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Electromagnetic Biology and Medicine

ISSN: 1536-8378 (Print) 1536-8386 (Online) Journal homepage: https://www.tandfonline.com/loi/iebm20

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To cite this article: Mehmet Esref Alkis, Hakki Murat Bilgin, Veysi Akpolat, Suleyman Dasdag, Korkut Yegin, Mehmet Cihan Yavas & Mehmet Zulkuf Akdag (2019) Effect of 900-, 1800-, and 2100-MHz radiofrequency radiation on DNA and oxidative stress in brain, Electromagnetic Biology and Medicine, 38:1, 32-47, DOI: 10.1080/15368378.2019.1567526

To link to this article: https://doi.org/10.1080/15368378.2019.1567526

Published online: 22 Jan 2019.

ELECTROMAGNETIC BIOLOGY AND MEDICINE
2019, VOL. 38, NO. 1, 32–47
https://doi.org/10.1080/15368378.2019.1567526

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ABSTRACT

Ubiquitous and ever increasing use of mobile phones led to the growing concern about the effects of radiofrequency radiation (RFR) emitted by cell phones on biological systems. The aim of this study is to explore whether long-term RFR exposure at different frequencies affects DNA damage and oxidant-antioxidant parameters in the blood and brain tissue of rats. 28 male Sprague Dawley rats were randomly divided into four equal groups ($n = 7$). They were identified as Group 1: sham-control, Group 2: 900 MHz, Group 3: 1800 MHz, and Group 4: 2100 MHz. Experimental groups of rats were exposed to RFR 2 h/day for 6 months. The sham-control group of rats was subjected to the same experimental condition but generator was turned off. Specific absorption rates (SARs) at brain with 1 g average were calculated as 0.0845 W/kg, 0.04563 W/kg, and 0.03957, at 900 MHz, 1800 MHz, and 2100 MHz, respectively. Additionally, malondialdehyde (MDA), 8-hydroxydeoxyguanosine (8-OHdG), total antioxidant status (TAS), and total oxidant status (TOS) analyses were conducted in the brain tissue samples. Results of the study showed that DNA damage and oxidative stress indicators were found higher in the RFR exposure groups than in the sham-control group. In conclusion, 900-, 1800-, and 2100-MHz RFR emitted from mobile phones may cause oxidative damage, induce increase in lipid peroxidation, and increase oxidative DNA damage formation in the frontal lobe of the rat brain tissues. Furthermore, 2100-MHz RFR may cause formation of DNA single-strand breaks.

ARTICLE HISTORY
Received 16 August 2018
Accepted 2 December 2018

KEYWORDS
900-, 1800-, and 2100-MHz RFR; comet assay; mobile phone; oxidative stress; DNA damage; nitric oxide

Introduction

The mobile phone technology, one of the fastest growing technologies in the world, has become a popular and indispensable part of daily life. Owing to the technological advancements, significant improvements have been achieved in the internet data speed and quality, and communication technologies such as Wi-Fi, UMTS, Bluetooth, EDGE (Enhanced Data Rates for GSM Evolution), WiMAX (Worldwide Interoperability for Microwave Access), and 4G have been developed. As the communication systems become affordable and ubiquitous, people spend most of their time with their mobile phones everywhere: at home, at work, in public places, and at school. Therefore, the possible harmful effects of radiofrequency radiation (RFR) have become a concern for people (Hardell et al., 2009).

Cell phones emit RFR in the form of nonionizing electromagnetic radiation. The effects of electromagnetic fields (EMFs) emitted by mobile phones on living organisms and human health have become one of the most important research topics in recent years. For this reason, researchers are conducting various scientific studies to examine the health problems that may occur as a result of RFR exposure and to minimize the effects on people (Akdag et al., 2016; Chauhana et al., 2017; Dasdag and Akdag, 2016; Dasdag et al., 2004, 2009, 2008; Sahin et al., 2016; Zothansiama. et al., 2017). There are several studies reporting that radiofrequency waves emitted by mobile phones may cause many harmful effects on the cellular and molecular level such as DNA damage, different types of cancer, oxidative stress, lipid peroxidation, increase of free radicals, DNA fractures in the brain, and abnormalities in chromosomes (Akdag et al., 2016, 2018; Cam et al., 2012; Chauhana et al., 2017; Dasdag et al., 2015; Deshmukh et al., 2013; Bioinitiative Report 2012; Megha et al., 2015). Long-term exposure to RFR raises the concern that there may be a cumulative effect of

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RFR from the mobile phone in the society (Person et al., 2012). These possible cumulative biological effects have a strong correlation with the intensity and duration of RF exposure (Sahin et al., 2016).

Some researchers aimed try to explain interaction mechanisms of neurobiological effects of RFR and conducted studies in relation to the effects of RFR on blood–brain barrier. In a recent study, Sirav and Seyhan (2016) reported an increase in blood–brain barrier permeability in male rats after 20 min of exposure to either 900-MHz or 1800-MHz pulsed RFR, whereas an effect was found in female rats only after exposure to the 900-MHz field. Tang et al. (2015) also reported an increase in blood–brain barrier permeability in rats after repeated exposure to a 900-MHz field. There are studies that reported no significant effects of RFR exposure on the blood–brain barrier. Finnie et al. (2009a, 2009b) reported no significant effects on the blood–brain barrier in mice after exposure to RFR (900 MHz, 4 W/kg, 60 min/day, 5 days/week for 104 weeks). More recently, De Gannes et al. (2017) reported no significant changes in blood–brain barrier and neuronal degeneration in rats after a single (2 h) or repeated (2 h/day, 5 days/week for 4 weeks) exposure to GSM-1800 and UMTS-1950 signals up to a brain average SAR of 13 W/kg.

The biological effects of EMF can be recorded at intensities much less than the thermal threshold (Ayrapetyan, 2017), and classic thermodynamics theories fail to explain this phenomenon (Binhi and Rubin, 2007; Foster, 2006). Some researchers try to explain these effects in terms of a quantum mechanical approach, considering different biochemical reactions with participation of uncoupled electrons, such as the electrons transferring cytochrome *c* to cytochrome oxidize during oxidation of malonic acid, the activity of Na^+/K^+-adenosine triphosphate (ATPase), and during other target reactions (Ayrapetyan, 2017; Belyaev, 2012; Binhi, 2012; Blank and Goodman, 2012). However, high sensitivity of formation and breaking processes of hydrogen bonds to EMF that occur in cell aqua medium (Ayrapetyan, 2017; Chaplin, 2006), and especially during metabolically driven collective dynamics of intracellular water molecules (Ayrapetyan and De, 2014), makes the role of individual biochemical reactions inessential in non-thermal (NT) effect of EMF on intracellular metabolism. In this respect, the so-called water hypothesis seems more reliable for explaining the biological effect of EMF. As the valence angle of water molecules between O–H bonds, which determines its dissociation and physicochemical properties, is highly sensitive to different environmental factors (Ayrapetyan, 2017; Ayrapetyan et al. 1994a, 2015; Chaplin, 2006), according to this hypothesis, EMF can modulate cell metabolism by changing physicochemical properties of water, which is a common medium for metabolic reactions in cells and organisms. Ayrapetyan et al. (1994a, 1994b, 2015) have shown, in their previous studies, that the effect of EMF on physicochemical properties of water solutions and formation of reactive oxygen species (ROS) in it depends on Ca^{2+} concentration in water solution, temperature, background radiation, light, and gas composition of the medium. It is known that the formation of H_2O_2 in physiological solution (PS) upon the impact of EMF is one of the main messengers for modulation of cell metabolism (Ayrapetyan et al., 2005; Gapeyev et al., 2009). Previously, it has also been shown that the effects of ELF EMF and microwave (MW) on H_2O_2 contents in PS depend on chemical and physical characteristics of the environmental medium (Baghdasaryan et al., 2012). Narinyan and Ayrepetyan (2017) indicate that MW-treated PS injection leads to the increase of cAMP and decreases cGMP content; MW-induced activation of cAMP-dependent Reverse (R) Na^+/Ca^{2+} exchange, which has a poisoning effect on cell metabolism, could be considered as a potential harmful effect able to lead to cell pathology. Thus, on the basis of data in their studies, Ayrapetyan et al. (2017) concluded that NT MW has an activation effect on cAMP-dependent R Na^+/Ca^{2+} exchange leading to the increase of [Ca2+]*i*, which brings intracellular poisoning and imbalance induced water influx causing an increase of membrane permeability for Na^+ of cell membrane. Therefore, Ayrapetyan, (2017) suggested that MW has a hazardous effect on an organism and is able to generate cell pathology.

Current concerns on mobile phone exposure are mainly focused on the brain. Because the mobile phone is usually held close to the head and brain while talking (Kesari et al., 2011; Su et al., 2018), the antenna of the mobile phone radiates RFR EMFs that can penetrate into 4–6 cm of the human brain (Kesari et al., 2011). At the same time, the brain is one of the most oxygen-consuming organs that cause the production of brain-reactive oxygen radicals, and it is the target of reactive free radicals as it includes high amounts of lipid and polyunsaturated fatty acids (Dasdag et al., 2012; Nazıroglu et al., 2009). In addition, the enzymatic antioxidant defense system of the brain is also weak (Sahin et al., 2016). It is therefore highly susceptible to EMF-induced oxidative damage induced by brain-ROS. If ROS is not controlled by enzymatic and non-enzymatic antioxidant defense system, it may cause oxidative damage. An increase in the free radical concentration and the traceability of free radicals can be observed under the influence of RFR (Ongel et al., 2009). During oxygen metabolism, ROS species occur in cells. But cells have a natural antioxidant defense system to eliminate the harmful effects of ROS. Oxidative stress occurs in cells when there is an increase in the production and the amount of ROS, and in turn, it affects the natural antioxidant defense system

(Curtin et al., 2002). Higher levels of free oxygen and nitrogen can cause oxidative damage by attacking basic biomolecules (proteins, lipids, and DNA) and cell structure (Esmekaya et al., 2016; Jing et al., 2012).

DNA single- or double-strand breaks, primary lesions that are not repaired or incorrectly repaired, may cause carcinogenesis or chromosomal aberrations leading to cell death, micronucleus, sister chromatid exchange formation, and mutations (Akdag et al., 2016; Lai and Singh, 2004). Contradictory results have been reported in studies on genetic damage in different tissues of short- and long-term exposure to RFR emitted by mobile phones. It has been reported that in some *in-vivo* and *in-vitro* studies with different RFR frequency, RF exposure is reported to induce DNA strand breaks (Cam and Seyhan, 2012; Deshmukh et al., 2015; Gandhi et al., 2015; Garaj-Vrhovac et al., 2011; Lai and Singh, 2004; Paulraj and Behari, 2006; Yao et al., 2008), while others reported no significant effects on DNA damage and genotoxicity (Falzone et al., 2010; Luukkonen et al., 2010; Su et al., 2017, 2018).

Despite the rapid increase in research on the effect of different frequency RFR emitted by mobile phones on brain tissue, there is still no consensus on biological results. In addition, while only long-term usage of RFR emitted by mobile phones provides clear results, the short-term exposure studies and contradictory investigations on the effects on DNA damage, oxidative stress, and damages caused by oxidative stress were the main motivations to conduct this research. In this study, we tried to determine the level of DNA damage caused by RFR exposure from RF signal generators that create identical cellular phone signals at three different RF frequencies (900 MHz, 1800 MHz and 2100 MHz) by applying the Comet assay technique. In addition, MDA, 8-OHDG, TAS, TOS, OSI levels, and serum NO levels were analyzed from brain tissue samples to determine the effects of RFR on oxidative stress, lipid peroxidation, and oxidative DNA damage.

Material and methods

Animals

28 Sprague Dawley male adult rats (3–4 months, average weight 282,42 ± 16,18 gr) were obtained from the Dicle University Health Sciences Research and Application Center. After 1 week of adaptation period, rats were randomly divided into four equal groups (n = 7). They were identified as Group 1: sham-control, Group 2: 900-MHz RF, Group 3: 1800-MHz RF, and Group 4: 2100-MHz RF. During the study, the animals were kept in the laboratory environment under 12/12 h day/night periods, 22°C room temperature, and 45% relative humidity. Normal tap water and pellet feed (TAVAS Inc., Adana, Turkey) were given as ad libitum to feed. All experimental protocols applied on the rats were conducted in accordance with the standards set by Dicle University, Prof. Dr. Sabahattin Payzın Health Sciences Research and Application Center Experimental Animals Local Ethics Committee (DUHADEK). In addition, approval of the local ethics committee was taken before the study.

Exposure and field measurements

Three signal generators (900, 1800, and 2100 MHz, PM10 type Everest, Adapazari, Turkey) which could emit identical cellular phone signal at three GSM bands of 900 MHz, 1800 MHz, and 2100 MHz were used. Particular signal channels in each respective GSM band were chosen as the transmission of dummy messages. During RFR application, the rats were restricted within the plexiglass cages as illustrated in Figure 1.

The RFR emitted by the signal generators was exposed to RF application group rats for 6 months every day and 2 h/day (900 MHz to Group 2, 1800 MHz to Group 3, and 2100 MHz to Group 4) by using a specially designed plexiglass where the generator antenna was placed in the center of the plexiglass carousel. The antennas of the generators were equivalent to those of mobile phones. RFR applications were made in laboratory environment at the same time each day and at normal room temperature, and the same experimental procedure was applied to sham-control group rats except the RF generator was

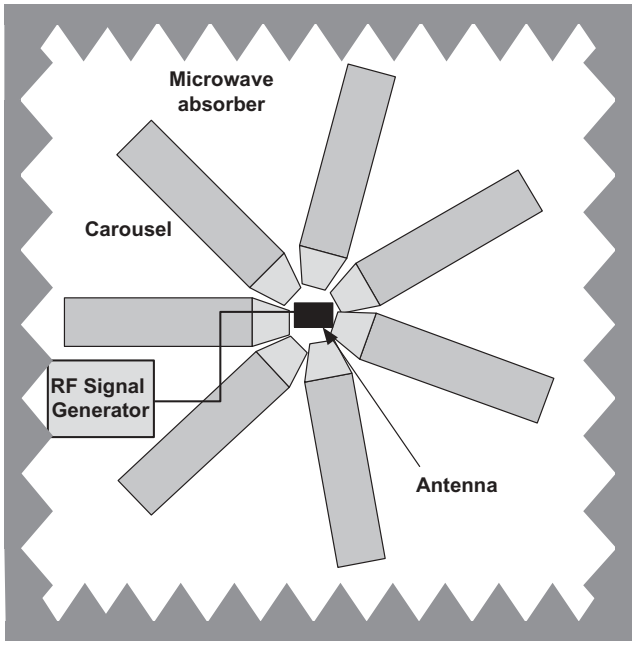

Figure 1. RFR experimental setup.

turned off. Electromagnetic power density (mW/cm^2) and electric field (V/m) measurements were conducted with EMR 300 (NARDA, Pfullingen, Germany) active field probe. These field measurements ensured that the generators were working properly and expected electric field levels due to a tyrpical phone usage were maintained. After the last application, all rats studied were euthanized by taking blood from their hearts with cardiac puncture under ketalar anesthesia. Blood samples centrifuged within a short period of time (approximately half an hour) for 5 min with a 5000 rpm centrifuge device (Heraeus® Labofuge® 200 c, USA) and the serums were taken after 10–15 min. Serum samples were transferred to eppendorf tubes with plastic caps and stored at −20°C until the day of the analysis. Then, the NO values of the stored serum samples were examined. Immediately after intracardiac blood ingestion, the rat's brain tissues were received and stored at −80°C for analysis. Then, the brain tissue samples taken from rats were homogenized with PBS (phosphate buffer saline, pH: 7.4) solution and DNA damage in brain tissues was determined using the Comet assay technique. In addition, MDA, 8-OHDG, TAS, TOS, and OSI analyzes were performed in the brain tissue. The total amount of protein was measured by the Bradford method in all tissue samples via spectrophotometer (Bradford, 1976).

SAR measurements

In the experimental setup, the EMF values near and around the antenna were constantly measured using EMR 300 field probe. While these measurements ensured the proper operation of signal generators, they also provided the basis for electromagnetic simulation of the rats for SAR analysis, where measured electric field values were used as reference to simulate the average input power to the antenna in the simulations. EMF simulations were carried out using CST Microwave Studio. This particular solver is based on finite integration technique (FIT) which is similar to commonly used finite-difference time domain (FDTD) technique except spatial derivatives were replaced with integration in the simulation domain. It is claimed by CST that charge and energy conversation is preserved in FIT using integral form of Maxwell's equations contrary to the differential forms used in FDTD. This particular formulation leads to stable numerical results in time-domain.

The rat model plays a vital role in SAR simulations. Volumetric pixel (voxel) rat model which was formed used computerized tomography scans of a rat was commercially available and acquired for this study. In voxel model, every tissue has its electrical and thermal properties measured at cellular phone frequencies. Thus, this voxel model is extremely accurate and similar voxel sets for several human models also exist for industry standard SAR calculations. Electric field and SAR distribution were simulated using CST with this rat voxel model. The simulated electric field values around the rats were consistent with the measured data using electric field probe. In SAR calculations, a representative rat with 320 g weight was used. This weight was approximately equivalent to the average weight of the rats used in the experiments. SAR distributions at 900 MHz, 1800 MHz, and 2100 MHz are shown in Figure 2. SAR values for 10 g and 1 g averages as well as point SAR are summarized in Table 1. It was observed that SAR values decreased as frequency increased due to increasing attenuation of electromagnetic waves inside the rat body at higher frequencies. Whole body maximum point SAR values are 0.638, 0.166, and 0.174 W/kg for 900, 1800, and 2100 MHz, respectively. Body maximum SAR is expected to exhibit a mean variation of ± 0.017 (W/kg) over the rats in the exposure groups.

Comet assay analysis (single cell gel electrophoresis)

The Comet assay analysis method, also known as the single cell gel electrophoresis method, is a fast, sensitive, and relatively simple method used to detect DNA damage at the single cell level. The alkaline version of the method is used to measure single-strand damage of DNA (Cam and Seyhan, 2012; Singh et al., 1988). DNA double-strand breaks can also be observed in case the Comet assay is used under neutral conditions (Erel et al., 2009; Jha, 2012). The alkaline version was used in our study. The supernatant of brain tissue homogenate was used for analysis (Cerda, 1998). In brief, each microscope slide was precoated with a layer of 0.5% normal melting point agarose in distilled water and dried thoroughly at room temperature. Next, 100 mL of 0.8% low melting point agarose in PBS at 37°C was mixed with 10 mL of the cell suspension and dripped onto the first layer. Slides were allowed to solidify for 5 min at 4°C in a moist box. The coverslips were removed and the slides were immersed in freshly prepared cold lysis buffer containing 25 g SDS in TBE, for 7 min at 4°C. The slides were removed from the lysis buffer, drained, and placed in a horizontal electrophoresis unit filled with fresh alkaline electrophoresis solution (TBE), containing 54 g Tris, 27.5-g boric acid, 20-mL EDTA (pH 8.4) for 20 min to allow the DNA to unwind. Electrophoresis was performed for 2 min at room temperature at 64 V and was adjusted to 250 mA. Subsequently, the slides were washed with distilled water for 5 min. in order to remove the alkali ions and detergents. After

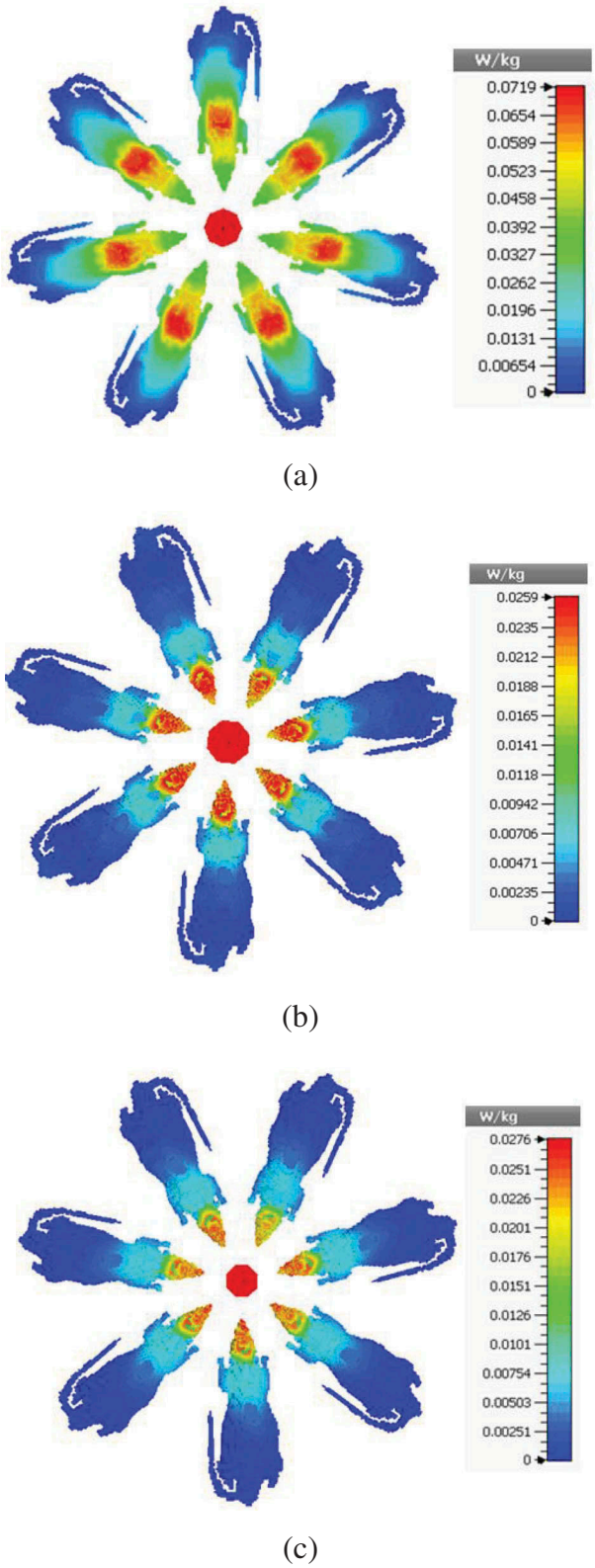

Figure 2. SAR distribution for 10 g average: (a) 900 MHz, (b) 1800 MHz, and (c) 2100 MHz.

neutralization, the slides were stained with 50 mL of ethidium bromide (1 mg/mL) and covered with a coverslip. All steps were performed under dim light to prevent further DNA damage (Haines et al., 1998). Observations were made at a magnification of 400x using a fluorescent microscope (Olympus, Japan). The images of 100 randomly chosen nuclei were analyzed by the comet assay software (CASP, publicly available, http://www.casp.of.pl, Wroclaw, Poland) (Akdag et al., 2016).

From the comet parameters tail intensity (TI, DNA% in the tail of the comet) and tail moment (TM) variables, which have been widely used in recent years since give more clear results, have been examined. TM is expressed as tail diameter/head diameter or DNA% in tail × tail length (Singh et al., 1988).

Table 1. Simulated SAR values of brain at three different frequencies.

	Brain (gray matter)		
Frequency	10 g (W/kg)	1 g (W/kg)	Point (W/kg)
900 MHz	0.0543	0.0845	0.1697
1800 MHz	0.0246	0.0456	0.0933
2100 MHz	0.0235	0.0396	0.0726

Total antioxidant level (TAS) measurement

TAS measurement of the brain tissue has been conducted by fully automatic colorimetric measurement method developed by Erel (2004b). In this method, a standardized solution of the Fe^{2+}-o-dianisidine complex enters the fenton-type reaction with the standardized hydrogen peroxide solution and induces OH radicals. This potent ROS oxidizes colorless o-dianhydride molecules to yellow–brown-colored dianisidyl radicals at low pH. Advanced oxidation reactions develop between dianisidyl radicals, increasing color formation. The antioxidants in the sample suppress oxidation reactions and color formation. This reaction is measured spectrophotometrically for results. The results are given as micromolar troloxy Eqv./liter (Erel; 2004a, 2004b). Total antioxidant capacity measurement was performed using a TAS kit (Rel Assay, Turkey, Catalog No. RL0017) and values were read on a plate reader (Thermo Scientific Multiskan FC, 2011–06, USA) at 660-nm wave length.

Total oxidant level measurement (TOS)

TOS measurement was performed by the fully automatic colorimetric measurement method developed by Erel (2005). In this method, the oxidants present in the sample oxidize the ferrous (Fe^{2+}) ion-o-dianisidine complex to the ferric ion. Glycerol molecules that are abundant in the reaction medium accelerate oxidation reactions. In the acidic environment, ferric ions create

a colorful complex with xylene orange. The color intensity measured spectrophotometrically is directly proportional to the total amount of oxidant molecules present in the sample. The analysis is calibrated with hydrogen peroxide and the results are expressed in micromolar hydrogen peroxide equivalents per liter (μmol H_2O_2 Equiv./Liter). Total oxidant capacity measurement was performed using a TOS kit (Rel Assay, Turkey, Catalog No. RL0024) and read on the plate reader (Thermo Scientific Multiskan FC, 2011 −06, USA) at 530-nm wave length.

Calculation of oxidative stress index (OSI)

After TAS and TOS values were determined, OSI, which is a sign of the degree of oxidative stress, is calculated follows (Erel, 2005):

OSI = [TOS (μmol H_2O_2 Equiv./L)/TAS (μmol troloks Equiv./L) × 100]

Malondialdehyde (MDA) measurement

Malondialdehyde (MDA) measurement was performed by ELISA method. This method is based on coloration using the enzyme-labeled conjugate and enzyme subtilization to demonstrate specific antigen-antibody binding. The commercial MDA ELISA kit (Eastbiopharm, Catalog No. CK-E10376) was used for the measurement of MDA and the values were read on the plate reader (Thermo Scientific Multiskan FC, 2011–06, USA) by ELISA (enzyme-linked immunosorbent assays) method.

8-Hydroxydeoxyguanosine (8-OHdG) measurement

8-Hydroxydeoxyguanosine (8-OHdG) is a critical biological marker of oxidative stress and carcinogenesis and one of the most important products of DNA oxidation. 8-OHdG measurement was performed by ELISA method. This method is based on coloration using the enzyme-labeled conjugate and enzyme subtilization to demonstrate specific antigen-antibody binding. The 8-OHdG measurement was performed using a commercial 8-OHdG ELISA kit (Eastbiopharm, Catalog No. CK-E11652) and its values were read on the plate reader (Thermo Scientific Multiskan FC, 2011–06, USA) by ELISA method.

The absorbance of the standards is determined and line-line graphs are obtained as absorbance on x-axis, concentration on y-axis, and results are expressed in the form of ng/mL.

Serum total nitrite level measurement

Serum total nitrite levels are evaluated as a sign of nitric oxide (NO). Since direct measurement of NO is very difficult, the levels of metabolites are used, and indirect methods are preferred to obtain information about the amount. In this study, serum total nitrite levels were measured according to Cortas and Wakid's (1990) method. The results were calculated and evaluated in mol/L.

Data analysis

SAS (Statistical Analysis System) 9.4.1 was used in the statistical analysis of the study data. The Kolmogorov–Smirnov test was performed to determine whether the data fit the normal distribution and the normal distribution of the data was determined. One-way variant analysis (one-way ANOVA) was used to determine whether there was a difference between the groups. As a result of the variance analysis, the Duncan multiple comparison tests were used to determine which groups were different in terms of variables. Results were expressed as a mean ± standard deviation and values less than $p < 0.05$ were considered statistically significant.

Results

Comet assay findings

At the end of the study, the TM and tail intensity (%) of the Comet parameters indicating the level of DNA damage caused by different RFR in the frontal lobe of the brains of the experimental groups were examined by comparing them with the sham-control group and with each other (Table 2).

As a result of statistical analysis to determine whether there is a difference between sham, 900 MHz, 1800 MHz, and 2100 MHz in terms of tail intensity and TM parameters, the difference between the groups in TM variance

Table 2. Tail moment and tail intensity (%) results of sham-control and experimental groups, statistically evaluation, and Duncan grouping.

	Tail moment (mean ± SD) and Duncan grouping	Tail intensity (%) (mean ± SD) and Duncan grouping
Group 1 (Sham)	38.949 ± 7.606^{A}	22.321 ± 2.678^{B}
Group 2 (900 MHz)	$42.255 \pm 7{,}606^{A}$	24.287 ± 3.592^{B}
Group 3 (1800 MHz)	45.942 ± 9.179^{A}	26.531 ± 2.733^{B}
Group 4 (2100 MHz)	48.194 ± 10.039^{A}	37.553 ± 8.583^{A}
P	$^{ns}P = 0.2285$	$^{*}P = 0.0001$

There is no statistically significant difference between groups with the same letter for each column. There is a significant difference between different alphabetic groups. *A significant difference found between the groups ($p < 0.01$). ^{ns}No significant difference found between the groups ($p > 0.05$).

was not statistically significant ($p > 0.05$), but the difference between groups was found to be statistically significant in terms of tail intensity ($p < 0.01$). The Duncan multiple comparison tests were used to determine which groups were different from each other. As a result of the Duncan test, the difference between the groups of Sham-control, 900 MHz, and 1800 MHz was not statistically significant ($p > 0.05$) and the difference between the 2100-MHz group and other groups was statistically significant ($p < 0.01$) (Table 2).

As evident in Table 2, it was determined that the tail intensity and TM values of (900 MHz, 1800 MHz, and 2100 MHz) groups increased as the applied RFR increased. A significant increase in tail formation (density) was found for the 2100-MHz group with respect to Sham-control, 900-MHz, and 1800-MHz groups, indicating that exposure to higher frequency radiation could increase DNA damage gradually (Figure 3).

The results of the Comet technique we used to detect DNA damage in the frontal lobe of the brain cells of the rats show that DNA damage can be mentioned only in 2100 MHz when the groups exposed to 900-MHz, 1800-MHz and 2100-MHz RFR for 6 months compared to the sham-control group and each other. The Comet images indicating single-strand breaks in DNA are given in Figure 4.

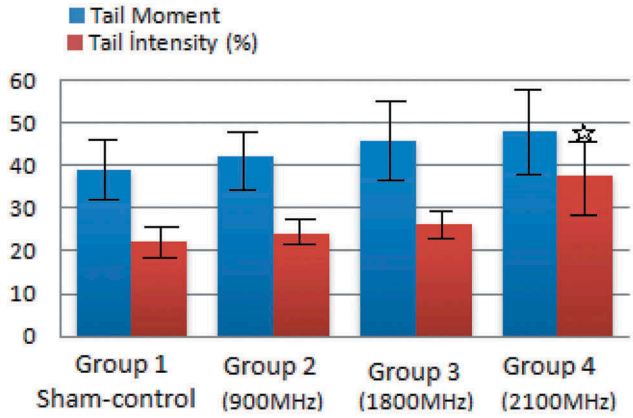

Figure 3. Tail moment and tail intensity (%) levels, showing DNA damage in the frontal lobe of the brain of rats exposed to long-term (2 h/day, 6 months) RFR emitted by generators that generate signals similar to three different RF frequencies that are heavily used in mobile telephone networks. Values are given as Avg. ± SD (*significant compared to the control and other groups at the level of 0.01 ($p < 0.01$)).

TAS, TOS, OSI, MDA, 8-OHdG, and NO analysis findings

Results of measured TAS, TOS, OSI, 8-OHdG, MDA, and NO were given in Table 3 as mean ± standard deviation ($n = 7$).

One-way variance analysis was performed to determine whether there was a difference in TOS variable among the groups. As a result of the analysis, the difference between the groups was statistically significant ($p < 0.01$). The Duncan multiple comparison tests were used to determine which groups were different from each other. As a result of the Duncan test, the difference between 1800-MHz and 2100-MHz groups was statistically insignificant ($p > 0.05$). The difference between 900 MHz and the other groups and the difference between sham and the other groups were statistically significant ($p < 0.01$).

There was a statistically significant decrease in TAS level of all experimental groups compared to sham group ($p < 0.01$). The difference between groups 900 MHz and 1800 MHz was statistically insignificant ($p > 0.05$), and the difference between the sham group and the other groups, and the difference between the 2100-MHz group 4 and the other groups were statistically significant ($p < 0.01$).

As a result of the one-way variance analysis, it was found that all the experimental groups had a statistically significant increase in OSI, MDA, and 8-OHDG parameters compared to the sham group ($p < 0.01$). The Duncan multiple comparison test was used to determine which groups differed in terms of these variables. As a result of the Duncan test, the difference between each group and the other groups was statistically significant ($p < 0.01$).

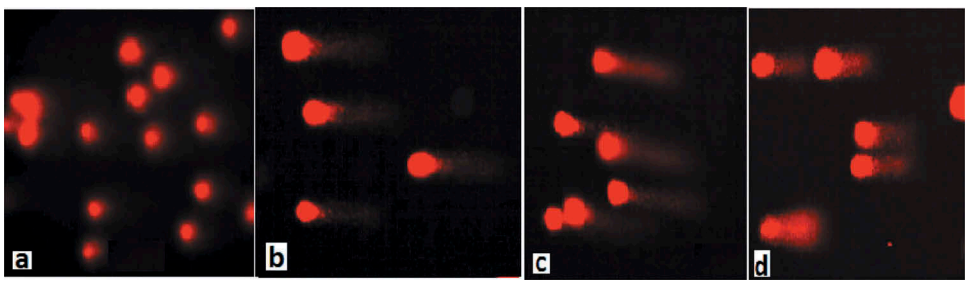

Figure 4. Example images of brain DNA damage under fluorescent microscope: (a) sham-control, (b) 900 MHz, (c) 1800 MHz, and (d) 2100 MHz.

Table 3. TOS, TAS, OSI, 8-OHdG, MDA, and NO results of sham-control and experimental groups, statistically evaluation, and Duncan grouping.

	TOS (μmol/L)	TAS (μmol/L)	OSI (AU)	8-OHdG (ng/ml)	MDA (ng/ml)	NO (mol/L)
Group 1 (Sham)	7.386 ± 0.67^{C}	1.418 ± 0.27^{A}	5.346 ± 1.01^{D}	23.597 ± 2.80^{D}	28.676 ± 3.79^{D}	12.657 ± 3.93^{B}
Group 2 (900 MHz)	9.090 ± 0.94^{B}	0.905 ± 0.08^{B}	10.169 ± 1.81^{C}	31.849 ± 4.10^{C}	33.625 ± 3.60^{C}	14.028 ± 1.39^{BA}
Group 3 (1800 MHz)	11.935 ± 0.78^{A}	0.843 ± 0.05^{B}	14.247 ± 1.67^{B}	43.914 ± 2.35^{B}	39.322 ± 3.55^{B}	15.414 ± 1.34^{A}
Group 4 (2100 MHz)	11.583 ± 0.75^{A}	0.676 ± 0.12^{C}	17.575 ± 3.32^{A}	52.244 ± 5.11^{A}	59.374 ± 4.63^{A}	15.428 ± 2.32^{A}
P	$^{*}P = 0.0001$	$^{*}P = 0.0001$	$^{*}P = 0.0001$	$^{*}P = 0.0001$	$^{*}P = 0.0001$	$^{*}P = 0.0141$

There is no statistically significant difference between groups with the same letter or including the same letter for each column. There is a significant difference between different alphabetic groups. *A significant difference found between the groups ($p < 0.01$).

Comparisons of the RFR groups with the sham-control group also showed an increase in NO levels in the three RFR groups. The increase between the sham-control group and the 900-MHz group was statistically insignificant ($p > 0.05$) and the increase between the sham-control group and the 1800-MHz group and the 2100-MHz groups was statistically significant ($p < 0.05$). When the RFR groups were compared among themselves, the difference between them was found to be statistically insignificant ($p > 0.05$). Graphical representations of TOS, TAS, OSI, 8-OHdG, MDA, and NO Avg.± SD values of sham-control and application groups are given in Figures 5 and 6.

There is a significant difference ($p < 0.01$) between TAS, TOS, OSI, 8-OHdG, and MDA parameters in the frontal lobe of the brain cells between sham and experimental groups as well as between experimental groups (Figures 5 and 6). Compared to the sham-control group, there was a significant increase in the serum NO level at the groups of 1800 MHz and 2100 MHz ($p < 0.05$). These results show us that different frequency RFRs can change the biochemical parameters of brain cells.

Discussion

Despite many studies on the effects of RFR emitted from mobile phones on biological systems in recent years, there is no complete consensus on harmful effects to date. However, with the rapid progress and development of mobile phone technology, the potentially harmful effects may become a serious concern due to increased use by children and younger people who are more sensitive to radiation than adults (Challis, 2005).

Water is an important part of cell and has a determining role in cell metabolism; however, non-thermal MW radiation can change physicochemical properties of skin and sub-skin water contents (Ziskin, 2006). According to Narinyan and Ayrapetyan (2017), NT MW-induced changes of cell hydration can be a primary messenger for NT MW signal transduction from cell aqua medium into intracellular metabolism. Moreover, the penetration of MW in brain tissue depends on tissue hydration and little energy is absorbed by brain tissue (Nikoghosyan et al., 2016). NT MW radiation leads to the activation of R Na^{+}/Ca^{2+} exchange, which cause to the rising of intracellular Ca^{2+} (Narinyan and Ayrapetyan,

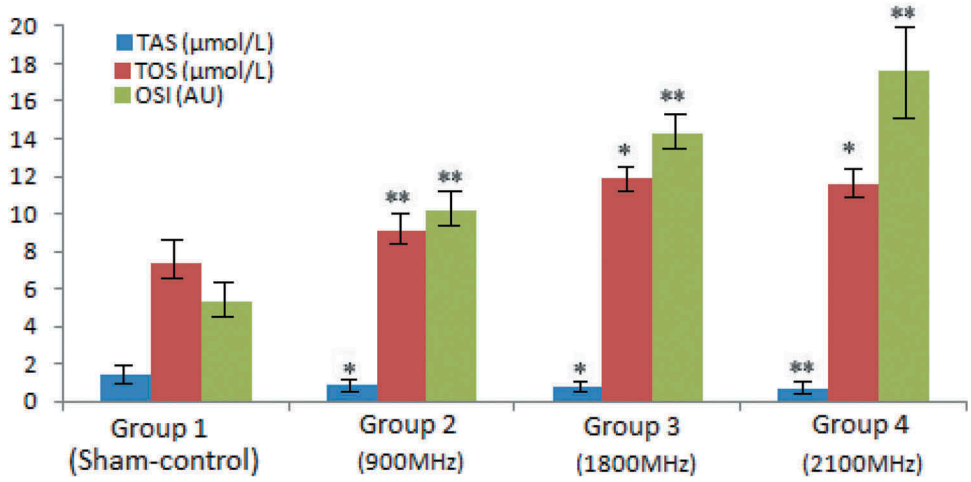

Figure 5. Showing TAS, TOS, and OSI levels in the frontal lobe of the brain of rats exposed to long-term (2 h/day, 6 months) RFR emitted by generators that generate signals similar to three different RF frequencies and sham-control. Values are given as Avg. ± SD (*significant compared to the control group ($p < 0.01$); **significant compared to both the control group and other groups ($p < < 0.01$)).

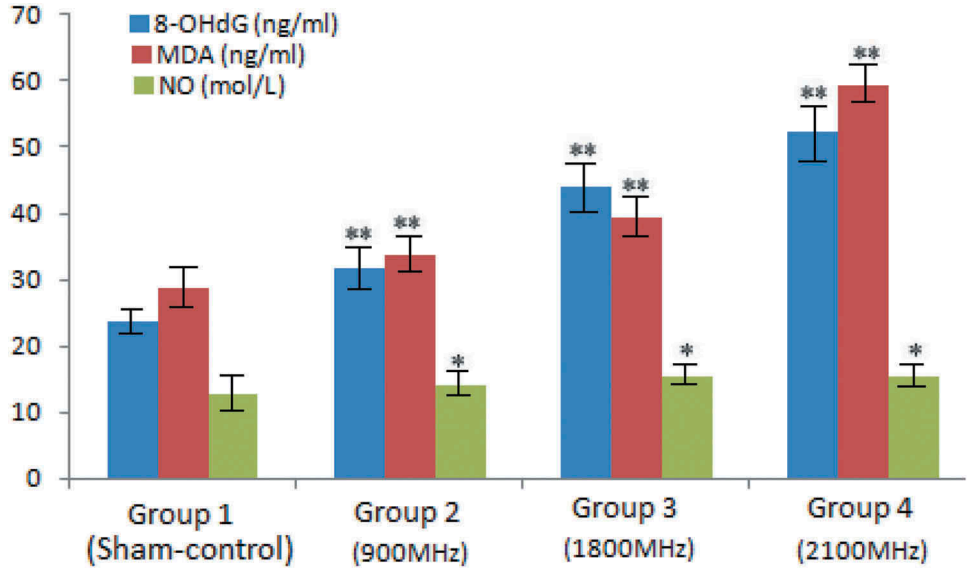

Figure 6. Showing 8-OHdG, MDA, and NO levels in the frontal lobe of the brain of rats exposed to long-term (2 h/day, 6 months) RFR emitted by generators that generate signals similar to three different RF frequencies and sham-control. Values are given as Avg. ± SD (*significant compared to the control group ($p < 0.01$); **significant compared to both the control group and other groups ($p < 0.01$)).

2017). It was shown that the effect of EMF on physico-chemical properties of water solutions and formation of ROS in it depends on Ca^{2+} concentration in water solution, temperature, background radiation, light, and gas composition of the medium (Ayrapetyan et al., 1994a, 2015). The effect mechanism of RFR on human health and which frequencies used in mobile phones are more harmful remain as a major debate. In addition, in 2011 the International Agency for Research on Cancer (IARC) classified RFR as a possible carcinogen for humans (2B) (IARC 2011). Therefore, we have conducted our study to research whether the long-term application of RFR emitted by generators that produce identical signals to three different GSM band frequencies (900 MHz, 1800 MHz and 2100 MHz) causes the single-strand DNA damage in the frontal lobe of the brain of rats as well as its effects on oxidant and antioxidant parameters in blood or brain tissue, and cause oxidative stress-induced damage.

Several studies have shown that RFR exposure can lead to oxidative stress in various tissues. In a study by Esmekaya et al. (2011), investigating the effects of oxidative and antioxidant levels on brain tissues of female rats exposed to pulse-modulated RFR at a frequency of 1800 MHz for 20 min daily for 1 month, it was observed that RFR-induced lipid peroxidation in brain tissues increased MDA and NO levels and decreased GSH level. Guler et al. (2016) showed that oxidative DNA damage and lipid peroxidation were increased in liver and brain tissues of all rabbits exposed to 1800-MHz RFR. Eser et al. (2013) found that rats exposed to electromagnetic radiation (900 MHz, 1800 MHz, and 2450 MHz) for 1 h/day for 2 months showed a significant decrease in TAS level, but a significant increase in TOS and OSI levels. Dasdag et al. (2012) reported that long-term (2 h/day, 7 days/week for 10 months) application of 900-MHz RFR increased the levels of MDA, protein carbonyl, and beta amyloid protein levels in brains of rats. Chauhan et al. (2017) reported that 2.45-GHz MW radiation may cause histopathological and oxidative changes in rats. Zothansiama. et al. (2017) state that 900- and 1800-MHz RFR have caused a significant increase in lipid peroxidation (LOO) in human peripheral blood lymphocytes (HPBL). On the other hand, Zmyslony et al. (2004) showed that 5 and 15 min of acute RFR did not change ROS production, in the study in which they researched the effect of 930-MHz RF continuous wave (5 mW/cm^2 and 1.5 W/kg SAR) on ROS levels. Dogan et al. (2012) reported that 20 days of application of 2100-MHz (3G) RFR did not seem to have a harmful effect on the oxidative stress of rat brain tissue. Irmak et al. (2002) found increased SOD levels in rabbits exposed to 900-MHz radiation from mobile telephones for 7 days (30 min/day).

As a result of our study, total oxidative level (TOS), oxidative stress index (OSI), and MDA levels of the experimental groups were significantly higher than the sham-control group ($p < 0.01$). On the contrary, brain total antioxidant capacity (TAS) levels of experimental groups were significantly lower than sham group

($p < 0.01$). The findings obtained in our study are consistent with the results of previous studies (Esmekaya et al., 2011; Chauhana et al., 2017; Eser et al., 2013;). However, the findings obtained in this study show that RF exposure can cause oxidative stress by damaging the balance between oxidant and antioxidant, and may increase the damage caused by oxidative stress. As the frequencies in RF applications increase in 900-MHz, 1800-MHz, and 2100-MHz groups, TAS levels decreased and TOS, OSI, and MDA levels increased. The frequency of RF might affect the DNA damage (Akdag et al., 2016; Vijayalaxmi et al., 2012).

NO, which acts as a mediator in central nervous system neurons and plays a role in the realization of many brain functions, is one of the most important reactive nitrogen derivatives formed in biological systems. NO reacts with superoxide, which can lead to a very strong cellular reactive radical called peroxynitrite ($ONOO^-$). Production of NO at high levels can lead to various neurological diseases (Brune et al., 1995). An increase in NO level was observed in tissue damage (Kato et al., 1994). There are many studies on the level of NO in biological systems of RFR. Yarıktas et al. (2005) state that rats exposed to 900-MHz electromagnetic radiation for 2 weeks (30 min/day, 5 days/week) showed a significant increase in NO levels in sinus and nasal mucosa. Ilhan et al. (2004) found that rats exposed to 900-MHz RFR from mobile phones for 1 h/day for 7 days had a significant increase in brain tissue NO levels. Ozgür et al. (2010) observed a significant increase in MDA and total NO levels and a decrease in superoxide dismutase (SOD), myeloperoxidase (MPO), and glutathione peroxidase (GSH-Px) activities in guinea pig liver exposed to RFR at 1800 MHz (SAR; 0.38 W/kg, 10 or 20 min/day, 10 days). They found that cell phone-like radiations can cause oxidative damage and can alter the activity of antioxidant enzymes in the liver. Ozgüner et al. (2006) reported that NO levels in the retinal tissue of rats were increased by the effect of 900-MHz RFR (30 min/day, 2 months) and that long-term exposure to mobile phone radiation could cause oxidative stress in retinal tissue. Olgar et al. (2015) stated that 2100-MHz RFR applied for 2 h a day for 10 weeks caused a significant increase in cardiac tissue NO levels in rats. Esmekaya et al. (2016) reported that 900-MHz RFR application resulted in a significant increase in NO levels in brain tissue and a significant decrease in GSH levels in rats. On the other hand, Irmak et al. (2002) found increased SOD and decreased NO levels in rabbits exposed to 900-MHz radiation from a mobile phone for 7 days (30 min/day). Dasdag et al. (2008) reported that the long-term application of 900-MHz RFR emitted by mobile phones significantly increased MDA and TOS levels in rat liver and increased serum NO level but the increase in the group exposed to radiation was significant compared to the cage control group, and it was insignificant compared to the sham group.

In our study, when the experimental groups were compared with the sham-control group, an increase in NO level was observed in the three experimental groups. However, it was found that the increase between the sham-control group and 900-MHz group was statistically insignificant ($p > 0.05$), while the increase between the sham-control group of 1800 MHz and 2100-MHz groups was statistically significant ($p < 0.05$). Moreover, the difference between the experimental groups was statistically insignificant ($p > 0.05$). The results of our study at 1800 and 2100 MHz are parallel with the results of a number of studies investigating the oxidative stress effects of RFR on brain tissue (Esmekaya et al., 2011, Esmekaya et al., 2016; Olgar et al., 2015; Ozgür et al., 2010). The inconsistency of the findings from the 900-MHz group with the findings of many other studies may be due to different exposure parameters. It is known that DNA damage that can occur is related to the cell type and experimental setup (exposure time, RF frequency, SAR, continuous or pulsed wave, exposure as mobile phone user, etc.) (Desai et al., 2009; Vijayalaxmi and Prihoda, 2012). The data obtained from NO analysis show that RFR exposure at frequencies of 1800 MHz and 2100 MHz may play a role in oxidative damage by increasing nitrogen free radical production in rats.

Endogenous and exogenous sources cause oxidative DNA damage with different mechanisms in living organisms. Several studies have shown that exposure to electromagnetic radiation from mobile telephones can increase cancer incidence and increase DNA damage in brain cells (Dizdaroglu, 2015; Kesari et al., 2013; Paulraj and Behari, 2006). These damages result in mutation or cell death in cases where they are not repaired or incorrectly repaired. Some altered DNA bases are thought to be potentially harmful to the integrity of the genome. 8-OHdG is the most known of these base modifications. It is known that the hydroxyl radical interacts with all the components of DNA and this interaction can result in damage to the purine, pyrimidine bases, and the deoxyribose backbone. Permanent modification of genetic material caused by oxidative stress is the first step in mutagenesis, carcinogenesis, and aging. In addition, free radical-mediated DNA damage was detected in various cancerous tissues (Young, 2007). Free radicals affect directly on the nitrogenous bases in the DNA molecule, causing changes

bases. Due to the presence of a large number of negatively charged phosphate groups in DNA, Fe and Cu transition metal ions are permanently bound to DNA, and at the same time, Fe and Cu ions freed from proteins in the cell due to oxidative stress can also bind to DNA. The binding of Fe and Cu metal ions to the deoxyribose sugars of DNA makes the DNA the target of hydrogen peroxide (H_2O_2), and creates a hydroxyl radical with a high reactivity ($OH^{\bullet}$) as a result of Haber–Weiss and Fenton reactions (Lai et al., 2004; Phillips et al., 2009). In addition, the Cu^{+2} ions bind to the oxidation-prone regions of guanine-rich cytoplasm, which have the lowest ionization potentials of DNA components with high affinity. Here, guanine damage occurs in the guanine as a result of reaction with H_2O_2 (Celik, 2011).

The hydroxyl radical, which makes various modifications to the purine and pyrimidine bases, causes the formation of many oxidized products. The most abundant and most mutagenic one of DNA oxidation products is 8-OHdG. Therefore, 8-OHdG measurement is accepted directly as an indicator of oxidative DNA damage and this method is usually applied to determine oxidative DNA damage (Atmaca et al., 2009). Xu et al. (2010) observed a significant increase in the level of 8-OHdG in cortical neuron cells exposed to 1800-MHz (SAR; 2 W/kg) RFR. Guler et al. (2016) reported that 8-OHdG levels in male and female rabbits exposed to generators producing signals equivalent to 1800-MHz GSM signal in antenatal and postnatal periods were significantly increased compared to the control group. Gurler et al. (2014) reported a significant increase in the level of 8-OHdG in both brain tissue and plasma of rats exposed to 2450 MHz low-level EMF for 1 h/day for 30 days. Burlaka et al. (2013) observed a significant increase in the level of 8-OHdG in the embryos of quail to which they applied 900-MHz RFR (0.25 μW/cm^2, SAR:3 μW/kg). In contrast, Khalil et al. (2012) reported that exposure to GSM 900-MHz (30 min/day, 30 days, SAR: 1.0 W/kg) mobile phone RF did not significantly increase the level of 8-OHdG in blood serum, brain, and splenic tissues of rats. Sahin et al. (2016) applied 2100-MHz RFR for a group of rats for 10 days and to another group for 40 days. At the end of the exposure period, they observed that the oxidative DNA damage (8-OHdG) was increased in the 10-day exposed group but decreased in the 40-day exposed group compared to their control groups.

In our study, 8-OHdG levels of the experimental groups were significantly higher than the sham-control group ($p < 0.01$). Our results are compatible with many literature findings (Burlaka et al., 2013; Guler et al., 2016, 2014; Khalil et al., 2012; Sahin et al., 2016; Xu et al., 2010). The difference between the application groups was also found to be statistically significant ($p < 0.01$). Our findings show that RFR can cause oxidative DNA damage (8-OHdG) in rats by increasing oxidants in their frontal lobe of the brains.

High-frequency RFR may have a genotoxic effect on tissue (Dogan et al., 2017). Reports up to now on RFR and DNA damage are controversial and the precise mechanism of DNA strand breaks due to RFR is still unknown. Disruptions in DNA spiral can occur due to degradation of DNA repair or damage caused by DNA-DNA and DNA-protein cross-links and/or DNA adduct formation. In addition, RFR can induce the formation of free radicals in brain cells that can cause DNA chain breaks (Deshmuck et al., 2013; Paulraj and Behari, 2007). Single- and double-strand breaks may occur in DNA. Most single-strand breaks can easily be repaired by DNA repair mechanisms. However, it is known that DNA double-strand breaks are very critical for cells and can lead to cell death or apoptosis if not repaired properly (Akdag et al., 2016; Desai et al., 2009). Several techniques have been developed to analyze single and double DNA strand breaks. The most commonly used method is microgel electrophoresis, which is also known as Comet assay or single cell gel electrophoresis (Phillips et al., 2009).

In this study, we investigated DNA single-strand breaks that RFR could cause in frontal lobe of the brain tissue using the Comet assay method. TM and tail intensity, the most frequently used ones among the comet parameters, were measured. The TM and tail intensity values of the experimental groups were found to be higher than that of the sham group, but the increase in the TM parameter was statistically insignificant ($p > 0.05$) as a result of the statistical analyzes performed, and the increase in the tail intensity parameter was found to be significant only in the 2100-MHz group ($p < 0.01$).

The concept of TM (tail length × tail density) as a parameter for DNA migration was described by Olive et al. (1990). Nevertheless, there is still no consensus among researchers about how to calculate the TM in the most appropriate way. Some agents cause long, fine tails, while others cause short, thick tails (Rojas et al., 1999). In many studies, it has been reported that tail density (% DNA in the tail) gives clearer and more accurate results and should be preferred for alkaline Comet analysis (Kennedy et al., 2012; Kolarevic et al., 2016).

Our Comet assay results show that 2100-MHz RFR may be more harmful and may increase DNA damage by inducing DNA single-strand breaks in frontal lobe of the rat brain tissues. 900-MHz and 1800-MHz findings of

our study are parallel with the findings of Vershaeve et al. (2006), Trosic et al. (2011), and Akdag et al. (2016), while the 2100 MHz findings of our study are parallel to the findings of Kesari et al. (2014)

Deshmukh et al. (2013) showed that in the evaluation made using the alkaline Comet assay technique to determine whether DNA damage occurred in brain tissue of male Fischer rats that were exposed to MW radiation in three different frequencies as 900 (SAR: 5.953 x 10^{-4}W/kg), 1800 (SAR: 5.835 x 10^{-4}W/kg) ve 2450 (SAR: 6.672 x 10^{-4}W/kg) MHz for 30 days, low SAR MW radiation exposure at these frequencies caused DNA strand breaks in the brain tissue. Kesari et al. (2014) reported that MW radiation emitted by 3G (2100 MHz) mobile telephones induces significant DNA strand breaks in the brain. Yao et al. (2008) examined whether 1800-MHz RFR caused DNA damage in human lens epithelial cells by using the Comet assay method and observed that 1800-MHz 3-W/kg and 4-W/kg RFR induced significant DNA damage. Belyaev et al. (2006) stated that exposure of the rat brain to GSM MWs could lead to DNA breaks, changes in chromatin conformation, and gene expression. Cam and Seyhan (2012) conducted a study using the Comet assay technique and found that exposure to 900-MHz RFR resulting from a mobile phone in short-term (15 and 30 min) speech mode caused a significant increase in DNA single-strand breaks in the hair stem cells around the ear. Paulraj and Behari (2006) reported that chronic RF exposure caused a significant increase in DNA chain breaks in brain cells of rats in their studies made by using the Comet assay technique.

Contrary to these studies, it has been suggested in many studies that RFR exposure does not constitute significant cellular DNA damage. Verschaeve et al. (2006) reported that long-term exposure (2 h/day, 5 days/week, 2 years) of 900-MHz GSM signal at 0.3 and 0.9 W/kg SAR to rats did not significantly affect DNA strand breakdown levels in their cells. Trosic et al. (2011) reported that RFR radiation exposure (1 h/day) in mobile phone frequency range (915MHz GSM, power density; 2.4 W/m^2, SAR; 0.6 W/kg) did not cause DNA damage in brain tissues of rats. Akdag et al. (2016) reported that long-term (12 months) 2.4-GHz RFR application induced significant DNA damage in the testis tissue, but did not induce DNA damage in the brain, kidney, liver and skin tissues.

Our findings in this study show that RFR from generators that create signals similar to mobile phones can cause various damages to the frontal lobe of the brain. In addition, it was also observed that the level of damage was elevated with the increase in applied frequency, though the simulated SAR values indicated a decrease as frequency was increased. But SAR distributions were more concentrated around brain as higher frequency was used.

Conclusion

RFR at different mobile phone frequencies seems to cause oxidative stress, lipid peroxidation, and DNA damage by changing oxidant and antioxidant levels in frontal lobe of the brain tissue. However, the increase in the frequency and the increase in the level of damage suggest that RFRs at higher frequencies may negatively affect brain tissue and may lead to the development of damage. Our study is consistent with many recent studies and supports the hypothesis that RFR causes damage to biological tissues. However, in order to reach solid conclusions, detailed long-term studies at molecular level are definitely needed.

Disclosure Statement

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

Funding

This work was supported by the Dicle University [grant number Tıp.16.008].

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