up-regulated in addicted rats compared to controls, with no miRNAs down-regulated (Fig. 4).

Among these increased miRNAs, 10 up-regulated miRNAs by heroin addiction were found with quantitative information according to the criteria of p value < 0.05 and log2 (fold change) > 1.5 in comparison with the control group. Detailed information regarding the characteristics of these altered miRNAs can be found in Table 1; Fig. 4.

In the nucleus accumbens of the heroin-addicted rat brain, mir-129-1-3p was significantly increased (2.32 fold) compared to that of the control rats ($p = 0.0001$). In addition, the expression of mir-3068-3p was increased as 2-fold in the heroin-addicted rats' nucleus accumbens compared to the control rats ($p = 0.0001$) (Table 1).

Differential expression analyses of ventral tegmental area

In the VTA, addicted rats showed increased expression levels of 109 miRNA and decreased levels of 3 miRNAs compared to controls (Fig. 4).

Among these miRNAs, 26 up-regulated and one down-regulated miRNA by heroin addiction were found with quantitative information according to the criteria of p value < 0.05 and log2 (fold change) > 1.5 in comparison with the control group. Detailed information regarding the characteristics of these altered miRNAs can be found in Table 1; Fig. 5.

As seen from the Table 1, the highest level of altered miRNA's was observed in the expression of mir-872-5p as a 2.40-fold in the heroin-addicted rats compared to the control rats ($p = 0.006$). 85 fold). In addition, the levels of mir-183-5p ($p = 0.001$), mir-20a-5p ($p = 0.009$), mir-872-3p ($p = 0.014$), mir-325-5p ($p = 0.007$), mir-379-5p ($p = 0.014$),

Table 1 The up-regulated and down-regulated miRNAs in striatum, hippocampus, nucleus accumbens, and ventral tegmental area of addicted rats compared to the control rats

Striatum			Hippocampus			Nucleus Accumbens			Ventral Tegmental Area		
miRNA	Fold change	*p* value	miRNA	Fold change	*p* value	miRNA	Fold change	*p* value	miRNA	Fold change	*p* value
miR-18a-5p	3,85	0,00067	miR-153-3p	2,45	0,00019	miR-129-1-3p	2,32	0,00012	miR-872-5p	2,40	0,00631
miR-17-5p	3,49	0,00311	miR-130a-3p	2,11	0,00019	miR-3068-3p	2,07	0,00012	miR-183-5p	2,31	0,00125
miR-18a-3p	3,12	0,00311	miR-204-5p	2,09	0,00016	miR-16-5p	1,98	0,00895	miR-20a-5p	2,18	0,00870
miR-20a-5p	3,10	0,00800	miR-15b-5p	2,09	0,00085	miR-124-3p	1,80	0,01079	miR-872-3p	2,13	0,01418
miR-106b-5p	2,94	0,01038	miR-137-3p	2,00	0,00840	miR-101a-3p	1,67	0,02609	miR-325-5p	2,11	0,00696
miR-301a-3p	2,94	0,01043	miR-410-3p	1,99	0,00019	miR-384-3p	1,62	0,00921	miR-379-5p	2,08	0,01445
miR-872-5p	2,89	0,00821	miR-124-3p	1,98	0,00039	miR-384-5p	1,59	0,01079	miR-340-5p	2,03	0,02099
miR-15a-5p	2,69	0,03005	miR-126a-3p	1,95	0,00102	miR-187-3p	1,56	0,01982	miR-34b-3p	1,99	0,01972
miR-106b-3p	2,60	0,03662	miR-879-5p	1,94	0,00259	miR-301a-3p	1,55	0,04081	miR-193a-3p	1,96	0,01799
miR-500-3p	2,47	0,02444	miR-384-3p	1,92	0,00617	miR-192-5p	1,52	0,01982	miR-126a-3p	1,94	0,02822
miR-339-5p	2,31	0,04447	miR-151-3p	1,91	0,00011				miR-30e-5p	1,92	0,02675
miR-450b-3p	-1,64	0,04133	miR-101b-3p	1,89	0,00198				miR-30b-5p	1,89	0,03102
			miR-181c-5p	1,89	0,00019				miR-128-3p	1,83	0,02789
			miR-98-5p	1,89	0,00069				miR-30c-5p	1,81	0,03615
			miR-30b-5p	1,86	0,00019				miR-16-5p	1,79	0,04427
			miR-652-3p	1,84	0,00016				miR-219a-5p	1,75	0,03186
			miR-381-3p	1,81	0,00142				miR-181b-2-3p	1,73	0,03598
			miR-181a-5p	1,80	0,00011				miR-1843a-5p	1,72	0,03858
			miR-192-5p	1,79	0,00142				miR-24-2-5p	1,68	0,03150
			miR-484	1,78	0,00037				miR-15a-5p	1,67	0,03812
			miR-99a-5p	1,78	0,00092				let-7d-5p	1,66	0,04417
			miR-92b-3p	1,74	0,00013				miR-27a-3p	1,63	0,04860
			miR-22-3p	1,73	0,00019				miR-181c-3p	1,61	0,04950
			miR-100-5p	1,73	0,00081				miR-323-3p	1,59	0,03026
			miR-300-3p	1,70	0,00069				miR-124-3p	1,59	0,04366
			miR-34c-5p	1,70	0,00033				miR-32-5p	1,50	0,04701
			let-7d-5p	1,69	0,00019				miR-103-1-5p	-1,51	0,00788
			miR-93-5p	1,68	0,00042						
			miR-29a-3p	1,68	0,00048						
			miR-26a-5p	1,66	0,00037						
			miR-128-3p	1,66	0,00016						
			miR-325-5p	1,62	0,03209						
			miR-25-3p	1,62	0,00110						
			miR-331-3p	1,61	0,00215						
			let-7b-5p	1,59	0,00021						
			miR-543-3p	1,59	0,01389						
			miR-338-5p	1,58	0,00294						
			miR-140-3p	1,58	0,00040						
			miR-27a-3p	1,57	0,01443						
			miR-326-3p	1,56	0,00337						
			miR-154-5p	1,56	0,03038						

and mir-340-5p ($p = 0.020$) in the heroin-addicted rats' VTA were 2-fold higher than that of the control rats. On the other hand, in the VTA of the heroin-addicted rats, the expression of mir-103-1-5p were significantly decreased (1.51 fold) compared to that of the control rats ($p = 0.008$) (Table 1).

Differential expression analyses of frontal cortex

As a result of the study, compared to the control group, there was no statistically significant change in the expression miRNA depending on the heroin addiction in the frontal cortex (Fig. 6).

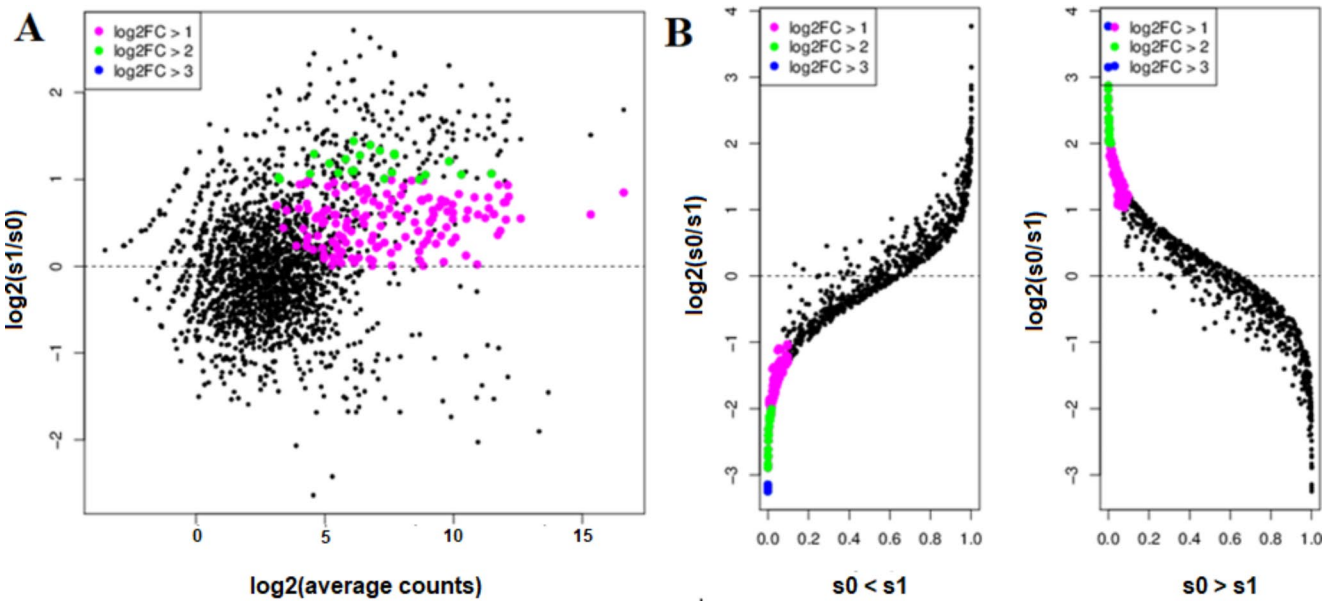


Fig. 3 Graph showing differentially expressed miRNAs in hippocampal tissue between S1 (addicted group) and S0 (control group) (**A**). Graph showing the variation in the proportions of mature 3p and 5p miRNAs derived from the same precursor miRNA in the hippocampal tissue S1 (treatment group) and S0 (control group) (**B**). Log_2Fold Change > 1, 2 or 3 are shown in pink, green, and blue, respectively

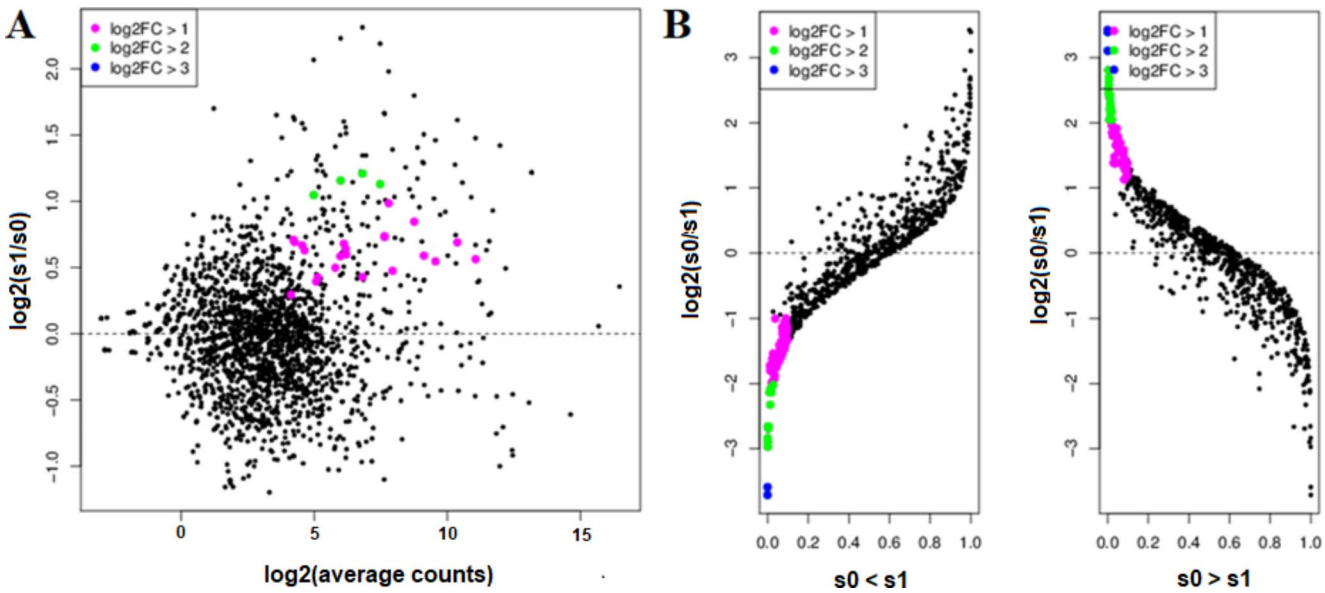


Fig. 4 Graph showing differentially expressed miRNAs in nucleus accumbens tissue between S1 (addicted group) and S0 (control group) (**A**). Graph showing the variation in the proportions of mature 3p and 5p miRNAs derived from the same precursor miRNA in the nucleus accumbens tissue S1 (treatment group) and S0 (control group) (**B**). Log2Fold Change > 1, 2 or 3 are shown in pink, green, and blue, respectively

Discussion

The development of new generation nucleic acid sequencing technologies facilitates obtaining information at the genome or transcriptome level from many biological samples simultaneously. Therefore, the bioinformatics interpretation of the large data sets created and the subsequent verification of these data in the laboratory environment accelerated the accumulation and development of knowledge at the molecular level. Herein, to provide new insights to elucidate the molecular mechanism of heroin addiction, we compared the levels of miRNA between the heroin addicted and control groups in different brain regions using next generation sequencing methods.

Substances used for drugs can cause changes in nuclear functions and transcription of certain genes by disrupting

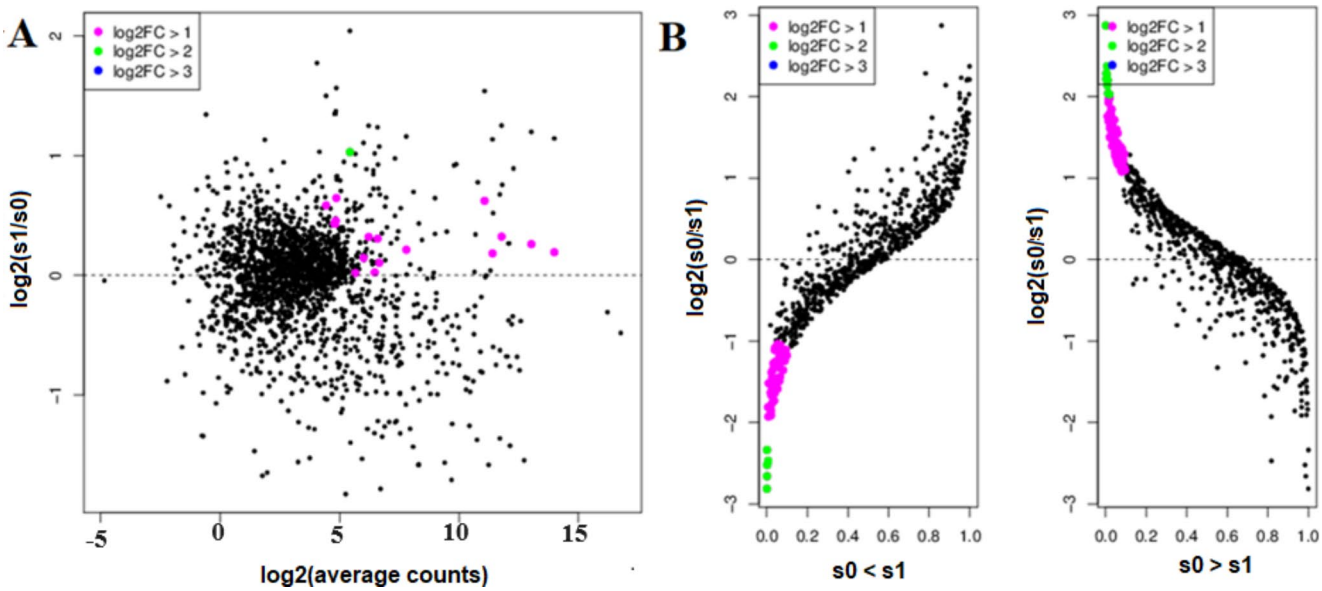
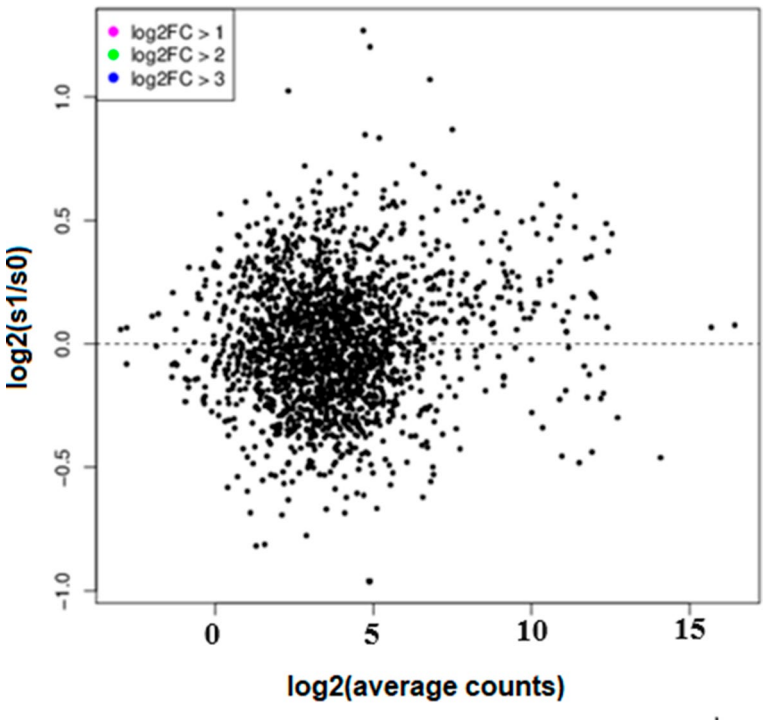


Fig. 5 Graph showing differentially expressed miRNAs in VTA tissue between S1 (addicted group) and S0 (control group) (**A**). Graph showing the variation in the proportions of mature 3p and 5p miRNAs derived from the same precursor miRNA in the VTA tissue S1 (treatment group) and S0 (control group) (**B**). Log2Fold Change > 1, 2 or 3 are shown in pink, green, and blue, respectively

Fig. 6 Graph showing differentially expressed miRNAs in the frontal cortex tissue



intracellular signal transduction. In previous studies, many miRNAs have been found to be responsible for the development of morphogenesis and substance dependence such as cocaine dependence (Hollander et al. 2010). The emerging regulatory role of miRNA were shown in the studies of addiction-related pathophysiological events in different regions of the brain and tissues (Occhipinti et al. 2023). For instance, in a previous study, the examination of the VTA by microarray method after methamphetamine use in rats showed that 78 miRNAs and 150 mRNAs were expressed at different levels (Bosch et al. 2015). In addition, Kim et al. (2018) found that 62 miRNAs were altered and exhibited differential expression patterns in the nucleus accumbens of morphine addicted samples. Among these altered miRNAs, the expression of miR-124 changed in the different brain regions by variable addicted substance abuse (Occhipinti et

al. 2023). Thus, it has been reported that acute morphine administration reduces the expression of miR-124 in the nucleus and cytoplasm of microglia, while in long-term morphine administration, the expression level of miR-124 increases and inhibits p65 and TRAF6-dependent TLR signaling (Qiu et al. 2015). In addition, cocaine administration upregulates the miR-124 expression in the striatum of mice (Forget et al. 2022). In our study, the expression of miR-124-3p upregulated in hippocampus (1.98-fold), nucleus accumbens (1.80-fold), and VTA (1.59-fold) of the heroin-addicted rats. According to previous studies, miR-124-3p is the most common miRNA in the neurons because of its cell division inhibiting activity (Yoo et al. 2009). The increase in the miR-124-3p expression due to heroin abuse may be related to its function in the neuronal differentiation by regulating cellular skeleton of the major nuclei involved in reward effects (Kaya et al. 2023; Nolan et al. 2020). However, miR-124-3p has an important role in maintaining the resting state of microglia. When miR-124-3p is overexpressed, microglia often enter the M2 polarized state that release anti-inflammatory mediators for neuroprotection (Ponomarev et al. 2011; Yang et al. 2019). Particularly, miR-124-3p have target genes functioning in neuroinflammation such as TNF receptor, STAT3, GSK3B, RELA, and BDNF. The interaction of miR-124-3p and these genes regulates the expression of pro- or anti-inflammatory proteins that cause further neuronal damage or neuronal growth and repair (Wang et al. 2023). For example, suppression of STAT3 inhibits astrogliogenesis and promote neurogenesis (Chen et al. 2013; Hong et al. 2023). In a drug addiction study, the transfer of miR-124-3p into astrocytes by exosomes results in an increase in the expression of GLT1, a glutamate transporter (Jarvis et al. 2020). The dysregulation of glutamate transporters leads to excessive extracellular glutamate levels, contributing to excitotoxicity and synaptic dysfunction. The observed upregulation of miR-124-3p in the nucleus accumbens and VTA may suggest an adaptive response to enhance GLT1 expression, thereby promoting efficient glutamate uptake and protecting neurons from excitotoxic damage (Men et al. 2019). In the hippocampus, increased miR-124-3p may support synaptic plasticity and cognitive functions that are often impaired in addiction (McNeill and Van Vactor 2012). Collectively, the upregulation of miR-124-3p in these key brain regions likely serves as a protective response aimed at counteracting the neuroinflammatory, excitotoxic, and synaptic disruptions induced by heroin. By modulating these critical pathways, miR-124-3p may enhance neural resilience and help maintain homeostasis within the brain's reward circuitry, thereby mitigating some of the adverse neuroadaptations associated with heroin addiction. On the other hand, in our study, the increase in the miR-500-3p expression may regulate the expression of GAD67 that metabolizes glutamate into GABA (Huang et al. 2016). GABAergic neurons are also vital for regulating the activity of dopamine. A reduction in GABA release leads to increased dopamine activity, enhancing reward signals and promoting addictive behaviors (Steffensen et al. 2006; Asada et al. 1997). Additionally, impaired GABAergic inhibition can result in excessive glutamate release, causing excitotoxicity and disrupted synaptic plasticity, which are associated with learning and memory deficits in addiction. It was also shown that chronic use of heroin can impairs transcriptional events associated with glutamatergic neurotransmission in the striatum of heroin addicts (Egervari et al. 2017). In our study, the upregulation of miR-500-3p due to heroin use may decrease GABA production by suppressing GAD67, thereby disrupting GABA's inhibitory control over dopamine and glutamate neurons in the striatum. In addition, it was found that miR-500-3p has a role in inflammatory process (Donate et al. 2013). These results suggest that, heroin addiction may alter brain as a neuro-adaptation for the substance abuse for proper functioning against to heroin-mediated neuroinflammation (Guzel et al. 2018) and generation of the seeking behavior due to excess glutamate. On the other hand, miR-106b-5p and miR-106b-3p level was shown to be increased in the striatum, which was previously suggested as a state of chronic inflammation in epileptic seizures (An et al. 2016). Chronic long-term administration of opioids, including heroin, induces glial activation and increases plasma and brain pro-inflammatory cytokines (Chen et al. 2012; Butelman et al. 2024). Elevated levels of inducible nitric oxide synthase (iNOS) during opiate addiction have also been implicated in neuroplastic changes that facilitate the development of opioid tolerance and dependence (Chen et al. 2012). Furthermore, previous studies also demonstrated that miR-106b promotes neuroinflammation by upregulating iNOS, thereby increasing nitric oxide production and contributing to microglial activation and neuronal degeneration (Yu et al. 2021). Additionally, miR-106b-5p's upregulation has been associated with oxidative stress and apoptotic pathways in ischemic brain injury, further implicating it in the exacerbation of neuroinflammatory responses (Neag et al. 2022). Therefore, our findings suggest that heroin addiction may exacerbate neuroinflammation through the modulation of miR-106b expression. In addition, the increased levels of miR-106b-5p and miR-106b-3p in the in reward and addiction circuitry contribute to the progression of heroin addiction by neuroadaptation mechanisms through iNOS-related neuroplastic changes.

In addition, the level of these miRNAs increased in the psychiatric conditions like schizophrenia and autism, and neurodegenerative diseases like Alzheimer's disease and Parkinson disease (Moreau et al. 2011; Stott et al. 2023; Xie

et al. 2022; Segaran et al. 2021). Most of these disease conditions may cause psychosis, that is a collection of symptoms like delusions and hallucinations that occur together over a period of time similar to substance-induced psychosis occurred by alcohol or other drug use (Moreno-Küstner et al. 2018). In literature, some microRNAs were determined as biomarkers for understanding and addressing of cognitive deficits in psychosis or onset of psychosis (Zhang et al. 2023a, b). In the current study, 14 of upregulated heroin addiction related miRNAs (miR-181b, miR-30e, miR-124-3p, miR-193a, miR-29a-3p, miR-26a, miR-15b, miR-652, miR-137, miR-22-3p, miR-16b-3p, miR-16b-5p, miR-17, and miR-103) were also associated with psychosis in previous studies related to psychiatric diseases such as schizophrenia and bipolar disorders (Zhang et al. 2023a, b; Tonk et al. 2024; Szwajca et al. 2024; Shafiee-Kandjani et al. 2023; Thomas and Zakharenko 2021; Grosu et al. 2023). In these studies, especially miR-103 associated with conversion to psychosis, as seen an upregulation it in VTA of our heroin-addicted rats (Zheutlin et al. 2017; Jeffries et al. 2016).

Furthermore, one of the increased miRNAs in the striatum of our heroin-addicted rats was miR-339-5p that has previously been found to be upregulated in alcohol-induced neuroinflammation through NF-κB pathway to inhibit pro-inflammatory cytokines (Zhang et al. 2014). As a pro-inflammatory miRNA, miR-301a was also overexpressed in inflammation-related diseases like facilitating inflammation-associated tumorigenesis in glioblastoma by activating NF-κB and STAT3 (Ma et al. 2015; Sun et al. 2021). The nearly 3-fold increase of miR-301a expression in the striatum and 1.55-fold increase in the nucleus accumbens in our addicted rats may suggest that heroin produces a persistent inflammation to give harm to brain regions at the latter times.

In the present study, the heroin-related most dramatic increase was observed in the level of striatal miR-18a-5p. In addition, the other arm (miR-18a-3p) generated from the miR-18a locus also significantly increased (3.12-fold) in the striatum. The upregulation of miR-18a-5p was detected in stress conditions that regulates the expression of glucocorticoid receptor and serotonin transporter in the hippocampus and VTA (Uchida et al. 2008; Zurawek et al. 2017). In addition, it was suggested that miR-18a-5p expression is related to neurogenesis, synaptic remodeling, and oxidative stress (Taylor et al. 2019). Furthermore, miR-872-5p, another miRNA involved in stress response (Zurawek et al. 2017), was upregulated in the striatum and ventral tegmental area of heroin-addicted rats. It was concluded that increased expression of miR-872-5p regulates forkhead box protein O3a (FOXO3a) expression to promote neural stem cell proliferation (Li et al. 2023). On the other side, overexpression of miR-15a-5p, as observed in the striatum and VTA of our heroin-addicted rats, suppresses the apoptosis through ERK1/2 pathway (Li et al. 2020; Liu et al. 2020a, b). In addition, targeting of NR2B (an NMDAR subunit) by miR-15a-5p may be related to the heroin addiction mechanism (Li et al. 2020). Our results may indicate that high levels of miR-18a-5p and miR-872-5p are necessary for neuroprotection and neural repair against heroin addiction as an adaptation mechanism as recently observed for alleviating early brain injury (Zhang et al. 2023a, b). In addition, in the current study, miR-17-5p highly upregulated (nearly 3.5-fold) in the striatum of the heroin-addicted rats. It was known that the expression of miR-17-5p is abnormal in various age-associated disorders, such as Alzheimer's disease, vascular and frontotemporal dementia (Ning et al. 2022; Hu et al. 2020; Piscopo et al. 2018). Due to its role in neurovascular protective effects, we can suggest that heroin addiction may increase angiogenesis in the striatum through miR-17-5p expression (Pan et al. 2023). Furthermore, the miR-20a-5p upregulated in heroin-addicted rats compared to the control rats in the both striatum (nearly 3-fold) and VTA (2-fold). miR-20a-5p functions in regulation of cell apoptosis (Qin et al. 2021) and hypoxia-induced autophagy (Wang et al. 2015). Previously, it was found that miR-20a-5p was one of the upregulated miRNAs after status epilepticus in the hippocampus (Sun et al. 2013). In the ischemic and hypoxia models, miR-20a-5p was shown to downregulate NeuroD1 and Kif5A, which are required for the growth of dendrites, and the elimination of neurotoxic substances, respectively (Zhong et al. 2021; Cao et al. 2022). Therefore, our results may suggest that heroin abuse activates the apoptotic pathways in addition to activation of neurogenesis in the rat striatum and VTA.

The most dramatic alterations as heroin-addicted upregulation of miRNAs were noted in the striatum of rats. This upregulation was related to either inflammation or an adaptation against to neuroinflammation in addition to increase in the apoptosis. This result may be related that the striatum has the ability of being a core motor control center to form cellular and molecular adaptations on exposure to addictive drugs (Berke and Hyman 2000; Choi et al. 2020). For example, previous studies performed in the striatum showed that acute heroin consumption can result a rapid increase of dopamine in animals while chronic heroin use can decrease the dopamine transporter's levels in humans (Marinelli et al. 1998; Xu et al. 2017a, b). Therefore, they suggested that the use of addictive drugs (including heroin) is associated with dopaminergic activation in the striatum (Schultz et al. 1998). These changes may also be related to the altered miRNAs as shown in our study.

Previous human studies also showed that heroin consumption could produce molecular changes in the hippocampus of adolescents and young adults (Choi et al. 2020). In our study, most dramatic changes in the miRNA profiles

of heroin-addicted rats were observed as upregulation of miR-153-3p, miR-130a-3p, miR-204-5p miR-15b-5p, and miR-137-3p as nearly 2-fold. In contrast, researchers also found that downregulation of miR-153-3p and miR-137-3p are nominally associated with cocaine dependence (Cabana-Domínguez et al. 2018). In other studies, it was also showed that miR-153-3p could cause neurodegeneration in the brain through PI3K/GSK3 insulin signaling pathway on the exposure of adverse conditions like cigarette smoking or hypoxia (Fu et al. 2022; Sun et al. 2023). In addition, upregulation of miR-137-3p can result neurotoxicity and impairments in neurons (Tang et al. 2018; Chen et al. 2017). Another miRNA acting on the PI3K/GSK3 pathway is miR-130a-3p that was also increased in our heroin-addicted rat hippocampus (Li et al. 2022). These upregulation in the miR-130a-3p expression that decreases the expression of Acsl4, a member of the acyl-CoA synthetases (ACS) family that has neuroprotective and anti-inflammatory effects in the brain (Cui et al. 2021; Jia et al. 2019). Therefore, upregulation of miR-130a-3p increased the levels of active forms of AKT, GSK-3β and PI3K promoting neuronal differentiation. However, there are several neuroprotective functions of miR-130a-3p on the progression of neurodegenerative diseases or regulation of neurotransmitter synthesis (Zhang et al. 2017; Greco and Rameshwar 2007; Wang et al. 2021). A recent study suggests that the neuroprotection by miR-130a-3p on hippocampal tissue was related to the decrease in the expression of death-associated protein kinase 1 (DAPK1), which controls the cell cycle, apoptosis, and autophagy (Wang et al. 2021).

On the other hand, in heroin-addicted rats, we observed an overexpression of miR-15b-5p that could decrease cell proliferation, induce apoptosis and produce cytotoxic activities (Luo et al. 2017). There are also several studies in the literature showing the relation between upregulation of miR-15b-5p and ageing (Pinto-Hernandez et al. 2023).

While morphine administration decreased the hippocampal level of miR-204-5p, heroin addiction increased the hippocampal level of miR-204-5p in our study (McAdams et al. 2015). It was also proposed that miR-204-5p could be related to the cytotoxicity and impairment in the learning by inhibiting the TrkB/Akt pathway through BDNF (Liu et al. 2020a, b). The mechanism of impaired learning and memory by upregulation of miR-204-5p was also showed by the further inhibition of the target gene *EphB2* and its downstream signaling pathway, NMDAR-ERK-CREB-Arc, which may be explain learning and memory problems in substance abuse (Liu et al. 2023). In addition, it was found that miR-204-5p ameliorates neurological injury in a stroke by targeting to EphA4/PI3K/AKT pathway (Shi et al. 2023). These studies pointed the critical role of miR-204-5p in the synaptic plasticity of rat hippocampal neurons (Guan et al. 2023). Therefore, the upregulation of the miR-204-5p and miR-130a-3p in heroin-addicted rats may alter the existing brain to adapt it to the new conditions related to the substance abuse. These alterations may also be related to the association between heroin addiction and upregulation in hippocampal LTP that follow impairments of synaptic plasticity (Bao et al. 2007). Based on previous studies and our current data, we may speculate that heroin addiction promotes LTP in the hippocampus resulting to alterations in the synaptic plasticity for neuroadaptation.

In previous studies, the size of the nucleus accumbens in heroin-dependent patients was decreased compared to that of healthy controls, indicating heroin-related apoptosis or neurotoxicity (Seifert et al. 2015). In the current study, we observed that only two miRNAs upregulated nearly 2-fold in the heroin-addicted rats' nucleus accumbens that has essential role in behavioral changes related to addiction and is the target of many addictive drugs (Shabashov et al. 2012). One of them was miR-129-1-3p whose detrimental role in the dopaminergic neurons as increase in the apoptosis was observed in methamphetamine use (Deng et al. 2022). The other one was miR-3068-3p which function in glutamate-induced excitotoxicity through acting on KCNIP4, a voltage gated potassium channel (Su et al. 2020). The expression of miR-3068-3p was also studied in the methamphetamine use and they found that it has a function in regulating the methamphetamine sensitization (Liu et al. 2021a, b).

Lastly, VTA is a critical place of dopamine involved in heroin-conditioned immunomodulation. In VTA, heroin addiction in rats increased the expression of miR-872-5p/miR-872-3p) which is involved in stress response (Zurawek et al. 2017) and miR-20a-5p which functions in regulation of cell apoptosis (Qin et al. 2021) as like in the striatum. In addition to these miRNAs, approximately 2-folds increase was also observed in the miR-183-5p, miR-325-5p, miR-379-5p, and miR-340-5p expressions of the VTA. The function of miR-183-5p was noted as regulation of neurite outgrowth and neuroprotection of dopaminergic neurons (Roser et al. 2018). In the repeated methamphetamine injections, increased miR-183-5p expression and decreased glucocorticoid receptor gene expression were observed previously (Song et al. 2022). On the other hand, the miR-325-5p expression was not well studied in the literature. In some studies, the targets of miR-325-5p were determined as C-C motif chemokine ligand 2 (CCL2) and histone deacetylase 3 (HDAC3) suggesting its function on immunomodulation and epigenetic alterations by histone de-modelling (Fanliang 2023; Wu et al. 2019). The upregulation of miR-379-5p inhibited the viability, migration, and invasion of the neuronal cells (Yang et al. 2021). In addition, it was found that miR-379-5p directly bound to MAP3K2 that activates the JNK/c-Jun signaling pathway and suppress the

neuroprotective event (Mo et al. 2022). However, the elevation of miR-340-5p decreased p38 expression, subsequently inhibiting the inflammatory reaction suggesting for neuroadaptation to substance use (Qian et al. 2020). These previous studies suggest that heroin addiction may alters stress response and neuroinflammation in the VTA of the rats.

Interestingly, it was not found any heroin-related alterations in the miRNA expressions of prefrontal cortex that is believed to engage decision-making and impulsive control in addiction. In the literature, a limited number of studies were performed for the effects of heroin on the alterations of miRNAs of prefrontal cortex (Zanda et al. 2023a). On the contrary to our results, Zanda and her colleagues found that 55 miRNAs were altered due to heroin craving. In that study, the animals were in 21-day heroin abstinence and the high dose and low dose heroin usage were compared. In another study performed by Zanda et al. (2023b), they concluded that heroin self-administration may regulate 77 miRNAs in the orbitofrontal cortex of rats in the 2-day heroin abstinence. The lack of any change in the miRNA expressions as seen in our study and the abstinence-dependent alterations in the miRNA as seen in previous studies may highlight the unique vulnerabilities of prefrontal cortex during periods of heroin cessation. This can be explained by some neurochemical alterations. During long-term substance use, neuroadaptative modifications occur in the reward circuits involving dopamine, glutamate, and gamma-aminobutyric acid (Koob and Volkow 2010). Upon withdrawal, the abrupt lack of these substances can lead to neurochemical imbalances that disproportionately affect the prefrontal cortex. Therefore, in our study, the interaction between prefrontal cortex and its compensatory mechanisms against to heroin-related damage may mask potential changes in the prefrontal cortical miRNAs. Although our findings may appear counterintuitive in light of the prefrontal cortex's established role in addiction, additional research is necessary to investigate the effects of heroin on molecular changes in the prefrontal cortex.

In the present study, heroin addiction led to upregulation of different miRNAs in the striatum, hippocampus, Nucleus accumbens and VTA. However, there was a limited number of miRNAs, which decreased due to heroin use. Most of the upregulated miRNAs have a role in the neuroinflammation, apoptosis and in the stress response. However, we also observed a significant increase in the miRNAs related to the neuroprotection or synaptic plasticity to adapt the brain to new environment for fighting heroin-dependent impairments. Actually, reorganization due to long-term heroin abuse may affect variety of cellular functions in the brain, such as cellular signaling, apoptosis, and intracellular trafficking. Therefore, we can conclude that the biological response to heroin might inherently favor the up-regulation of certain miRNAs as part of adaptive or compensatory mechanisms in response to stress or neurochemical alterations to restore homeostasis or mitigate the impact of the addiction. However, further investigations would be necessary to make our conclusions more reliable for alterations of the levels of miRNAs due to heroin abuse.

In summary, miRNAs may be critical regulators for formation of heroin addiction-related molecular damage in the different part of the brains to disrupt several behavioral or functional mechanisms. Therefore, a miRNA therapy including small inhibitory molecules against to these altered specific miRNAs determined by computational tools for determination of specific pathways could potentially mitigate the heroin-dependent molecular alterations in the brain as previously shown in literature (Diener et al. 2022; Gowen et al. 2021; Rao et al. 2018). These findings highlight the potential of miRNAs that function in neuroinflammation (miR-124-3p, miR-500-3p, miR-106b, miR-339-5p, and miR-301a miR-124-3p) as therapeutic targets for developing interventions to mitigate the neurotoxic effects of heroin.

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Author contributions All authors contributed to the study conception and design. Material preparation and data collection were performed by Ertugrul Kilic, Sadrettin Pence, Mustafa Guzel, Yalcin Buyuk, and Sibel Kuras. The data analysis was performed by Halime Hanım Pence and Birsen Elibol. The first draft of the manuscript was written by Halime Hanım Pence and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability All data supporting the findings of this study are available within the paper. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This study was approved by the Committee for Animal Research Ethics in Istanbul Medipol University (30.09.2015/73).

Consent for publication Not applicable.

Competing interests All persons gave their informed consent prior to their inclusion in the study. The authors declare that they have no conflict of interest.

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