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EFFECTS OF EXTREMELY LOW-FREQUENCY MAGNETIC FIELD ON HEALTHY FIBROBLASTS AND BREAST CANCER CELLS

ÇOK DÜŞÜK FREKANSLI MANYETİK ALANIN SAĞLIKLI FİBROBLAST VE MEME KANSERİ HÜCRELERİNE ETKİSİ

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ABSTRACT

Objective: Modern people are exposed to many environmental factors, including Extremely Low-Frequency Magnetic Fields (ELF-MF). ELF-MFs are emitted from everything that produces electricity or that it passes through. Some studies have shown no significant detrimental effect of ELF-MFs on biological systems, while other studies have shown that ELF-MFs increase the risk of the development of childhood leukaemia (1). Moreover, the 40 Hz-7mT range ELF-MF has been used as a magnetotherapy instrument (2). In this study, we aimed to compare the effect of ELF-MF on healthy dermal fibroblasts and breast cancer cells (MCF7).

Material and Method: After the administration of 1 mT-50 Hz ELF-MF to healthy and cancer cells for different exposure times, apoptosis/necrosis levels were investigated and cell cycles and proliferation indexes were examined. The Analytic Hierarchy Process (AHP) was applied to find the most effective dose.

Results: The ELF-MF did not show any significant effect on MCF7 cells. However, it caused increased apoptosis and decreased proliferation of healthy fibroblast cells. Furthermore, no changes in the cell cycle were observed in either cell line. As a result of AHP, the most effective exposure was determined to be 1 hour.

Conclusion: Our results showed that while the ELF-MF reduces the viability of healthy fibroblasts, it has not observed therapeutic effect on breast cancer cells.

Keywords: Extremely low-frequency magnetic field, ELF-MF, apoptosis, proliferation, MCF, healthy fibroblasts

ÖZET

Amaç: Modern insan, çok düşük frekanslı manyetik alan (ELF-MF) da dâhil olmak üzere birçok çevresel etkene maruz kalmaktadır. ELF-MF, içinden elektrik geçen veya üreten her şeyden yayılır. Bazı çalışmalar ELF-MF'nin biyolojik sistemler üzerinde önemli bir zararlı etkisi olmadığını göstermişken, diğer çalışmalar ELF-MF'nin çocukluk çağı lösemisi geliştirme riskini arttırdığını göstermiştir (1). Dahası, 40 Hz-7mT gücündeki ELF-MF bir magnetoterapi aracı olarak kullanılmaktadır (2). Bu çalışmada, ELF-MF'nin sağlıklı dermal fibroblastlar ve meme kanseri hücreleri (MCF7) üzerindeki etkisinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Farklı maruziyet süreleri için sağlıklı ve tümör hücrelerine 1 mT-50 Hz ELF-MF uygulandıktan sonra apoptoz/nekroz seviyeleri araştırılmıştır; hücre döngüleri ve proliferasyon indeksleri incelenmiştir. En etkili dozu bulmak için Analitik Hiyerarşi Süreci (AHP) uygulanmıştır.

Bulgular: ELF-MF, MCF7 hücreleri üzerinde herhangi bir anlamlı bir etki göstermemiştir. Bununla birlikte, sağlıklı fibroblast hücrelerinde apoptozun artmasına ve proliferasyonunu düşmesine sebep olmuştur. Ayrıca, her iki hücre hattında da hücre döngüsünde herhangi bir değişiklik gözlemlenmemiştir. AHP sonucunda en etkili maruziyetin 1 saat olduğu belirlenmiştir.

Sonuç: Elde ettiğimiz sonuçlar, ELF-MF'nin sağlıklı fibroblastların canlılığını azaltırken meme kanseri hücreleri üzerinde herhangi bir terapötik etki yaratmadığını göstermiştir.

Anahtar Kelimeler: Çok düşük frekanslı manyetik alan, ELF-MF, apoptoz, proliferasyon, MCF, sağlıklı fibroblast

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INTRODUCTION

Extremely low frequency (ELF) fields are electromagnetic fields (EMF) with frequencies below 300 Hz. They are included in the lower part of the electromagnetic spectrum. Many studies have reported that ELF exposure causes significant changes in cell survival, cell cycle progression, DNA integrity, and proliferation (3-8). However, there are many conflicting studies regarding the consequences of ELF-MF in cells (5). Some studies have shown that magnetic therapy can be utilized as an invasive method used in the treatment of several diseases (9-17). In contrast, other epidemiological studies have concluded that continuous environmental magnetic field exposure increases the risk of cancer (18, 19). The cellular response to ELF-MF may depend on many parameters including frequency, waveform, the strength and the exposure duration of the electromagnetic field, and genetic/biological characteristics of the cells (4, 20, 21).

The present study investigated and compared the effect of ELF-MF on healthy fibroblasts and breast cancer cells. Healthy and tumour cells were exposed to a 1 mT ELF-MF at 50 Hz frequency for 1, 3, and 5 hours, and then the cell cycle, proliferation, and apoptosis/necrosis were observed in comparison.

MATERIAL AND METHOD

In-vitro ELF-EMF exposure system

In vitro exposures were performed using the Helmholtz paired coil-based ELF exposure system (Figure 1) settled in a 5 % CO_2 incubator at 37°C. A 50 Hz sinusoidal magnetic field, which was homogeneous throughout the axis of the coil pair, was generated with this system. The identical coils configured in the Helmholtz design were made up of 100 turns of copper wire with a diameter of 13 cm. The power generator which produced the AC magnetic field was connected to the coils. The coils were settled in a horizontal plane to produce a vertically oriented magnetic field. The distance between the coils was 6.5 cm. The electrical parameters of the coils are given in Table 1. The magnetic field was measured using a Hall-Effect Gaussmeter (Yokogawa, Tokyo, Japan). The petri dishes containing cell suspensions were located at the centre of the coil-based exposure system which had a homogenous ELF-EMF distribution. The cells were exposed to a 50 Hz ELF-MF with a field strength of 1 mT for 1, 3, and 5 hours.

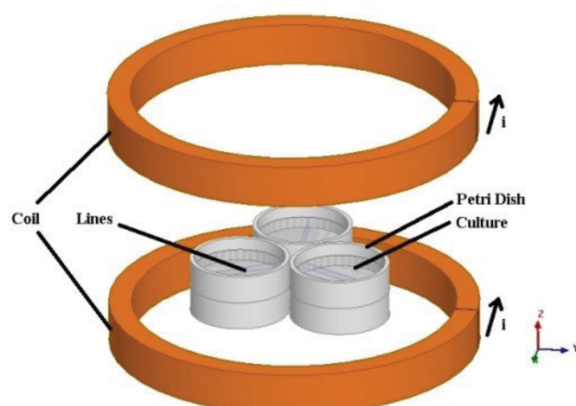


Figure 1: Schematic diagram of the Helmholtz coil-based ELF exposure system.

Table 1: The electrical parameters of the coils.

Coil Parameters	Value
Number of turns	100
Inner diameter (cm)	11.4
Outer diameter (cm)	13
Thickness (cm)	1.5
Resistance	5.15
Inductance	5.4

Cell culture

Human, neonatal, healthy primary dermal fibroblast (ATCC® PCS-201-010™) and MCF7 cell lines (ATCC® HTB-22™, human metastatic breast cancer cells) were maintained in Dulbecco's modified Eagle medium supplemented with 10% heat-inactivated fetal bovine serum (FBS), 50 U/ml penicillin and 50 µg/ml streptomycin. The cells were cultured in a 95% humidified atmosphere containing 5% CO_2 at 37 °C. These adhesive cells were passaged every three days by trypsinization and washed with Ca and Mg-free phosphate-buffered saline (PBS) and fed with the same media. They were seeded on a 24-well plate 24 h before starting the experiments. 2×10^5 cells were plated for each well. The control group, consisting of both healthy fibroblasts and MCF7 cells, was kept in a separate incubator with the same conditions and was not exposed to an ELF-MF.

Cell survival

WST-1 Assay (Roche, Cell Proliferation Reagent WST-1) was applied for cell viability. This is a colorimetric test for the relative quantitation of cell proliferation in a culture medium. Briefly; after the exposures, 10000 cells/well in 90 µl DMEM were plated in 96-well plates and 10 µl of cell proliferation reagent WST-1 was added to each well and incubated for 2 hours. After incubation, the plate was read with the TECAN-Sunrise ELISA Reader (Switzerland) at 450 nm with a reference of 630 nm. The reference readings were subtracted from the original readings at 450 nm. The results were presented as a percent of cell viability (% of control). All experiments were performed in triplicate under blind conditions.

Annexin-V-FITC/ Propidium iodide (PI) Staining

The percentages of apoptotic and necrotic cells were analysed using Annexin-V-FITC and Propidium Iodide (PI)

staining (eBioscience, Annexin V-FITC Apoptosis Detection Kit) using a flow cytometer (BD Bioscience, FACSCalibur) in this study. The change in the plasma cell membrane is one of the earliest features of apoptosis. The exposure of phosphatidylserine (PS) from the cytoplasmic surface of the plasma cell membrane to the external surface is one of the hallmarks of early-phase apoptosis. The membrane remains intact in this phase. The translocation PS to the external surface may be determined using several fluorescence probes. Annexin-V is a 35–36 k DA Ca^{2+} dependent anti-coagulant protein and has a high affinity for binding PS. Necrotic cells are permeable for Propidium Iodide (PI) which intercalates in DNA bases and emits red fluorescence.

Briefly, when ELF treatments were applied, the cells were washed and resuspended in 195 µl binding buffer at a density of $2x10^5$ cells/ml. Then, 5 µl Annexin-V-FITC (eBioscience) dye was added to each cell suspension (195 µl). The cells were gently vortexed and incubated for 10 min in the dark. Afterwards, the cells were washed at 1200 rpm for 5 minutes, the supernatant was discarded and the pellet was resuspended in 190 µl binding buffer. 10 µl PI (20 µg/ml) was added to each cell suspension and the samples were read and analysed using the FacsCalibur Flow Cytometer (Becton–Dickinson). All experiments were performed in triplicate under blind conditions.

Analytical Hierarchy Process (AHP)

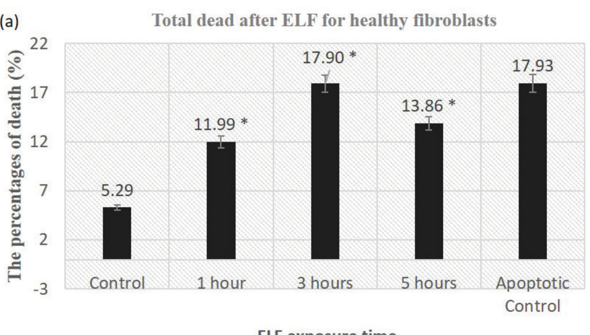
AHP is a numerical method that allows you to sort decision options and select one of them according to the multiple criteria specified. To implement this method, the following steps are performed: first, each decision option is given numerical points showing how much it meets the set criteria. For example, we used the averages of our test results. Then, by making binary comparisons, a matrix is created for each alternative. These matrices are normalized and their consistency is checked. Then, with the help of matrix algebra, an average score is obtained for each alternative. The alternative with the highest score is the most appropriate alternative according to the decision maker's comparisons.

Statistical method

All data were analysed using the independent one-tailed Student's t-test. $p<0.05$ was considered as statistically significant.

RESULTS

Our data showed that the ELF-MF did not affect proliferation, apoptosis, and cell cycle of breast cancer cells (MCF7). However, the proliferation of healthy breast fibroblasts was decreased (Figure 2) and apoptosis (Figure 3) was increased significantly. For the first time, the effect of ELF-MF on healthy fibroblasts and breast cancer cells was investigated simultaneously.



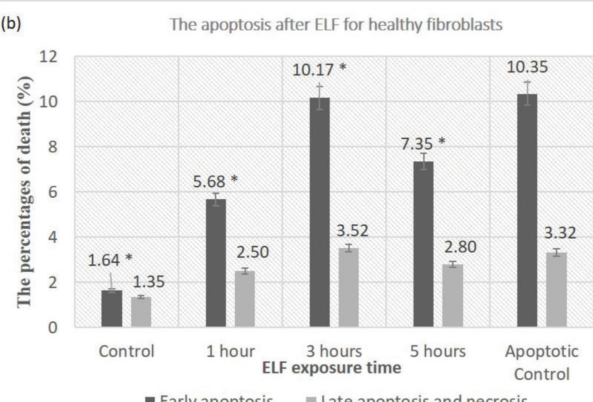


Figure 2: The total dead (a), early apoptosis, late apoptosis and necrosis (b) percentages after 1 mT-50 Hz ELF-MF exposures on healthy fibroblasts. It was observed that the ELF-MF triggers apoptosis but does not cause necrotic death. *The statistically significant percentages.

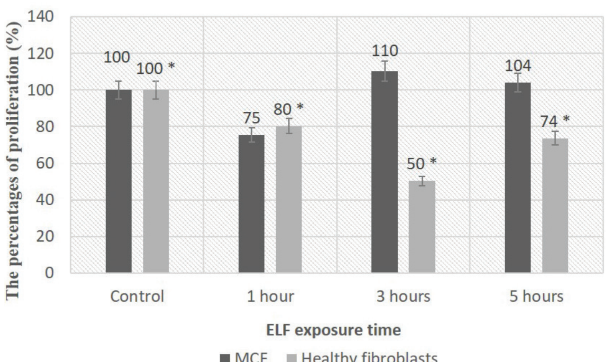


Figure 3: The figure shows viability rates in breast cancer cells and healthy fibroblasts after 1 mT-50 Hz ELF-MF exposure. *The statistically significant percentages.

The AHP method was applied and as a result of the AHP matrix, we concluded that 1-hour ELF-MF exposure was the most effective exposure time.

DISCUSSION

Studies have shown that ELF-MFs can have different effects in different tissues/cell lines. The biological mechanism of the cells' response to it has not been elucidated yet. After ELF-MF exposure, activation of inflammatory pathways or significant reactive oxygen species (ROS) accumulation occurs in some cell lines, while some other cell lines were found to have no significant effect. This may be due to genetic differences. Although ELF-MFs seem to have very low energy to cause mutations in DNA, they may make the cells more vulnerable to the harmful effects of the environment by epigenetic means and thus pave the way for tumour formation. Indeed, a study showed that ELF-MFs did not directly affect the methylation or histone modifications of leukaemia cells but made them susceptible to DNA and histone modifications by stabilizing active chromatins (1). Some groups showed that oxidative stress levels were increased and reactive oxygen species (ROS) accumulation occurred after ELF-MF exposure (22, 23). The increase in the amount of ROS formation may cause DNA damage implicitly and apoptotic cell death. ELF EMFs may affect the permeability of the plasma cell membrane which may cause dysfunction of ion channels existing on the membrane. Moreover, it has been observed that free radical scavengers have the ability to prevent genotoxic effects. These observations supported the idea the ELF-EMFs may induce ROS production which may lead to DNA damage (8, 24). The Fenton reaction in which hydroxyl radicals are generated may play an important role in free radical generation in ELF exposed systems (25). Moreover, it was indicated that the ELF-MFs altered some antioxidant genes such as *SOD2, GSTM3, MGST1,* and *MGST3* (26). Some groups showed that immune cell activation occurred due to the 50 Hz and 1 mT ELF-EMF exposure. ELF EMFs may also induce cytokine formation (IL-IB) in addition to free radicals in human monocytes (27-29).

In this study, we have seen the effects of ELF-MFs on two different cell lines, one healthy group and one tumour cells group, with a healthy primary dermal fibroblast and with human metastatic breast cancer cells (MCF7). The apoptotic activity of cancer cells exposed to ELF-MFs has been investigated in different tumour types in the literature. A 50 Hz, 45 mT ELF treatment for 1- 2.5 h induced apoptotic cell death in Human Myelogenous Leukemic cell lines (HL60 and ML-1) cells (30). No significant change was observed in the apoptotic rate of healthy peripheral leukocytes in the same exposure conditions (30). The number of apoptotic cells and micronucleus formation was increased significantly when SCL II (human squamous cell carcinoma) cells were treated with 50 Hz and 0.8–1 mT ELF-EMF for 48 and 72 h (31). Chen et al (32) reported a significant reduction in viability of HeLa cells that were exposed to a 60 Hz, 1.2 mT ELF for 72 h. Similarly, in another study, the survival rate of PC–12 cells was decreased when they were exposed to the ELF at 60 Hz (33). The short term effects of exposure to a 1.5 mT, 1 Hz ELF field has been shown in human colon adenocarcinoma cells. The proliferation rate of cells was significantly decreased due to 360 min ELF exposure (33). Dexamethasone induced cell proliferation inhibition was observed in HCA–2 human adenocarcinoma cells that were exposed to 25 Hz, 1 mT ELF for durations of between 45 and 120 min (34). ELF EMFs may also be used in cancer treatment. A 0.5 mT (1 h per day) ELF-EMF exposure reduced implanted tumour growth in mice (35). Similarly, the survival rate of human colon and breast adenocarcinoma cells was decreased due to 1 mT ELF exposure (36).

The results of our study showed that the ELF-MF did not affect breast cancer cells. However, it led to the death of healthy cells. Also, the ELF-MF did not alter the cell cycle of healthy fibroblasts showing that it did not cause any arrest i.e. the DNA repair mechanism might not work. Although ELF-MFs have been shown to cause changes in inflammatory pathways, immune system, ROS accumulation, histones, and some genes, studies to date have still needed research on how the mechanism works. The study we conducted showed the damaging effect of ELF-MFs on healthy cells.

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