

Long term and excessive use of 900 MHz radiofrequency radiation alter microRNA expression in brain

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Abstract

Purpose: We still do not have any information on the interaction between radiofrequency radiation (RF) and miRNA, which play paramount role in growth, differentiation, proliferation and cell death by suppressing one or more target genes. The purpose of this study was to bridge this gap by investigating effects of long-term 900 MHz mobile phone exposure on some of the miRNA in brain tissue.

Materials and methods: The study was carried out on 14 Wistar Albino adult male rats by dividing them into two groups: Sham ($n = 7$) and exposure ($n = 7$). Rats in the exposure group were exposed to 900 MHz RF radiation for 3 h per day (7 days a week) for 12 months (one year). The same procedure was applied to the rats in the sham group except the generator was turned off. Immediately after the last exposure, rats were sacrificed and their brains were removed. rno-miR-9-5p, rno-miR-29a-3p, rno-miR-106b-5p, rno-miR-107 and rno-miR-125a-3p in brain were investigated in detail.

Results: Results revealed that long-term exposure of 900 MHz RF radiation only decreased rno-miR107 ($\text{adj}P^* = 0.045$) value where the whole body (rms) SAR value was 0.0369 W/kg. However, our results indicated that other microRNA evaluated in this study was not altered by 900 MHz RF radiation.

Conclusion: 900 MHz RF radiation can alter some of the miRNA, which, in turn, may lead to adverse effects. Therefore, further studies should be performed.

Keywords: Mobile phones, 900 MHz RF radiation, miRNA, brain, diseases

Introduction

Wireless technological equipment has led to a dramatic increase in electromagnetic pollution and man-made sources have by far exceeded those of natural origin. Based on the data released by the International Telecommunication Union

(ITU 2014) the number of mobile-cellular subscriptions worldwide is approaching the number of people on earth and mobile-cellular subscriptions will reach almost 7 billion by end of 2014 (ITU 2014). Therefore public opinion focused on the adverse effects of these technologies especially on mobile phones.

As it is known, the mobile phones operate at Global System for Mobile (GSM) modulated frequencies, in Europe in the 900 MHz and 1800 MHz bands (International Commission on Non-Ionizing Radiation Protection [ICNIRP] 2009). The most widely accepted mechanism of interaction between radiofrequency radiation (RF) and biological systems is based on tissue heating that occurs when tissue or total body temperature increases for more than 1°C overloading cell thermoregulatory capacity. However, effects happening at non-thermal level have still to be investigated and very little is known about their molecular mechanism. On the other hand, it should be noted that the International Agency for Research on Cancer in 2011 classified RF electromagnetic fields as possible carcinogen to humans, opening this field for further investigation (IARC 2011).

Living organism is a complex electrochemical system where electron transfer is recognized as one of the essential requirements for communication between molecules (Kovacic and Somanathan 2010). Therefore, to be knowledgeable about operation of the system is very important to understand communication of cellular system. One of the recent and popular parameters to understand cell system is microRNAs (miRNA).

miRNA are small and non-protein-coding RNA molecules. They play critical roles in growth, differentiation, proliferation and cell death by suppressing one or more target genes. More than 50% of miRNA are found in cancer-associated regions of the genome or in fragile sites; this suggests that miRNA have important roles in the pathogenesis of neoplasias (Tunalı and Tiryakioglu 2010). It was also stated that the

discovery of miRNA has revealed an unexpected and spectacular additional level of fine tuning of the genome on how genes were used again and again in different combinations to generate the complexity that underlies, for instance, the brain. Several intriguing studies have linked miRNA as major regulators of the neuronal phenotype, and implicated specific miRNA in the regulation of synapse formation and plasticity. Dysfunction of miRNA pathways is also slowly emerging as a potentially important contributor to the pathogenesis of major neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (Strooper and Christen 2010). Therefore, miRNA represent new stars in the gene regulation galaxy, and there is a strong interest among researchers in different fields to understand their mechanism of action and to identify their targets (Sevignani et al. 2006).

Most of the studies performed on the interaction between radiation and miRNA have been usually focused on the effects of ultraviolet and ionizing radiation (Simone et al. 2009, Zhou et al. 2012). However, research into the interaction between RF radiations emitted from mobile phones and microRNA, especially on the interaction between 900 MHz RF radiation and brain, is not available yet. Therefore, the aim of this study was to investigate the effect of long-term exposure of 900 MHz RF radiation, which is widely used in daily life, on some miRNA in brain. In this study, effects of long-term 900 MHz radiofrequency exposure on mo-miR-9-5p, mo-miR-29a-3p, mo-miR-106b-5p, mo-miR-107 and mo-miR-125a-3p were observed in rat brain.

Material and methods

Subjects and animal care

Fourteen Wistar Albino adult male rats with initial average weight of 300 ± 50 g were acquired from the Medical Science Application and Research Center of Dicle University. The rats were fed with standard pelleted food (Tavas Inc., Adana, Turkey) in a standard Plexiglas cage. They were separated equally into two groups such as sham exposed ($n = 7$), and exposure ($n = 7$), and kept on a 14/10 h light/dark schedule. During the study, the ambient temperature (22°C) and the relative humidity (45%) were maintained in the normal range for these animals. All animal procedures were in agreement with the Principles of Laboratory Animal Care and the rules of Scientific and Ethics Committee of Dicle University Health Research Center.

Exposure and field measurements

A GSM signal generator (900 PM10 type Everest Comp., Adapazari, Turkey), which produces 900 MHz band RF waveform identical to the one in mobile phones was used in the study to expose the rats. Emitted power (omnidirectional on the plane perpendicular to the antenna axis) of the generator was fixed during the exposure. The antenna of the generator was equivalent to that of a typical mobile phone. The rats were confined in a Plexiglas carousel and exposed to 900 MHz RF exposure emitted from the generator. The carousel was surrounded with electromagnetic absorber material backed by metal to isolate outdoor electromagnetic fields from the test set-up during the study duration of 12 months. The

experimental set-up is illustrated in Figure 1. Power density and the electrical field were measured by field probe EMR 300 (Narda, Pfullingen, Germany).

The rats in the experimental group were exposed to RF radiation 3 h per day (7 days a week) for 12 months. For the sham group, the rats were placed in the carousel and the same procedure was applied to the rats (3 h per day, 7 days a week for 12 months), except that the generator was turned off, i.e., no RF signal was present. The antenna of the generator was placed at the center of the Plexiglas Carousel to provide ideal exposure conditions. The distance of the antenna from the head of the rats was 1 cm. All rats were kept under identical conditions for 12 months with free access to food and water. At the end of 12th month, the rats were intra-peritoneally administered a combination of 6 mg/kg of 2% xylazine hydrochloride (Rompun) and 75 mg/kg ketamine hydrochloride (Ketalar) for anesthesia. Afterward, the brain of each rat was removed and expression of some miRNA such as rno-miR-9-5p, rno-miR-29a-3p, rno-miR-106b-5p, rno-miR-107 and rno-miR-125a-3p was determined. All measurements, analysis and evaluations were performed by persons who were unaware of the groups so that the subsequent analysis could be performed blind.

Specific absorption rate (SAR) measurement

In our experimental set-up, the electromagnetic field values were measured with an Electric-field probe, while the transmitter was operating, then, these measured values were used in the electromagnetic field solver to find the field

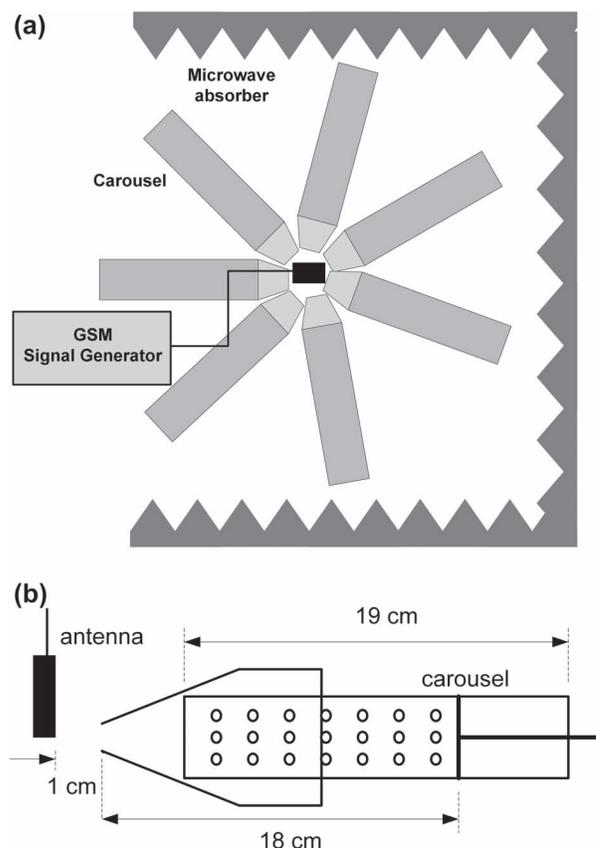


Figure 1. Experimental set-up, (a) top view, (b) side view for one carousel.

distribution inside the rat. Simulations were performed using CST Microwave Studio, an electromagnetic field solver based on finite integration technique (FIT). FIT is similar to a finite difference time domain (FDTD) technique, but it employs discretization on general non-orthogonal grids using integral form of Maxwell's equations rather than differential forms. Charge and energy conservation inherit to Maxwell's equations are preserved with FIT, which leads to very stable numerical results in time-domain. The Voxel (volumetric pixel) rat model, which was formed using computerized tomography scans of a rat, was used in the electromagnetic field simulations. The simulation model consisted of electric field distribution inside and around the rat. Simulated field values were consistent with measured electric field data which were obtained with field probe. In SAR calculations, a representative rat with 320 g weight which corresponds to average weight in the exposure group was used. Whole body maximum point SAR value is expected to exhibit a variation of ± 0.121 (W/kg) over the rats in the exposure group.

RNA extraction

Total RNA was extracted from rat brain tissue using Tri-Reagent (Sigma).

Reverse transcriptase PCR reactions (RT-PCR)

Reverse transcriptase reactions contained 5 μ l of extracted total RNA, 50 nM stem-loop RT primer, 1 \times RT buffer, 0.25 mM each of dNTPs, 50 units of modified M-MuLV Reverse Transcriptase (Thermo Scientific, Vilnius, Lithuania), 25 units of RiboLock RNase inhibitor (Thermo Scientific, Vilnius, Lithuania) and nuclease-free water to a total reaction volume of 15 μ l. The reaction was performed on an automated Thermal Cycler (Techne Flexigene, Cambridge, UK). RT-PCR conditions for 30 min at 16°C, 30 min at 42°C, 5 min at 85°C and then held at 4°C.

Quantitative-Comparative CT ($\Delta\Delta C_T$) Real-time PCR

Quantitative-comparative C_T ($\Delta\Delta C_T$) Real-time PCR was performed in an ABI Prism 7500 Real-Time PCR System (Applied

Biosystems) using the SDS 2.0.6 software. The specific primers and fluorogenic ZNA™ probes (Paris et al. 2010) for the microRNA were designed using Primer Express 3.0 software (Applied Biosystems) and are listed in Table I. The rno-miR-26b-5p was used as an endogenous control microRNA. The mixed RNA created from the sham group were used as a Reference RNA sample. Primers and probes were purchased from Metabion International AG, D-82152 Martinsried/Deutschland. The 25 μ l PCR included 3 μ l RT-PCR product, 12.5 μ l of 2X TaqMan Universal PCR Master Mix (Applied Biosystems), 900 nmol of each primer (Primer F and Universal Primer R) and 200 nmol TaqMan® probe. The reactions were incubated in a 96-well plate of preincubation at 50°C for 2 min and at 95°C for 10 min, followed by 40 cycles at 95°C for 15 sec and at 60°C for 90 sec. Amplifications and analysis were performed in an ABI Prism 7500 Real-Time PCR System (Applied Biosystems), using the SDS 2.0.6 software for allelic discrimination (Applied Biosystems). All reactions were run in triplicate.

Statistical analysis

The data were processed and analyzed using the statistical package SPSS-11.5 for Windows. Normality assumption of $2^{-\Delta\Delta C_T}$ values was checked by Shapiro Wilk test. Since the normality assumption of $2^{-\Delta\Delta C_T}$ for miR125a-3p was not met, the comparison between groups was performed using Mann-Whitney U test. On the other hand, normality assumption of $2^{-\Delta\Delta C_T}$ for mir9-5p, mir29a, mir107, mir106b-5p, miR107, the comparisons between groups were performed using independent *t*-test. Descriptive statistics for $2^{-\Delta\Delta C_T}$ values were expressed as mean, standard deviation, median, first quartile (25th percentile) and third quartile (75th percentile). Box-plot graph was used to represent data distribution of mir9-5p, mir29a, mir107, mir106b-5p, miR107 and miR125a-3p variables according to the groups. Significant differences (two-tailed *p*) less than 0.05 were regarded as significant. However, the *p* values given in Table II are Benjamini-Hochberg adjusted *p* values.

Table I. Primer/probe sequences of the miR analyzed by quantitative RT-PCR.

miR name	Primer/probe sequence**
rno-miR-26b-5p	rno-miR-26b-5p-RT, 5'-GTCGTATGCAGTGCAGGGTCCGAGGTATTTCGACTGCATACGACACCTAT-3' rno-miR-26b-5p-F, 5'-GCCGCTTCAAGTAATTCAGG-3'
rno-miR-9-5p	rno-miR-26b-5p-PR, 5'-FAM-TG(pdC)ATA(pdC)GA(pdC)A(pdC)CTATCC-ZNA4-BHQ-1-3' rno-miR-9-5p-RT, 5'-GTCGTATGCAGTGCAGGGTCCGAGGTATTTCGACTGCATACGACTCATA-3' rno-miR-9-5p-F, 5'-GCCGCTCTTTGGTTATCTAGCT-3'
rno-miR-29a-3p	rno-miR-9-5p-PR, 5'-FAM- TG(pdC)ATA(pdC)GA(pdC)T(pdC)ATA(pdC)AG-ZNA4-BHQ1-3' rno-miR-29a-3p-RT, 5'-GTCGTATGCAGTGCAGGGTCCGAGGTATTTCGACTGCATACGACTAACC-3' rno-miR-29a-3p-F, 5'-GCCGCTAGCACCATCTGAAAT-3'
rno-miR-106b-5p	rno-miR-29a-3p-PR, 5'-FAM- TG(pdC)ATA(pdC)GA(pdC)TAA(pdC)CGAT-ZNA4-BHQ1-3' rno-miR-106b-5p-RT, 5'-GTCGTATGCAGTGCAGGGTCCGAGGTATTTCGACTGCATACGACATCTGC-3' rno-miR-106b-5p-F, 5'-GCCGCTAAAGTGCTGACAGT-3'
rno-miR-107	rno-miR-106b-5p-PR, 5'-FAM- TG(pdC)ATA(pdC)GA(pdC)ATCTGCAC-ZNA4-BHQ1-3' rno-miR-107-RT, 5'-GTCGTATGCAGTGCAGGGTCCGAGGTATTTCGACTGCATACGACTGATAG-3' rno-miR-107-F, 5'-GCCGAGCAGCATTGTACAGGG-3'
rno-miR-125a-3p	rno-miR-107-PR, 5'-FAM- TG(pdC)ATA(pdC)GA(pdC)TGATAG(pdC)C-ZNA4-BHQ-1-3' rno-miR-125a-3p-RT 5'-GTCGTATGCAGTGCAGGGTCCGAGGTATTTCGACTGCATACGACGGCTCC-3' rno-miR-125a-3p-F, 5'-GCCGCACAGGTGAGGTTCTTG-3' rno-miR-125a-3p-PR, 5'-FAM-TGCATACGACGGTCCCA-ZNA4-BHQ1-3' miR-Universal-R, 5'-GTGCAGGGTCCGAGGTAT-3'

*pdC, Substitution of C-5 propynyl-dC (pdC) for dC is an effective strategy to enhance base pairing. Using these base substitutions, duplex stability and melting temperatures are raised by C-5 propynyl-C 2.8° per substitution.

Table II. Statistical comparison of miRNA levels between the sham and exposure groups.

miRNA	Sham exp. group			900 MHz RF exp. Group			adjP*
	Median	%25-75	Mean \pm SD	Median	%25-75	Mean \pm SD	
miR9-5p	4.217	0.960-5.546	4.004 \pm 3.786	0.559	0.463-0.687	0.717 \pm 0.489	0.053
miR29a-3p	0.206	0.079-0.651	0.739 \pm 1.134	0.398	0.183-0.431	0.386 \pm 0.328	0.396
miR106b-5p	0.267	0.098-0.319	0.276 \pm 0.273	1.204	0.417-1.266	0.941 \pm 0.582	0.058
miR107	2.693	2.174-3.706	3.472 \pm 3.127	0.519	0.496-0.829	0.697 \pm 0.421	0.045
miR125a-3p	0.251	0.198-0.369	0.444 \pm 0.543	0.961	0.734-1.401	2,424 \pm 4.006	0.085

*Benjamini-Hochberg adjusted *p* values.

Results

The results of this study showed that the long term and excessive exposure of 900 MHz RF exposure (3 h per day, 7 days a week for 12 months) altered expression of some of the miRNA such as rno-miR-107. The results revealed that long term and excessive exposure of 900 MHz RF radiation only decreased rno-miR107 ($p = 0.045$) while other microRNA evaluated in this study was not altered by 900 MHz RF radiation. The results are summarized in Table II and Figure 2. However, point, 1 g and 10 g average SAR level of brain were found as 0.198 W/kg, 0.143 W/kg and 0.114 W/kg, respectively (Figure 3). However, whole body (rms) and whole body maximum point SAR was found as 0.0369 W/kg and 2.023 W/kg, respectively.

Discussion

Long term and excessive use of mobile naturally has been increasing the environmental electromagnetic field (EMF) levels. Uncontrolled mobile phone usage can turn into a habit and may continue throughout life being unaware of potential harmful effects of electromagnetic fields. Discussion on the health effects of radiofrequencies especially on wireless technologies such as mobile phones began at the beginning of 1990s and finally the International Agency for Research on Cancer (IARC) classified mobile phones as 2B at the end of contradictive discussions (IARC 2011). Although many of the contradictive studies on health effects of mobile phone exposure exist, sufficient studies are still not available on the side-effects of long term and excessive RF emitted from mobile phones. Therefore, health effects of long term and excessive use of mobile phones need to be studied and enlightened. Therefore, we investigated the health effect of

900 MHz RF radiation emitted from mobile phones on the rats' brain, which is exposed 3 h per day (7 days a week) for 12 months.

Recently, one of the most popular topics related to the health effect of wireless technologies is neurodegenerative disease such as Alzheimer's disease (AD), which is one of the most important health problems among developed countries. On the other hand, nowadays some of miRNA have been accepted as an indicator of AD. Therefore, new strategies related to the interaction between RF emitted from mobile phones and miRNA is very important in terms of explaining molecular interactions of RF.

Although studies on the effects of long term and excessive use of RF and AD are still insufficient, Arendash et al. (2010) claimed that long-term cell phone use (918 MHz; 0.25 W/kg) provided cognitive benefits. They showed that mice with AD long-term EMF exposure reduced brain amyloid-beta (A beta) deposition through decreased aggregation of A beta with an increase in soluble A beta levels. However, Soderqvist et al. (2010) proposed that transthyretin (TTR) might be involved in the findings of RF exposure benefit in mice with AD. In one of our previous studies, we also measured beta amyloid protein in rats which were exposed to long-term 900 MHz radiofrequency radiation and any alteration in amyloid beta level was not observed (Dasdag et al. 2012).

Since it is not possible to find any study on the effects of RF emitted from mobile phones and miRNA interactions, our study is the first to report the effects of long term and excessive exposure of 900 MHz RF radiation on some of the miRNA such as rno-miR-9-5p, rno-miR-29a-3p, rno-miR-106b-5p, rno-miR-107 and rno-miR-125a-3p in rat brain.

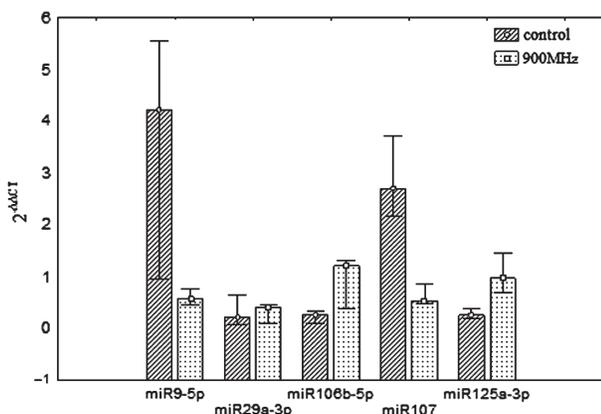


Figure 2. Comparison of sham and 900 MHz RF exposure groups.

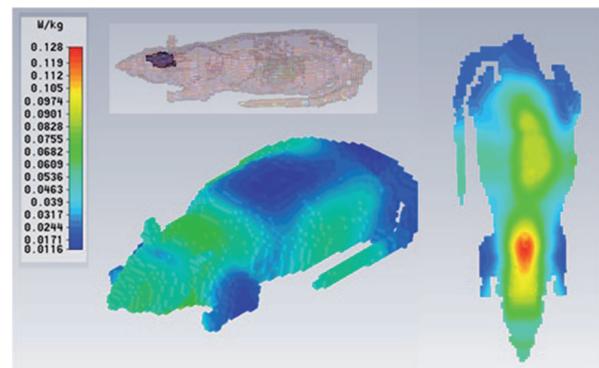


Figure 3. Rat model and SAR distribution (10 g average). This Figure is reproduced in color in the online version of *International Journal of Radiation Biology*.

miRNA are small RNA that post-transcriptionally regulate the expression of thousands of genes in a broad range of organisms in both normal physiological contexts and in disease contexts. miRNA expression profiling is gaining popularity because miRNA, as key regulators in gene expression networks, can influence many biological processes and also show promise as biomarkers for disease (Pritchard et al. 2012).

Determination of rno-miR-9-5p, rno-miR-29a-3p, rno-miR-106b-5p, rno-miR-107, rno-miR-125a-3p expression in brain may be associated with some diseases such as acute myeloblastic leukemia, alcohol dependence, Alzheimer's disease, autism and diabetes, which are developed depending on the alteration in transcription of genes such as BACE1, BDNF, GAB2, PSEN1, PSEN2, SIRT1, SLC1A2, VEGFA. As mentioned above, the results of this study showed that the long term and excessive exposure of 900 MHz RF exposure (3 h per day, 7 days a week for 12 months) alters expression of rno-miR-107.

It is also reported that alterations in the expression of microRNA contribute to the pathogenesis of different types of malignancies, including malignant lymphomas, but are also involved in normal development of hematopoietic cells (Garzon and Croce 2008). Koens et al. (2013) stated that primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL-LT) differ in their microRNA profiles. Nelson and Wang (2010) observed a correlation between decreased miR-107 expression and increased neuritic plaque counts and neurofibrillary tangle counts in adjacent brain tissue. However, Van den Hove et al. (2014) and Van Sprosen et al. (2013) reported miR-107 as epigenetically regulated miRNA linked to Alzheimer's disease and correlate with changes in neuronal development and neuronal activity. Expression profiling following induction of neuronal activity demonstrated that 31 miRNA, including miR-107 were upregulated by homeostatic plasticity protocols (Van den Hove et al. 2014). Huang et al. (2013) defined miR-107 and miR-103 as the strongest candidates, which are frequently deregulated in cancer. He et al. (2013) stated that low-expression of microRNA-107 inhibited cell apoptosis in glioma by upregulation of SALL4. They demonstrated that miR-107 was down-regulated in glioma tissues and up-regulation of miR-107 suppressed glioma cell growth through direct targeting of SALL4, leading to the activation of FADD/caspase-8/caspase-3/7 signaling pathway of cell apoptosis. Chen et al. (2013a) stated that miR-107 was located on chromosome 10 and was down-regulated in glioma cell lines, and they recently confirmed that miR-107 expression was reduced in glioma tissues and cell lines. They also found that miR-107 inhibited glioma cell proliferation, migration, and invasion. Sharma et al. (2013) reported decreased levels of circulating and tissue miR-107 in human esophageal cancer and observed significant down-regulation of miR-107 in neoplastic and pre-neoplastic esophageal tissues. Tu et al. (2013) defined miR-107 as one of tumor suppressor miRNA in head and neck squamous cell carcinoma and stated that miR-107 seemed to play complicated roles in regulating stemness or the epithelial-mesenchymal transition of tumor cells. Chen et al. (2013b) also demonstrated that p53-induced

miR-107 suppresses brain tumor cell growth and down-regulates CDK6 and Notch-2 expression, supporting its tumor suppressor role and utility as a target for glioma therapy. In our study we observed that rno-miR-107 expression was decreased ($\text{adj}P^* = 0.045$) in rat brain exposed to 900 MHz RF radiation for 3 h/day during one year. Therefore, it can be stated in light of the above discussion that cancer or some neurodegenerative disease may be triggered by or associated with long term and excessive 900 MHz RF radiation exposure, which reduced the rno-miR-107 expression in this study.

In summary, our study is the first report indicating that long term and excessive exposure of 900 MHz RF radiation emitted from mobile phones altered the expression of rno-miR-107 ($\text{adj}P^* = 0.045$) in rat brain. Our results revealed that long term and excessive exposure of 900 MHz RF radiation (3 h per day; 7 days a week for 12 months; one year) decreased rno-miR-107 value. Therefore, it can be claimed that long term and excessive exposure of RF radiation emitted from mobile phones may be associated with prognoses of some diseases. However, we note that this is the first animal study to investigate the effects of long term and excessive exposure of 900 MHz RF on miRNA expression. The results of this study may be replicated at a larger group of animals. Further investigation on the biological aspects of rno-miR-9-5p, rno-miR-125a-3p, rno-miR-106b-5p and rno-miR-107 dysregulation in brain may help us better understand the pathogenesis of many diseases.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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