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ABSTRACT

The aim of the present study was the investigation of the effects of mobile phones at different daily exposure times on the hippocampal expression of two apoptotic genes. Forty-eight male BALB/c mice were randomly divided into six groups with 8 animals in each group. Four experimental groups were respectively exposed to electromagnetic waves for 0.5, 1, 2 and 4 hours twice a day for 30 consecutive days. One experimental group was radiated for 4 hours once a day, while the control group did not receive any radiation during the experiment. The expression of both *Bax* and *Bcl2* mRNAs was upregulated in the mice exposed for one and two hours. Whilst the highest expressions were observed in the two-hours radiation in the exposed group, the expression of both studied genes was downregulated in animals with longer exposure to radiation in a duration-dependent manner. The highest ratio of *Bax*/*Bcl2* expression was observed in the mice that received radiation for four hours twice a day. These results revealed that mobile phone radiation can cause considerable changes in the balance of *Bax/Bcl2* mRNA expression in laboratory mice hippocampus.

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Electromagnetic Waves; apoptosis; *Bcl2*; *Bax*; hippocampus

Introduction

In recent years, the widespread use of mobile phones has led to a public debate about possible adverse health effects of the electromagnetic waves emitted on human health. This is because mobile phones use electromagnetic waves in the microwave range. Natural and artificial sources radiate electromagnetic waves at a wide range of frequencies. Radio Frequency (RF) is part of this range extending from 30 kHz to 300 GHz (Migault et al. 2019). The energy created by RF radiation cannot cause chemical effects in cells, but it indirectly causes biological effects, that can be categorized into thermal and non-thermal (Kıvrak et al. 2017). If the amount of energy absorption is low, non-thermal effects emerge and if it is higher, thermal effects will be observed too. The heat can be due to polar molecules (like water molecules) orienting in the radio-frequency oscillating field (Vasil'ev et al. 2019). RF waves are emitted from several sources like mobile phones and microwave ovens (Frah and Belyaev 2019). The researches on the biological effects of radio waves and microwaves on deoxyribonucleic acid (DNA) structure, chromosomal aberrations, gene expression, nervous system, and response to stress have been reviewed and discussed in detail (Batool et al. 2019; Ghatei et al. 2017; Kim et al. 2019; Tohidi et al. 2015, 2016).

The electromagnetic waves irradiated by mobile phones mostly affect the brain. Therefore, neuropsychiatric disorders occur such as Alzheimer's and Parkinson's disease and brain tumors (Nath 2018; Yang et al. 2017; Zhang et al. 2016). Epidemiological studies of Lonn *et al.* did not demonstrate an increase in the likeliness of brain tumors development if one used a mobile phone for less than ten years (Lonn et al. 2004). Nowadays, experimental studies on expression levels of the genes are commonly consulted for the effects of mobile phone radiation (Lamkowski et al. 2018).

Apoptosis is a genetically controlled form of cell death that occurs in both physiological and pathological

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AbbreviationsABI: Applied Biosystems; ANOVA: Analysis of Variance; Bax: Bcl-2-associated X protein; Bcl2: B-Cell Lymphoma 2; DEPC: Diethylpyrocarbonate;; MPJ: Mobile Phone Jammer; RF: Radio Frequency

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conditions. *Bcl2* family proteins are one of the key regulators of apoptosis (Toossi et al. 2013). At least, 15 *Bcl2* family members have been identified in mammalian cells. They function either as pro-apoptotic or anti-apoptotic regulators (Singh et al. 2019). The ratio of anti-apoptotic/pro-apoptotic proteins such as *Bcl2/Bax* determines in part how cells respond to apoptotic or survival signals. Some proteins such as tumor suppressor *p53* with multifunctional ability to protect DNA integrity are key regulators of *Bax* and *Bcl2* expression (Farnebo et al. 2010). Levels of p53 can be raised by DNA damaging agents and inducing the expression of pro-apoptotic *Bax* gene to trigger the apoptotic pathway (Chipuk et al. 2004; Miyashita et al. 1994).

Regarding current controversies on the probable effects of electromagnetic waves exposure on hippocampal cell apoptosis, molecular studies can contribute much by investigating detrimental effects of electromagnetic wave radiation on the hippocampus (Fragopoulou et al. 2018). Thus, the present study was designed to evaluate the effects of electromagnetic waves radiated by mobile phones at different daily exposure times on the expression of *Bcl2* and *Bax* genes in the hippocampus of BALB/c mice.

Materials and methods

A total of 48 male BALB/c mice (30–35 g body weight, 7–8 weeks old) were used in the present study. All procedures involving animals were in accordance with the Guide for the Care and Use of Laboratory Animals of Mashhad University of Medical Sciences, Mashhad, Iran. Animals were housed in individual cages at 22 ± 2°C with free access to pellet food and water, and were allowed a 12 h light/dark cycle.

Microwave radiation exposure

For all experiments, a mobile phone jammer (MPJ) for exposure was used which is a device to prevent receiving signals between cellular phones and base transceiver stations. An MPJ sends out waves with the same frequencies as those of mobile phones and all the bands for the cell phone network. This device equipped with four standard bands (900 MHz and 1800 MHz for CDMA and GSM) and accredited by International Telecommunication Union, produces waves with the same frequency and intensity as mobile phones with the homogeneous horizontal field. The maximum power output of this device (2 watts) reaches a distance of 2 m from each of its four antennas.

The animals were randomly divided into six experimental groups (n = 8). Each group was kept in a separate non-metal cage. The cages of the experimental groups were located at a distance of 2 meters from the device. At each stage of radiation, the cages of the experimental groups were taken out of the electromagnetic field half-an-hour, 1, 2, and 4 hrs twice a day fractionation separated by 12 hours for a period of 30 consecutive days (As shown in Figure 1). The environmental conditions of the experiment room resembled those of the animal room. At the end of the last day of radiation, the mice were anesthetized using chloroform and the hippocampus of their right hemisphere was dissected.

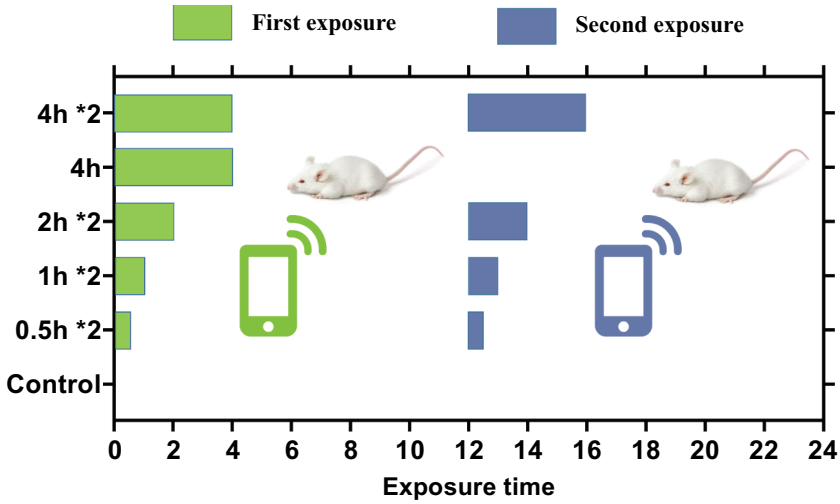

Figure 1. The timing diagram of the exposure to electromagnetic waves for 0.5, 1, 2 and 4 hours twice a day fractionation separated by 12 hours for a period of 30 consecutive days.

RNA extraction and cDNA synthesis

Hippocampi were collected in 1 ml of RNA stabilization reagent (RNAlater, Qiagen, Germany) and stored at −80°C until further analysis. Total RNA was isolated from hippocampal tissue using TriPure Isolation Reagent (Roche). One milliliter of TriPure Isolation Reagent was added to each sample. Then, 0.1 ml of chloroform was added to the reaction mixture followed by centrifugation at 12,000 × g for 15 min. The RNA was recovered from the aqueous phase by precipitation with an equal volume of isopropanol and incubated at +15 to +25°C to allow to form RNA. The precipitated RNA was collected by centrifugation at 12,000 g. The RNA pellet was washed twice with 75% ethanol by vortexing, then air-dried and resuspended in 50 µl of diethylpyrocarbonate (DEPC)-treated Ribonuclease (RNase) free water. RNA concentrations were determined via spectrophotometric absorbance at 260 nm. The integrity of the RNA was checked by visualization of 18S and 28S ribosomal bands on a 1% agarose gel. We used 1 µg of total RNA for reverse transcription to synthesize the first-strand complementary DNA (cDNA) using the oligo(dT)18 primers following the instructions of the RevertAid™ First Strand cDNA Synthesis kit (Fermentas, Germany).

Real-time polymerase chain reaction (real-time PCR)

Real-time reverse transcription PCR was performed to analyze the changes in hippocampal expression of Bcl2 and Bax genes. The primer sets were designed based on the sequences from the NCBI database. The related important information of these primers is presented in Table 1.

Each 15 µL RT-PCR reaction contained 1 µL cDNA, 7.5 µL SYBR green, 0.3 µL Rox, 0.3 µL primers for Bax and GADPH genes, and 0.15 µL primers for Bcl2 gene, with the respective amount of 5.6 and 5.9 µL of distilled water. Real-time PCR was performed with SYBR® Premix Ex Taq™ (Takara, Japan) and PCR parameters were firstly 95°C for 30 sec, and then 45 cycles of 95°C for 10 sec, 60°C for 30 sec, and 72°C for 15 sec. The real-time detection of emission intensity of SYBR Green bound to double-stranded DNAs was performed using the StepOne real-time PCR Applied Biosystems (ABI). GAPDH was used as an internal control and reference gene to normalize and measure the relative expression quantity of the target genes. The relative analysis of gene expression was performed through the standard curve and Relative quantitative method. In this method, the amounts of the unknown sample were calculated by drawing a standard curve at dilutions of 1, 10^{-1}, and 10^{-2}. Then, the obtained values were normalized for the reference genes. Next, based on a fold-change method, the values of the genes of the experimental groups and of the control group were compared.

Table 1. Primer sequences of target genes and reference genes.

Gene		Sequence	The length of the fragment (base pairs)
Bax	Forward	CTACAGGGTTTCATCCAG	**133**
	Reverse	CCAGTTCATCTCCAATTCG	
Bcl2	Forward	GTGGATGACTGAGTACCT	**118**
	Reverse	CCAGGAGAAATCAAACAGAG	
GAPDH	Forward	GAGAAACCTGCCAAGTATG	**123**
	Reverse	GGAGTTGCTGTTGAAGTC	

Statistical analysis

Statistical analysis was performed using the SPSS statistical package, version 15.0. The Kolmogorov-Smirnov test demonstrated a normal distribution for the quantitative variables. Significant differences between groups were determined using an independent sample t-test and one-way analysis of variance (ANOVA) followed by Tukey's test. A *P-value* of less than 0.05 was considered as statistically significant.

Results

In this investigation, the effects of mobile phone wave radiation on the expression of the apoptotic genes in the hippocampus of the laboratory mice were compared among the six groups with different exposure time for one month. As shown in Figure 2, the hippocampal expression level of *Bax* (as a proapoptotic gene) was upregulated in all groups. However, we did not find any significant difference between groups. The highest expression level of *Bax* was observed in two hours of radiation-exposed animals. Furthermore, *Bcl2* (as an antiapoptotic gene) expression levels was decreased significantly in the mice exposed to microwave radiation for (2*4 h) in comparison with (2*0.5 h) and (2*1h) groups ($p < .05$). The expression of both studied genes was downregulated in the animals with higher time exposure to radiation in a duration-dependent manner. *In-vivo* variation of *Bax/Bcl-2* ratio upon irradiation to 1–8 h of mobile phone microwaves was calculated for every given mouse, and the distribution is represented with horizontal box and whiskers plot in Figure 3. Interestingly, the ratio of Bax and Bcl2 expression was higher than the one in all microwave-exposed groups. The highest expression ratio (8.3) was obtained in the mice that received microwave radiation for four hours twice a day. This ratio was statistically different compared to other groups (p-value<0.001). The result of

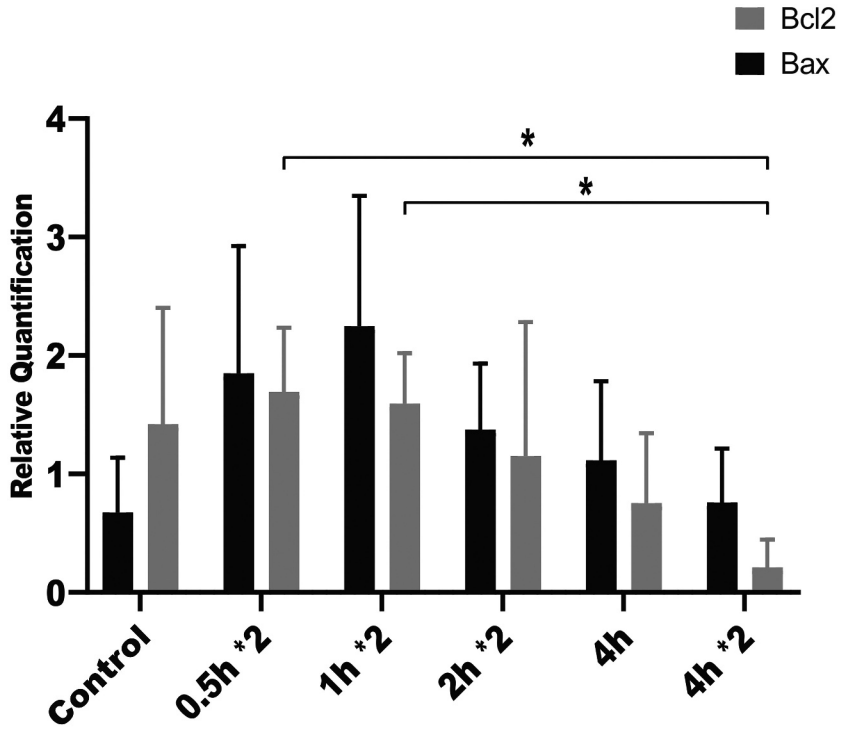

Figure 2. The relative expression of the Bax and Bcl2 in the hippocampus of all six groups studied. GAPDH mRNA was used as an internal control to measure the relative quantitation of the expression of Figure 2: target gene. Data are presented as means± S.D. * Represent P-value<0.05.

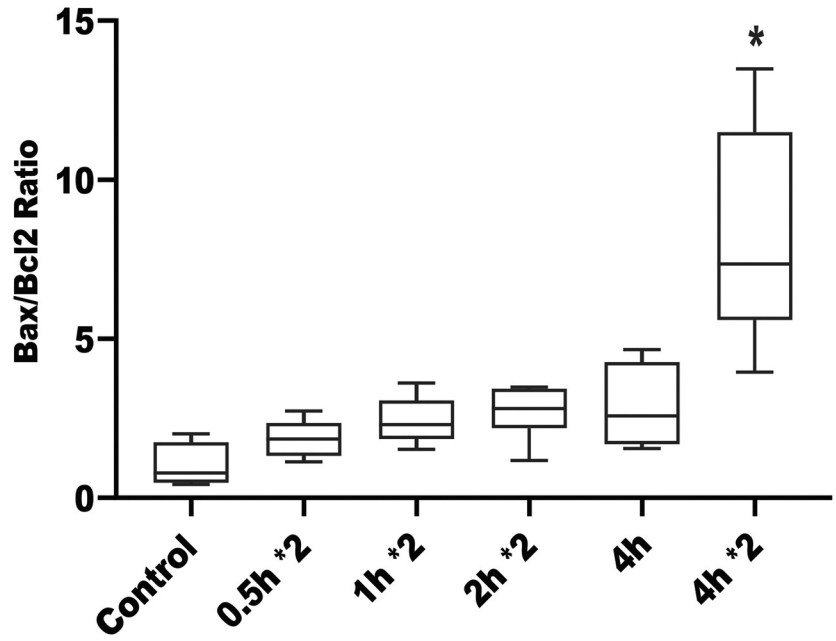

Figure 3. Distribution of Bax/Bcl-2 ratio in the hippocampus of all six groups studied. * Represent statistically significant difference with P-value<0.001.

Table 2. Tukey's multiple comparison test of the overall average of Bax/Bcl2 Ratio.

Tukey's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Significant?	Summary	Adjusted *P* Value
Control vs. 0.5 h *2	−0.8624	−4.056 to 2.332	No	ns	0.9586
Control vs. 1 h *2	−1.429	−4.623 to 1.765	No	ns	0.7390
Control vs. 2 h *2	−1.701	−4.895 to 1.493	No	ns	0.5807
Control vs. 4 h	−1.842	−5.341 to 1.657	No	ns	0.5920
Control vs. 4 h *2	−7.304	−10.62 to −3.985	Yes	****	<0.0001
0.5 h *2 vs. 1 h *2	−0.5663	−3.423 to 2.290	No	ns	0.9892
0.5 h *2 vs. 2 h *2	−0.8384	−3.695 to 2.018	No	ns	0.9417
0.5 h *2 vs. 4 h	−0.9800	−4.174 to 2.214	No	ns	0.9305
0.5 h *2 vs. 4 h *2	−6.442	−9.438 to −3.445	Yes	****	<0.0001
1 h *2 vs. 2 h *2	−0.2721	−3.129 to 2.585	No	ns	0.9997
1 h *2 vs. 4 h	−0.4137	−3.608 to 2.780	No	ns	0.9985
1 h *2 vs. 4 h *2	−5.875	−8.871 to −2.879	Yes	****	<0.0001
2 h *2 vs. 4 h	−0.1416	−3.336 to 3.052	No	ns	>0.9999
2 h *2 vs. 4 h *2	−5.603	−8.599 to −2.607	Yes	****	<0.0001
4 h vs. 4 h *2	−5.462	−8.781 to −2.142	Yes	***	0.0004

Tukey's multiple comparison test of the overall average of the *Bax/Bcl2* ratio is shown in Table 2.

Discussion

In the present study, the effects of different durations of mobile phone exposure were investigated on the BALB/c mice hippocampal expression of *Bcl2* and *Bax* genes as two regulators of apoptosis.

Radio frequencies of mobile phones can cause tensions and vibrations in the molecules of a biological sample, and rotation bipolar molecules such as water molecules through thermal and non-thermal effects. It can also cause disorders like changes in the levels of the anti-oxidants and in the permeability of cell membrane, which will alter cellular functions. As a result, there is a great likelihood that the expression of genes could also be altered (Cermak et al. 2017; Dasdag et al. 2019). Some researchers have already demonstrated the detrimental effects of mobile phone radiation as abnormalities of brain structure and function (Kim et al. 2019; Kumar et al. 2019). Some reports suggest a probable relationship between the duration of microwave radiation and changes in some gene expression (Ghatei et al. 2017; Liu et al. 2012; Tohidi et al. 2015). Both *Bcl2* and *Bax* are the apoptosis regulatory genes that work against one. However, any imbalance in the ratio can disturb the process of apoptosis.

In this study, the rise in the expression levels of *Bcl2* and *Bax* genes within the radiation range of zero to 1 hx2 can be due to electromagnetic radiation of mobile phones, which affected the expression levels of viral genes. Given that a cell can maintain a ratio of *Bax/Bcl2*, such adverse effects can be reduced (Raisova et al. 2001). The increase in the expression level of the apoptotic genes indicates that mobile phone waves affect the radiated hippocampus. In other words, mobile phone waves can affect cellular vital functions especially with the mentioned genes that are directly associated with the survival of a cell.

The results of this work demonstrated that radio frequencies emitted by mobile phones markedly disturbed the *Bax/Bcl2 mRNA* expression in mice hippocampus in a duration-dependent manner. This could be interpreted as a direct result of elongated electromagnetic wave radiation emitted by mobile phones which shortens the cell life and weakens its response to such damages (Liu et al. 2012). Some researchers previously revealed that *Bax/Bcl2 mRNA* expression will be accompanied by the modification of ROS mediate mitochondria-dependent pathways and DNA damage induction (Ali et al. 2018). Therefore, apoptosis induction by the upregulation of *Bax/Bcl2 mRNA* expression can be the result of oxidative stress-related biochemical changes in the hippocampus tissue. Notably, *Bax*/*Bcl2* mRNA expression was also introduced as a new prognostic biomarker in laryngeal squamous cell carcinoma (Giotakis et al. 2016) and breast cancer patients (Azimian et al. 2018), and indicates the high capability of *Bax*/*Bcl2* ratio.

As apoptosis grows, a larger number of cells are destroyed causing a malfunction in the afflicted region. In case of apoptosis reduction, there will be a higher risk of developing tumors. Hippocampus plays an important role in learning and solidifying memory (Lieberwirth et al. 2016), the removal of which can damage memory and learning capabilities. These observations can be explicated with regard to vital cellular functions and cellular physiology. Accordingly, electromagnetic waves affect the nucleus of the cell in different ways such as the direct damage to DNA and mRNA expression which can influence cell viability. As a reaction to

such effects, compensatory cellular mechanism help resume normal functioning and ensure blocking the adverse effects of the environmental factors.

Overall, it is indicated in this study that mobile phone waves changed the expression levels of *Bax*/*Bcl2* ratio in the hippocampus of the examined mice through a variety of radiation durations. The results did not provide strong evidence for significant differences between continuous and interrupted radiations by mobile phones. This could imply that compensatory cellular mechanism do not act efficiently to compensate for malfunctioning induced by interrupted mobile phone waves. It is noteworthy that this might be due to the distinct features of nerve cells and their lower capabilities to repair (Hall and Giaccia 2018). It seems that a small change in the sample size and radiation duration may lead to a significant difference between the expression levels of these *Bax* and *Bcl2* genes. Therefore, it is suggested that more researches be conducted with a greater sample size which are exposed to longer radiations. Thus, we can more reliably confirm a marked difference between the groups in terms of the expression levels of genes in hippocampus.

Conclusion

Overall, it can be concluded that longer exposure of mobile phone waves can cause considerable changes in the balance of *Bax/Bcl2 mRNA* expression in laboratory mice hippocampus, but the changes depended on the duration of radiation. In other words, an increase in the duration of radiation increased the risk of apoptosis in the hippocampus of the mice. Since our body is incessantly exposed to radiations from antennas, it is imperative to carry out more research in this regard. Further investigations with longer duration of exposure to radiation and more experimental techniques can be useful to identify the underlying cellular and molecular defects caused by mobile phone radiation in the brain.

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Highlights

The number of mobile devices are growing every day and smartphones are becoming important as a part of human life. This will more and more expose humans to non- ionizing radiation and endure adverse effects will be inevitable. For this reason, this study has been conducted to investigate the non-thermal effects of mobile phones at different daily exposure times on the hippocampal apoptotic gene expression. The most prominent result of these experiments was the great increase in the risk of apoptosis in the hippocampus of the mice that is depended on the duration time of exposure.

Ethical statements

All international, national, and institutional guidelines for the care and use of laboratory animals were followed and all animal procedures followed the regulations of the Institutional Ethical Animal Care Committee of Mashhad University of Medical Sciences

Disclosure statement

The authors have no conflict of interest to declare. This study financially supported by the research deputy of Mashhad University of Medical Sciences.

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