

Zinc Supplementation Ameliorates Electromagnetic Field-Induced Lipid Peroxidation in the Rat Brain

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BEDİZ, C.S., BALTACI, A.K., MOGULKOC, R. and ÖZTEKİN, E. *Zinc Supplementation Ameliorates Electromagnetic Field-Induced Lipid Peroxidation in the Rat Brain.* Tohoku J. Exp. Med., 2006, **208** (2), 133-140 — Extremely low-frequency (0-300 Hz) electromagnetic fields (EMFs) generated by power lines, wiring and home appliances are ubiquitous in our environment. All populations are now exposed to EMF, and exposure to EMF may pose health risks. Some of the adverse health effects of EMF exposure are lipid peroxidation and cell damage in various tissues. This study has investigated the effects of EMF exposure and zinc administration on lipid peroxidation in the rat brain. Twenty-four male Sprague-Dawley rats were randomly allocated to three groups; they were maintained untreated for 6 months (control, $n = 8$), exposed to low-frequency (50 Hz) EMF for 5 minutes every other day for 6 months ($n = 8$), or exposed to EMF and received zinc sulfate daily (3 mg/kg/day) intraperitoneally ($n = 8$). We measured plasma levels of zinc and thiobarbituric acid reactive substances (TBARS), and levels of reduced glutathione (GSH) in erythrocytes. TBARS and GSH levels were also determined in the brain tissues. TBARS levels in the plasma and brain tissues were higher in EMF-exposed rats with or without zinc supplementation, than those in controls ($p < 0.001$). In addition, TBARS levels were significantly lower in the zinc-supplemented rats than those in the EMF-exposed rats ($p < 0.001$). GSH levels were significantly decreased in the brain and erythrocytes of the EMF-exposed rats ($p < 0.01$), and were highest in the zinc-supplemented rats ($p < 0.001$). Plasma zinc was significantly lower in the EMF-exposed rats than those in controls ($p < 0.001$), while it was highest in the zinc-supplemented rats ($p < 0.001$). The present study suggests that long-term exposure to low-frequency EMF increases lipid peroxidation in the brain, which may be ameliorated by zinc supplementation. ——— electromagnetic field; lipid peroxidation; zinc; brain

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An electromagnetic field (EMF) is a force field associated with electric current, containing a definite amount of electromagnetic energy. EMF

is a major environmental concern, and may well constitute a risk to human health even at current pollution levels (van Wijngaarden et al. 2000;

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Yeniterzi et al. 2002; Qui et al. 2004). When a current passes through a conductor, heat is produced and is absorbed by living tissues, in the form of non-ionizing radiation. Each electrical home appliance from kitchen stove to television is an EMF source which may affect human health. So are home and office computers, which many of us use for hours each day. High levels of intensity and the power of EMFs and waves increase free radical formation (Moustafa et al. 2001; Zmyslony et al. 2004; Simko et al. 2006). Exposure to low-frequency EMF (0-300 Hz) can lead to cell death, as a result of the increase in free oxygen radicals and DNA damage (Blumenthal et al. 1997; Lai and Singh 2004; Yokus et al. 2005). It is still uncertain whether exposure to power-line frequency EMF may constitute a risk to human health. However, scientists believe that the longer the exposure to electrical and magnetic fields, the greater the harm caused (Kaune et al. 2002; Yokus et al. 2005). Electromagnetic radiation can also influence cells and molecules (Yasui and Otaka 1993; Yeniterzi et al. 2002). The incidence of coronary heart disease (Savitz et al. 1999), brain tumor (Savitz and Loomis 1995), leukemia (Tynes and Haldorsen 2003), lymphoma (Villeneuve et al. 2000), soft tissue malignancies (Stuchly et al. 1991; Beniashvili et al. 2005), headache and depression (van Wijngaarden et al. 2000; Iyer et al. 2003), birth and reproduction anomalies (Shaw 2001; Blaasaas et al. 2002), and Alzheimer disease (Qiu et al. 2004) was increased in those exposed to magnetic fields.

It has been noted that zinc has a relationship with many enzymes in the body and can prevent cell damage through activation of the antioxidant system (Powell 2000; Ozturk et al. 2003b; Ozdemir and Inanc 2005). One study has shown that zinc deficiency in the diet paved the way for cell damage in rat testicles (Oteiza et al. 1999). Furthermore, zinc deficiency increased the lipid peroxidation in various rat tissues, whereas zinc supplementation corrected the impairment (Shaheen and el-Fattah 1995; Ozdemir and Inanc 2005).

This study examined the effects of long-term

exposure to EMF and zinc administration on lipid peroxidation in the rat brain.

MATERIALS AND METHODS

The study was conducted on adult male Sprague Dawley rats at the Experimental Medicine Research and Application Center of Selcuk University. All animal procedures were approved by the Center's Ethical Committee. Twenty four rats (eight per group) were randomly divided into three experimental groups. All animals were fed with basic food and tap water and housed in similar cages. Control rats were exposed to sham EMF; sham-exposed rats were held in the same but non-energized cages as the EMF-exposed rats.

Rats were exposed to a 50-Hz EMF for 5 min every other day for 6 months (EMF), or exposed to a 50-Hz EMF in the same way and received a daily intraperitoneal injection of 3 mg/kg/day zinc sulfate in isotonic saline solution of less than 0.5 ml for 6 months (EMF + Zinc).

These animals were sacrificed at the end of the study and blood samples and brain tissues were removed for biochemical analyses. At the beginning of the study the mean weights of the rats were not statistically different. They were weighed at the end of the study, and weight gains recorded.

Formation of the magnetic field

EMF was generated by a single coil of an isolated copper wire (0.30 mm in diameter) wrapped around the plastic cages. The number of coils and wire diameter were determined to obtain the desired magnetic field of 50 mG, but avoid overheating that would cause suffering to the animals.

The coils around the cage supplied with a current (12 V exit voltage and 30 W exit power) through a transformer. The feeding voltage was controlled by a dimmer circuit in order to provide the desired field intensity. For fine tuning, a mechanical rheostat was used. An appropriate voltage regulator was used to prevent voltage undulations of the system. In Turkey and in most of Europe, 50-Hz is the electricity systems' alternative current frequency; magnetic field intensity used in this study was 50 mG.

Measurement of the magnetic field intensities

An exact (resolution: 1nT/0.01 mG on 20 mG range, accuracy: $\pm 1\%$ count) broadband magnetometer (Walker Scientific, USA; Broad Band AC magnetometer, BBM 3 D, Walker Scientific, Worcester, MA, USA) was used to

measure magnetic field intensities.

Cages

The animal cages were specially manufactured from polyvinyl chloride (PVC) in order to prevent possible distortions in the magnetic field and to form a homogeneous field. The size of each cage was 35 × 25 × 25 cm. The food and water bowls of the animals were also manufactured from glass and PVC. The cages were placed where the room's background magnetic field intensity was lowest (0.1 mG) in order to minimize the effects of environmental EMFs. The mean temperature of the room was 22°C and relative humidity rate was 55-60%.

Biochemical analyses

Plasma thiobarbituric acid reactive substances (TBARS). The thiobarbituric acid method was employed to analyze plasma malondialdehyde (MDA) levels. The absorbance of thiobarbituric acid-MDA complex at 532 nm was determined by a spectrophotometer (Schimadzu UV-1061, Kyoto) (Draper and Hadley 1990). Plasma TBARS levels were expressed as nmol/ml.

Brain Tissue TBARS. Samples of brain tissues were homogenized with 150 mM KCl at 4°C in order to obtain a 10% homogenate (Microsan Ultrasonic Cell Disruptor Misonic). Two ml HClO₄ was added to a 2 ml homogenate and centrifuged at 3,000 rpm for 15 min. The TBARS level was evaluated in the supernatant. 3 ml H₃PO₄, 1 ml 0.675% thiobarbituric acid, and 0.5 ml homogenate were mixed and kept in boiling-water for 45 min (Uchiyama and Mihara 1977). TBARS levels were measured at 532 nm and presented as nmol/g protein.

Erythrocyte glutathione (GSH) Activity. The erythrocytes were bathed 3 times in 1/5 isotonic saline solution. Erythrocyte GSH activity was determined according to Ellmann method as described by Atroshi and Sandholm (1981). The values were shown as mg/g hemoglobin.

Brain Tissue GSH Activity. Samples of brain tissue were homogenized 150 mM KCl at 4°C to obtain 10% homogenate (Microsan Ultrasonic Cell Disruptor, Misonix, NY, USA) and centrifuged at 3,000 rpm for 15 min. GSH level in the supernatant was determined by Ellmann method (Ellmann 1959). Tissue protein concentration was measured by the biuret method. The GSH level was expressed in mg/g protein.

Plasma Zinc. Plasma zinc levels were measured with inductively coupled plasma emission spectrophotometer ([ICP-AES] Varian Australia Pty Ltd., Mulgrave,

Victoria, Australia) atomic emission equipment. Zinc levels were expressed as μg/100 ml.

Statistical analyses

Statistical analyses were conducted using SPSS statistics software. The results were presented as mean ± s.d. Variance analysis was used and differences among groups were determined by least significant difference (LSD) tests. Level of significance was set at $p < 0.01$.

RESULTS

We measured TBARS levels in the plasma and brain tissues to evaluate oxidative stress, and reduced GSH levels in erythrocytes and brain tissues to assess the activity of the antioxidant system. Plasma TBARS levels were higher in EMF-exposed rats with or without zinc supplementation than those in controls (2.9 ± 0.4 , 8.2 ± 0.8 , and 5.0 ± 0.6 nmol/ml in control, EMF-exposed, and EMF-exposed and zinc-supplemented groups, respectively) ($p < 0.001$). Likewise, brain TBARS levels were higher in EMF-exposed rats with or without zinc supplementation than those in controls (18.5 ± 5.7 , 78.6 ± 9.5 , and 35.4 ± 6.3 nmol/g protein in control, EMF-exposed, and EMF-exposed and zinc-supplemented groups, respectively) ($p < 0.001$). These results indicate that EMF exposure causes an increase in TBARS (Fig. 1).

GSH levels were significantly decreased in the erythrocytes and brains of the EMF-exposed rats. In contrast, in the EMF-exposed and zinc-supplemented rats, the GSH level was significantly higher than in controls and in the EMF-exposed rats (1.8 ± 0.5 , 1.1 ± 0.3 , and 3.1 ± 0.5 mg/g hemoglobin in erythrocytes; 21.6 ± 6.5 , 13.2 ± 3.8 , and 35.8 ± 7.0 mg/g protein in brain tissue of control, EMF-exposed, and EMF-exposed and zinc-supplemented groups, respectively). EMF-exposed zinc-supplemented animals had the highest GSH levels both in erythrocytes and the brain ($p < 0.01$, Fig. 2).

Plasma zinc levels of the EMF-exposed rats were lower than those of control and EMF-exposed zinc-supplemented group, and the levels in control group were lower than those in EMF-exposed zinc-supplemented rats (125.1 ± 15.7 ,

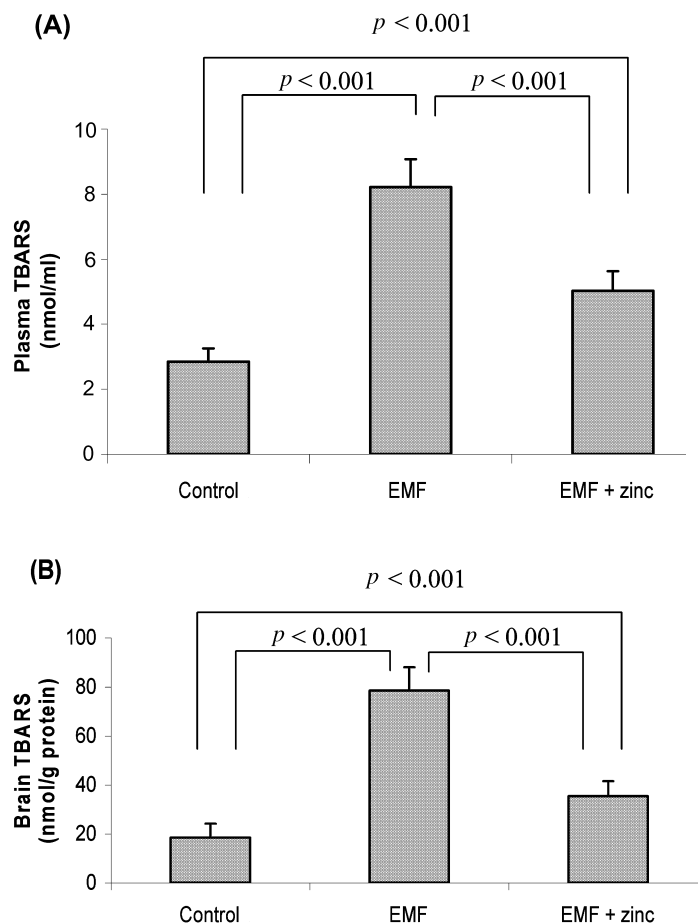


Fig. 1. Electromagnetic field (EMF) exposure increased TBARS levels in plasma (A) and brain (B). Zinc supplementation ameliorated the increase in rats ($n = 8$ in each group, mean \pm s.d.).

86.2 ± 12.4 , and $182.3 \pm 18.3 \mu\text{g}/100 \text{ ml}$ in control, EMF-exposed, and EMF-exposed and zinc-supplemented groups, respectively) ($p < 0.001$, Fig. 3).

Importantly, weight gains were similar among the three groups (105.4 ± 7.2 , 102.7 ± 10.9 , and $103.2 \pm 10.1 \text{ g}$ in control, EMF-exposed, and EMF-exposed and zinc-supplemented rats, respectively) ($p > 0.05$), indicating that intra-peritoneal zinc injection did not cause a significant disturbance in zinc-supplemented rats.

DISCUSSION

In this study, TBARS levels were significantly higher in both plasma and brain tissues of the rats, which were exposed to the EMF of 50-Hz frequency over 6 months. Several other studies

have shown that exposure to EMFs increased free radical formation in various tissues (Moustafa et al. 2001; Zmyslony et al. 2004; Simko et al. 2006). This study is consistent with the previous reports, showing that EMF caused lipid peroxidation in rat liver (Watanabe et al. 1997) and that EMF increased malondialdehyde formation in the rat liver and brain (Romodanova et al. 1990). The present study also revealed that plasma and brain GSH levels were decreased in EMF-exposed rats, which might indicate a reduction in antioxidant defence. Recently, Lai and Singh (2004) have reported that EMF exposure caused DNA strand breaks in brain cells and that damage increased with exposure time.

EMF may increase oxidative stress by altering intracellular calcium and/or iron homeostasis

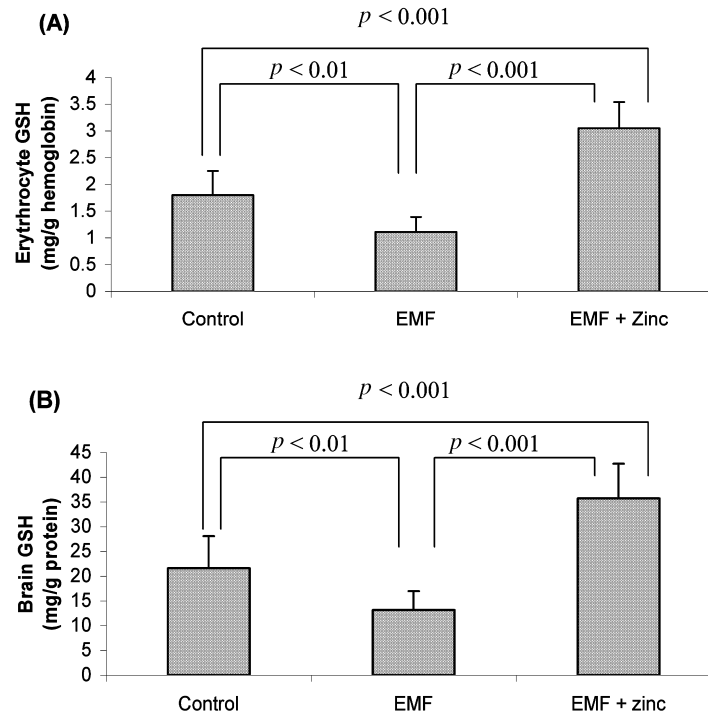


Fig. 2. EMF exposure decreased GSH levels in plasma (A) and brain (B). Zinc supplementation increased GSH levels in rats ($n = 8$ in each group, mean \pm s.d.).

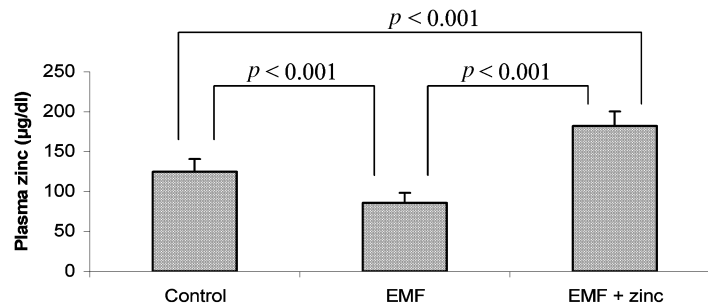


Fig. 3. EMF exposure decreased plasma zinc levels in rats ($n = 8$ in each group, mean \pm s.d.).

(Stevens 2004). Also, EMF impairs free radical scavengers (Reiter et al. 1998), which may contribute to the oxidative damage in the brain. Another contributing factor to EMF-induced oxidative stress may be a zinc deficiency. In consistent with the findings of this study, it has been reported that EMF exposure reduces the zinc levels in plasma and tissues (Ozturk et al. 2003a).

TBARS levels in the plasma and brain tissues of EMF-exposed rats were significantly higher than those of controls. Moreover, the plas-

ma zinc level was significantly lower in EMF-exposed group when compared to the controls. Several researchers reported that a deficiency of zinc in the organism led to lipid peroxidation in various tissues (Koterov and Shilina 1995; Shaheen and El-Fattah 1995; Parat et al. 1997; Ozturk et al. 2003b). It was shown that zinc deficiency caused or increased oxidative stress in rat testicles (Oteiza et al. 1996), kidney (Baltaci et al. 2004), liver (Sidhu et al. 2005), and brain (Yousef et al. 2002). TBARS levels in the plasma and

brain tissues of EMF-exposed and zinc-supplemented rats were significantly lower than those of EMF-exposed rats. Also, the GSH levels of the EMF-exposed and zinc-supplemented rats were higher than those of merely EMF-exposed rats. These results may indicate that zinc has a protective role on EMF-induced oxidative stress in brain cells. The zinc supplementation might contribute to antioxidant defense via elevating the GSH levels. The importance of the zinc on the antioxidant system was highlighted previously (Powell 2000). Earlier studies revealed that zinc deficiency induced free radical formation (Sakaguchi et al. 2002; Yousef et al. 2002) and that zinc supplementation might protect tissues fight against oxidative stress (Ozturk et al. 2003b; Baltaci et al. 2004; Sidhu et al. 2005). Cadmium-induced oxidative stress in rat testicles was increased with zinc deficiency, and zinc supplementation prevented this stress (Oteiza et al. 1999). In addition, Cao (1991) reported that MDA levels were increased in the livers of rats that were fed a zinc-deficient diet increased, whereas zinc supplementation prevented this unfavorable condition. It is note worthy that lipid peroxidation caused by hypothyroidism in rat testicles could be treated with zinc (Tahmaz et al. 2000).

Previously, some substances, such as vitamin E analog, melatonin, and erythropoietin were shown to protect brain cells. Lai and Singh (2004) have reported that EMF exposure caused DNA strand breaks in brain cells and that treatment with a vitamin E analog blocked magnetic field-induced DNA damage. Furthermore, melatonin (Gonenc et al. 2005; Tutuncular et al. 2005) and erythropoietin (Kumral et al. 2005) were reported to reduce lipid peroxidation in the brain. Zinc may also be considered as one of the preventive agents for oxidative stress in brain.

Plasma zinc levels were higher in EMF-exposed and zinc supplemented rats than those in control and EMF-exposed groups. Interestingly, EMF-exposed group had lower plasma zinc levels than those in the control group. This finding suggests that EMF exposure lowered the plasma zinc levels. Our observations of low zinc levels in the EMF-exposed rats were consistent with the study

of Ozturk et al. (2003a), who reported that plasma zinc levels were decreased significantly in rats exposed to an EMF. Therefore, reduced zinc levels may contribute to EMF-induced oxidant stress.

In this study, total brain tissue was used to evaluate TBARS and GSH levels. Actually, stressor agents have different effects on different brain regions (Gonenc et al. 2005). Some parts of the brain are considered to be more vulnerable to oxidant stress. Thus, lipid peroxidation in response to physical or chemical stressors may differ in some brain regions. Further studies would reveal whether some parts of the brain are more vulnerable to EMF exposure.

EMF is one of the stressor agents on the oxidative system. Several methods are used to determine oxidative stress in the organism. In our study, we measured of the amount of MDA, one of the end products of lipid peroxidation, by thiobarbituric acid method which was commonly used to determine oxidative stress in the clinical and experimental studies (Ozcelik et al. 2005; Ozdemir and Inanc 2005; Tutunculer et al. 2005; Unsal et al. 2005). Glutathione levels in erythrocytes and brain tissue were used to show the activity of the antioxidant system. However, the phenomenon of "oxidative stress," is a situation, in which the free radicals and other reactive species accumulate. Normally, a single measurement of one parameter does not provide a complete picture of the total environment. Further studies might reveal the effects of EMF on brain and to define precautions against oxidative damage.

Electrical home appliances are daily sources of comfort. Unfortunately, they are EMF sources and may negatively affect human health, and supplementation of zinc may alleviate the toxic effects of EMF.

CONCLUSION

1. Long-term exposure to EMF leads to lipid peroxidation in the rat brain.
2. Long-term exposure to EMF decreases plasma zinc levels in rats.
3. Zinc supplementation ameliorates the lipid peroxidation caused by EMF in the rat brain.

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