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Stereological Study on the Effect of Carnosine on of Purkinje Cells in the Cerebellum of Rats Exposed to 900 MHz Electromagnetic Field

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ABSTRACT

AIM: To evaluate the impact of carnosine on Purkinje neurons in rats exposed to a 900 Mhz electromagnetic field.

MATERIAL and METHODS: This study evaluated 24 rats divided into the following three different groups: a control group, a group exposed to the electromagnetic field, and a group that was injected with carnosine while being exposed to the electromagnetic field. The electromagnetic field group was exposed to a 900 Mhz electromagnetic field for an hour daily over 28 days. Thereafter, stereological analysis was performed histologically on cerebellar sections, and the number of Purkinje cells were counted.

RESULTS: The electromagnetic field group had remarkably fewer Purkinje cell compared to control. The electromagnetic field group plus 20 mg of carnosine had significantly more total Purkinje cells compared to the electromagnetic field group ($p<0.05$).

CONCLUSION: The present study showed that electromagnetic field exposure decreases the number of Purkinje cell, whereas carnosine protected the cerebellum from neural damage induced by electromagnetic field exposure.

KEYWORDS: Carnosine, Cerebellum, Electromagnetic field, Purkinje cell, Stereology, Rats

ABBREVIATIONS: EMF: Electromagnetic field, **EMFG:** Electromagnetic field group, **MHz:** Megahertz, **RF:** Radio frequency, **IP:** Intraperitoneal, **SAR:** Specific absorption rate, **ASF:** Area sampling fraction, **TSF:** Thickness sampling fraction, **SSF:** Section sampled fraction, **CE:** Coefficient of error, **CV:** Coefficient of variation

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INTRODUCTION

The widespread use of mobile phones in daily lives has made it almost impossible to avoid electromagnetic field (EMF) exposure from mobile phones (15), which widely utilize 900–1800 MHz radio waves for mobile communication (18). Therefore, people who use their mobile phones excessively are at risk of being exposed to intense EMF (16,19,37). Hence, considerable discussions have been undertaken regarding the potentially negative impacts of mobile phone emissions on the human nervous system (13). Several studies have shown that EMF influences several neuronal functions, including neuronal survival, learning, and memory. Some of these studies involve DNA associated with the formation of the blood–brain barrier, the neuroendocrine system, neuroelectrophysiology, protein synthesis, central nervous system cancer, gene expression, cell proliferation, embryonic process, DNA injury, and properties of cancer publicity (24,34).

Cerebellum plays a significant role in posture, muscle control, balance, and cognitive functions (29). Recent studies have shown that EMFs radiation by cell phones could affect the cerebellum (33,34).

Meanwhile, studies on cerebral ischemia and another brain injuries have shown that carnosine, an endogenous dipeptide found in many bodily tissues (7), exerts anti-oxidative, anti-glutamergic, and excitotoxicity effects on various neurons (5,7). Moreover, an experimental study on brain ischemia found that carnosine reduced mortality rates and had beneficial effects on the neurological function of animals (39).

Although various frequencies of EMF have been used in relevant research, no study has yet investigated the effects of 900 MHz EMF with carnosine administration (18,19,24). Hence, the current study aimed to determine the neuroprotective effects of carnosine among female rats exposed to a 900 MHz EMF using stereological methods.

MATERIAL and METHODS

Animals

This study had been approved by the local Animal Ethics Commission certified (approval number: 2013/82). Tests were applied after approval of the Erciyes University Ethics Committee for Experimental Animals. Rats were procured from the Headquarters for Experimental Animal Research (DEKAM) at Erciyes University (Kayseri, Turkey).

Histopathological procedures were proffered at the Erciyes University Faculty of Medicine, Department of Histology-Embryology (Kayseri, Turkey). Cell counts were determined at the Erciyes University Faculty of Medicine, Department of Anatomy (Kayseri, Turkey).

This study evaluated 24 adult 16-week-old female Wistar Albino rats weighing 200–250 g that were indiscriminately separated into three groups. The rats were kept in an environment with a 12 h light/dark cycle, which was ventilated with an aspirator and maintained at a temperature of 25° ± 2 °C and 40%–50% humidity. Rats were placed in standard transparent polycarbonate cages and fed a balanced diet with unlimited water. The experimental groups were as follows:

1. Control: not exposed to any material, EMF, or carnosine injection (n=6).
2. EMFG: exposed to EMF (900 MHz) 1 h daily over 28 days (27) (n=6). Rats were exposed to EMF daily from 11:00 to 12:00. The specific energy absorption rate (SAR) was about 0.008 W/kg for the entire body and 2 W W/kg regionally to the head. Moreover, the rats' positions were modified everyday along the exposure process. Similar systems have been used in previous studies (Figure 1) (3,38).
3. EMFG plus carnosine (CG): exposed to EMF (900 MHz) 1 h daily over 28 days (7,16). In the experimental process, this group was divided into two subgroups: carnosine administered at low (n=6) (10 mg/kg/day) and high doses (n=6) (100 mg/kg/day) with intraperitoneal injection provided 30 min before exposure (2,31,35). The rats were sacrificed after the experimental process and the number of Purkinje cells were counted using a stereological method performed histologically on sections of the cerebellum.

Histological Procedures

Rats were anesthetized using intraperitoneal urethane (1.25 g/kg) and were perfused intracardially with saline. Rat samples were fixed in neutral formalin consecutively. The cerebellums were immediately dissected, passed through xylene and alcohol, and finally embedded into paraffin for sectioning. Gelatin water was prepared so that the tissues need not be removed from the thick section. Gelatin was added to 500 g water as 5 g, and the water was stirred for 8–10 min at a temperature of 70 °C. Thereafter, the solution was placed into a container. The samples were kept in formaldehyde for one night in an oven at 60 °C to preserve the tissues before staining. Paraffin-embedded tissues were cut transversely using a rotary microtome (LeicaRM2135, Leica Instruments, Nussloch, Germany), subsequently obtaining 30-µm thick sections in the coronal plane using metal microtome blades (23). Slides were selected randomly from each tenth slide of the series to be investigated. Each cerebellar sample was mounted on slides coated with adhesive and stained with Hematoxylin and Eosin for stereologic analysis.

Exposure System

The current study utilized the same exposure system design as in previous study (4). The application of EMF and exposure system used is described in detail elsewhere (4,16,30,31). A special EMF exposure system comprising a circular lattice and a dipole antenna was utilized (1). An electromagnetic power unit that produced a 900 MHz continuous regulated EMF (2 W peak throughput power and 1 ± 0.4 mW/cm^2 power volume) was constructed at TEKNOPARK Relevance Laboratory (Kayseri, Turkey). Similar to previous work (4), the current study measured only the average rate for the entire brain. However, the SAR at the region morphological alterations were sought were not measured. Thus, the mean SAR rate of 2 W/kg denoted only the mean rate of the entire brain. Peak SAR was computed based on the model, with the

force intensity indications being performed employing an EMF meter (Kayseri Teknopark) (4).

EMF Presentation in Female Rats

Rats were exposed to the EMF using a dipole antenna to ensure close contact (4,7). The space between the animal and antenna was 1 cm, with the rat positioned perpendicular to the antenna. The rat's heads were placed at the direction from dipole antenna. The longitudinal axis of the rats was positioned vertical to one of the antennas (4).

Stereological Analyses

This study used a stereology workstation (Kayseri, Turkey) for stereological analyses. The system included a computer, picture capture card, CCD digital camera, microcator (Heidenhain, Traunreut, Germany), computer-controlled motorized sample stage (Prior Scientific, Cambridge, UK), and light microscope (Leica, Nubloch, Germany). The software program Stereo Investigator Software (MBF Biosciences, Williston VT, USA) was utilized to calculate, register stereological data, and capture digital images of parts. The system created microscopic views (a 100× Leica HCX Plan Apo objective) and presented them on a computer monitor to calculate the total number of Purkinje cells in the cerebellum. An optical fractionator process was used in the cerebellum at low magnification using a 5× oil objective (Figure 2).

The number of Purkinje cells in cerebellum of all animals were calculated using the optical fractionator method (3). Briefly, the Purkinje cell was calculated when the largest nuclear profile was focalized intermittently, coincidentally, and systematically inside the impartial virtual counting frames along the defined areas. The total number of Purkinje cells were computed according to the computed and sampling possibilities (34). All stereological examinations were blinded to obtained unbiased results.

The area sampling fraction (asf) was 625 μm^2/22,500 μm^2, the thickness sampling fraction (tsf) was 20 µm for cell counts, the section sampled fraction (ssf) was 1/10, and the impartial census frame dimension was 625 μm^2 for cell predictions. The first section was selected incidentally within the first 10 parts of each cerebellum. Tsf was 5 µm for the upper guard zone, while the average section thickness was 30 µm (25,30).

The total number of Purkinje cells in the cerebellum (N) was calculated using the following formula:

$$N = \sum Q \times \frac{1}{ssf} \times \frac{1}{asf} \times \frac{1}{tsf}$$

where ΣQ is the total dissector neuron number. Prediction of the total number of neurons was established from the sampling possibility and counted number of neurons (11). The suitability of the sampling procedure for the certainty of the forecast and suitable sampled cell number for the prediction of total number of Purkinje cells was tested using the coefficient of error and the coefficient of variation as indicated in the literature (11).

Statistical Analysis

The collected data were presented as mean ± standard deviation of each group. One-way analysis of variance was utilized to compare the number of Purkinje cells between each group. All statistical analyses were conducted using SPSS (Statistical Package for the Social Sciences, version 20, SPSS Inc., Chicago, USA), with a value of $p<0.05$ indicating statistical significance.

Figure 1: EMFG and EMF plus Carnosine group rats exposed to EMF.

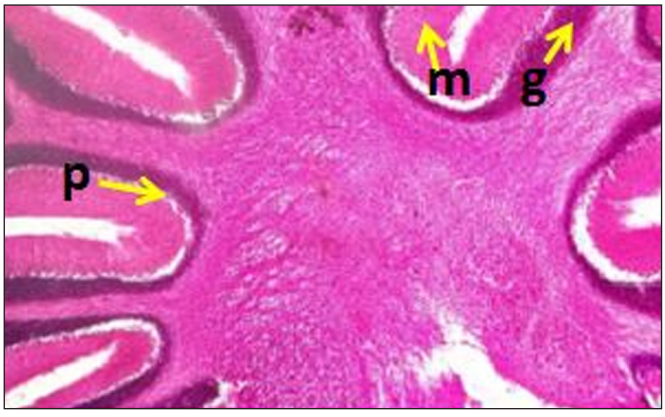

Figure 2: Cerebellar layer for normal histologic view: molecular (m), Purkinje (p) and granular (g) layers.

RESULTS

The morphological structures of cerebellar tissues in the control group were normal, with easily distinguishable granular, Purkinje, and molecular layers (Figure 2). More detailed microscopic examinations showed that Purkinje cells were uniformly arranged, and cell nuclei were had normal

morphology. All control sections showed that Purkinje cells had a normal cytoplasm across all magnifications (Figure 3).

Examination of the EMFG group found deterioration of cerebellar tissues in certain places, which could not be determined whether due to the effect of the tissue section or EMF (Figure 3). After repeated examination of the cerebellar layers, the granular, Purkinje, and molecular layers could be easily distinguished. More detailed microscopic examinations found that the Purkinje cells were uniformly arranged, and cell nuclei showed normal morphology.

In the EMFG plus carnosine (CG) group, all cerebellum samples showed a standard histological view, and the Purkinje cells clearly showed normal arrangement in all the sections. However, a more compact staining of the neuron cytoplasm was noted (Figure 3).

The number of Purkinje cells in female rats in the control, EMFG, and EMFG plus carnosine groups was then determined (Table I). Accordingly, a significant difference in the number of Purkinje cells was observed between the EMFG and control groups ($p=0.04$, $p<0.05$) Table II). Section analysis obtained 140–180 sections from each rat cerebellum. For systematic sampling, 1 out of every 20 sections were analyzed, and an average of 6–10 sections from each rat was examined.

The EMFG plus carnosine group had a significantly higher total number of Purkinje cells compared to the EMFG group ($p<0.05$). However, no significant difference was observed between the control and EMFG plus carnosine groups (Table II).

DISCUSSION

This study indicated that EMF exposure can decrease the average Purkinje cell numbers and that this decrease can be ameliorated by high carnosine dosages. Our findings showed that rats exposed to EMFG had a significantly lower number

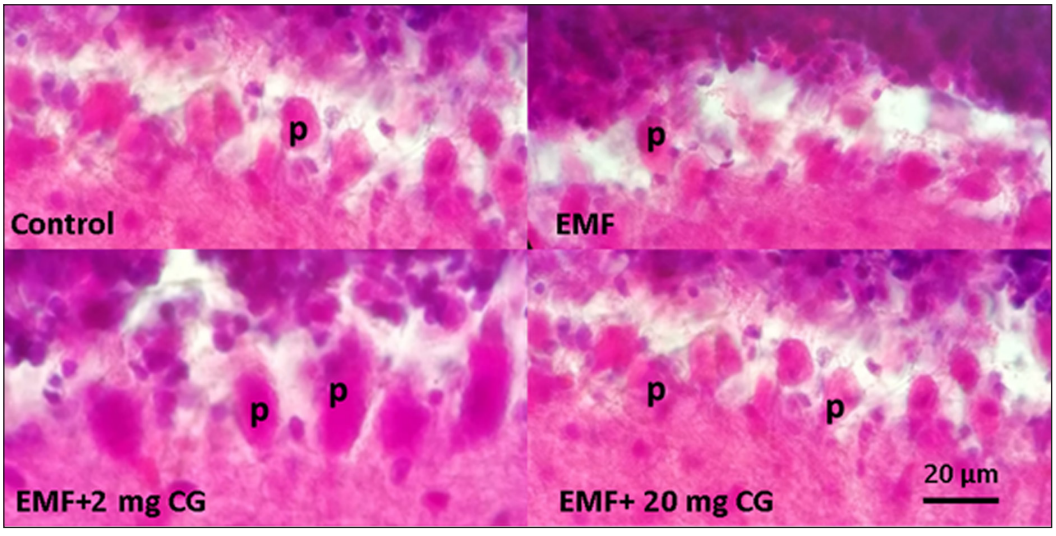

Figure 3: The photos of the groups are shown. Typical Purkinje (p) cell arrangement.

Table I: The Total Number of Purkinje Cell Numbers in the Cerebellums of the Female Rats, Min-Max and Mean± SD for all Groups and CV and CE of Stereological Analysis

Cerebellum	Control	EMFG	EMFG plus 2mg carnosine	EMFG plus 20mg carnosine
1	199,067	145,379	194,794	261,544
2	292,083	187,597	141,628	121,230
3	208,852	98,525	112,984	199,386
4	181,657	67,414	101,650	199,741
5	292,083	83,134	164,821	143,812
6	292,083	88,493	168,774	210,967
CE	0,02	0,03	0,02	0,02
CV	0,09	0,10	0,09	0,10
Min-Max	181,667-292,083	67,414-187,607	101,650-194,794	121,230-261,544
Mean ± SD	244,304 ± 53,055	111,757 ± 45,571	147,441 ± 35,545	189,446 ± 50,203

Table II: Statistical Analysis for Each Group Comparation Using One Way ANOVA

	Experimental groups		
Mean differences	EMFG	EMFG plus 2 mg carnosine	EMFG plus 20 mg carnosine
Control	132,547**	96,862**	54,857
EMFG		-35,684	-77,689*
EMFG plus 2 mg carnosine			-42,004

***: 0,05 level, **: 0,001 level the mean difference between two groups.*

of Purkinje cells compared to the control group. A study on the effects of cellphone radiation on cognitive function in mice exposed to a 900 MHz EMF for 2.5 h per day from a cell phone for 4 days found that animals exposed to an EMF during learning exhibited deficiencies in the transfer of spatial knowledge and acquired it much later compared to the control group (10).

Several studies have indicated that 900 MHz EMF influence neurons in the cerebellum (1,29,34). Many of these studies have stated that the EMFG showed significant decreases in cerebellar Purkinje cells and hippocampal pyramidal neurons (4,34).

Studies have shown that a reduction in the number of Purkinje cell indicates cerebellar damage (9). The hippocampus, cerebellum, and basal ganglia, all of which are brain-related structures, are known to be affected by exposure to 2 h of EMF produced by mobile phones at distinct forces (32). Several recent studies have shown that EMFs radiated by cell phones could influence the cerebellum (12,22,33,34). As such, scientists have investigated the impact of exposure to a 900 MHz EMF for 1 h per day over 28 days on the number of cerebellar Purkinje cells in 16-week-old female rats (1,29,34). The aforementioned study found that the EMF group had a remarkably lower number of the Purkinje cells compared to the Sham-EG and Non-EG groups. Other studies using the optical dissector method have also shown that cell phones significantly reduced the number of Purkinje cells in the developing cerebellum (29,34). Such results showed that long-term and sustained exposure to a 900 MHz EMF causes pathological effects on the cellular level in the brain of young adult rats. The abnormal number of Purkinje cells in rats exposed to EMF may have been caused by neuronal damage related to oxidative stress after exposure to a 900 MHz EMF (1).

One study reported degeneration and substantially fewer Purkinje cells in lobule I of the rat cerebellum within the early 24 h after only alcohol exposure on postnatal day (20). Another study noted that pups exposed to alcohol throughout pregnancy had remarkably reduced number of Purkinje cells (21). Scientists have proposed that diclofenac administered throughout the prenatal term might influence the Purkinje cells in the developing cerebellum (25,26,30). Another study indicated that exposure to a continuous 900 MHz EMF for an hour daily throughout adolescence can alter the cerebellar morphology and decrease the number of Purkinje cells in adolescent rats (1). In another study, caffeine had been shown to protect Purkinje cells in the cerebellum of rats exposed to an EMF (14). Although some studies have reported that exposure to a 900 MHz EMF promoted pathological effects on rat brains at the cellular level, no study has yet utilized carnosine during EMF exposure.

One study investigating the anti-ischemic effects of carnosine in mice showed that plasma levels of carnosine peak 30–45 min after intraperitoneal injection into rats (36). Another study revealed that carnosine exerted neuroprotective effects against retinal ganglion cell loss in optic neuropathy (17).

Evidence has suggested that 500–1000 mg/kg of carnosine is required to induce substantial neuroprotective effects against cerebral ischemia in rats (35). One study concluded that carnosine administered intravenously at 100, 500, 1000, and 2000 mg/kg for 14 days had no toxic effects and reduced cell death (31). After reviewing the available literature, we decided to administer 100 and 10 mg/kg of carnosine before EMF exposure for 28 days.

The current study has some limitations worth noting. First, the brain weight and volume of the rats were not measured. Secondly, we could not determine the cerebellar volume and weight of the rats. Very few studies on cell counting studies related to EMF have used protective agents. However, the stereological method has yet been used to determine the impact of carnosine on the number of Purkinje cells in female rats. For this reason, we believe that this study will facilitate the undertaking of further studies.

The current study showed that female rats exposed to EMF had reduced Purkinje cell count in the cerebellum, whereas the EMF plus 20 mg carnosine group exhibited improved total Purkinje cell counts. Therefore, high-dose carnosine could be suggested to prevent the effects of EMF exposure.

Scientists have stated that carnosine reduces neuronal cell death (28). In fact, one study that administered carnosine to 36 patients with Parkinson's disease aged 46–68 at a daily dose of 1.5 g for 30 days showed that neurological function improved and that DOPA therapy increased its effectiveness (6). Another study on 75 adult patients with chronic schizophrenia aged 18–65 years who were administered 2 g of carnosine per day for 3 months showed that carnosine should be considered an adjunct therapy to improve executive dysfunction in patients with schizophrenia (8).

Unfortunately, we could not identify any study in which carnosine had been used to protect Purkinje cells in the cerebellum. To convert these preclinical results into clinical therapy, exact adjustments on the pharmacological mechanism and carnosine dose are required. Overall, the current study showed that carnosine prevented the reduction in the number of Purkinje cells in the cerebellum after EMF exposure, indicating that carnosine can prevent EMF-induced neuron injury in the cerebellum.

ETHICS STATEMENTS

The work was certified with the Animal Ethic Committee of Erciyes University, protocol, 13/82 (12.06.2013). Histopathological procedures were conducted in the Department of Histology-Embryology in the Erciyes University, Faculty of Medicine. Cell counts process were obtained from Department of Anatomy in the Faculty of Medicine, Erciyes University.

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AUTHORSHIP CONTRIBUTION

Study conception and design: AA, NA, HK, MFS

Data collection: AA, NA

Analysis and interpretation of results: AA, NA, UD, OGS

Draft manuscript preparation: AA, NA, TE, MG

Critical revision of the article: AA, NA

Other (study supervision, fundings, materials, etc...): HK, UD, OGS

All authors (AA, NA, HK, MFS, TE, MG, UD, OGS) reviewed the results and approved the final version of the manuscript.

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