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BIOLOGICAL EFFECTS OF EXTREMELY LOW-FREQUENCY MAGNETIC FIELDS ON STIMULATED MACROPHAGES J774.2 IN CELL CULTURE

A. Kawczyk-Krupka,[1] A. Sieron,[1] J. Shani,[2,*] Z. P. Czuba,[3] and W. Krol[3,†]

[1]Department and Clinic of Internal Diseases and Physical Medicine, Silesian Medical University, 41-902 Bytom, Poland
[2]Department of Pharmacology, The Hebrew University School of Pharmacy, Jerusalem 91120, Israel
[3]Department of Microbiology and Immunology, Silesian Medical University, 19 Jordana Street, 41-808 Zabrze-Rokitnica, Poland

ABSTRACT

Studies with cell cultures indicate that extremely low-frequency magnetic fields may exert distinct biological effects on cellular systems. In the present study, selected biological effects of such magnetic fields are investigated in mammalian J774.2 macrophages in culture. J774.2 murine macrophages were exposed to extremely low-frequency magnetic field (ELF-MF) (25 Hz), and stimulated by lipopolysaccharide (LPS) and/or interferon-γ (IFN-γ). The generation of nitrite (NO_2^-), prostaglandin-E_2 (PGE_2), tumor necrosis factor-alpha (TNF-α), chemiluminescence, and proteins were measured. While 1.5 mT and 25 Hz frequency did not affect the viability of the cells, higher flux density (2.4 mT) impaired it significantly. A 24-h exposure of the cells to such frequencies increased their chemiluminescence

*Affiliated with the David R. Bloom Center for Pharmacy at the Hebrew University, Israel.
†Corresponding author. Fax: +48-32-272-2554; E-mail: wkrol@silesia.top.pl

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count rate and TNF-α levels, but not their PGE_2, NO_2^-, or protein concentrations. These results demonstrate that exposure of J774.2 cells to extremely low-frequency magnetic field, at certain flux densities, decreases cell viability and may have biological significance in the antitumoricidal effect of such magnetic fields.

Key Words: J774.2 macrophages; Extremely low-frequency magnetic field; Free radicals; Nitric oxide; TNF-α; Cell viability

INTRODUCTION

Extremely low frequency magnetic field (ELF-MF) may exert a variety of biological effects in vitro and in vivo, including some cell-sensitive physiological endpoint parameters.[1–5] Among these effects is modulation of DNA and RNA synthesis, cell proliferation, membrane signal transduction, enzyme activity as dependent on frequency, and induction of magnetic fields.

DNA content in human and animal cells, such as human acute myeloid leukemia (HL-60) and mouse fibroblasts, and the number of mammalian cultured cells, in general, decrease significantly after exposure to a 2H-mT/50-Hz magnetic field,[6] while exposure of cultured foreskin fibroblasts to 16 μT/76 Hz significantly increased ^{3}H-thymidine uptake by these cells.[7] Magnetic fields of 50 Hz, at a range of flux densities between 20 μT and 20 mT for up to 30 hr, do not affect the rate of DNA synthesis by healthy human fibroblasts.[8] Several studies have reported that ELF-MF activated proliferation of lymphocytes in vitro.[9,10]

Possible interrelation between ELF-MF and human carcinogenesis has been suggested in numerous studies,[5,11,12] but their results are not conclusive. The effect of a magnetic field depends on magnetic field intensity. No effect of ELF-MF on cell mutations was observed by Antonopoulos et al.[9] and Nguyen et al.,[13] while Miyakoshi et al.[14] observed induction of mutations in the hypoxanthine guanine-phosphoribosyl transferase gene in cultured human MeWo cells after their exposure to high-density magnetic fields.

During exposure of animals with transplanted tumors (Lewis tumor graft in mice, liver cancerous foci in rats, and Ehrlich tumor in mice) to ELF-MF, a significantly prolonged life span of these animals has been observed.[15–19] On the other hand, cytotoxic efficacy of ELF-MF against some particular cell lines (such as human adenocarcinoma, human A-431, and mouse C3H/Bi) has been reported.[20–22] It was suggested that the mechanism of the cytotoxic effect of the ELF-MF is related to its direct disruptive effect on the cell membrane, to its impairment of ionic balance through the membrane, to its initiation of apoptosis, and to diminution of DNA production. Another possible mechanism of ELF-MF action may be stimulation of cells in the immune system: after 13 weeks of exposure to ELF-MF, a statistically significant increase in NK cell function was observed in male rats.[23] Moreover, macrophages are well known to be the first line of anticancer defense in tumor tissues, either by reactive oxygen species or by reactive oxynitrogen intermediates, as well as by excretion of

Therefore, we decided to study the effect of ELF-MF exposure on some biological parameters of J774.2 murine macrophages in culture, with emphasis on those parameters, indicators, and mediators related to tumor growth.

MATERIALS AND METHODS

Materials

Phosphate-buffered saline (PBS), RPMI-640 medium, and inactivated fetal calf serum (FCS) were purchased from GIBCO Life Technologies (Paisley, UK). *N*-(1-naphthyl)-ethylenediamine dihydrochloride, sulphanilamide, heparin sodium (pyrogen-free), and trypan blue were purchased from Serva Chemicals (Heidelberg, Germany). Lipopolysaccharide (LPS) from *E. coli* (serotype 0127:B8) was purchased from Calbiochem (La Jolla, CA); interferon-γ (IFN-γ) and mouse tumor necrosis factor-α (TNF-α) ELISA kit from Genzyme (Cambridge, MA), phorbol-12-myristate-13-acetate (PMA), sodium nitrite and dimethyl sulfoxide (DMSO) from Sigma (St. Louis, MO). Cytotoxic detection kit, a colorimetric assay for quantification of cell death and cell lysis, based on measurement of lactate dehydrogenase (LDH) released from the cytosol of damaged cells into the supernatant, was purchased from Boehringer (Mannheim, Germany), and prostaglandin-E_2 (PGE_2) enzyme immunoassay kit from Cayman Chem. (St. Louis, MO).

Cell Culture

J774.2 murine macrophages were a gift from Prof. Sir John Vane, of the William Harvey Research Institute in London (England), via Prof. Janusz Marcinkiewicz of the Department of Immunology, Jagiellonian University Medical College in Krakow, Poland. This J774.2 cell line was originally established from a spontaneous mouse BALB/c reticulum cell sarcoma.[24] They were cultured either without stimulation or with stimulation by lipopolysaccharide (100 ng/mL) and/or interferon-γ (25 IU/mL). Activated J774.2 macrophages release free radicals of oxygen and nitrogen, eicosanoids (e.g., PGE_2) and cytokines (e.g., TNF-α). Propagation of the cells was performed biweekly, in RPMI-1640 medium supplemented with 10% FCS, 2 mM glutamine, 100 IU/mL penicillin-G-sodium, and 100 μg/mL streptomycin sulfate, in 5% CO_2/95% air at 37°C. For the actual study, the cells were centrifuged at $200 \times g$, resuspended in RPMI-1640 medium supplemented with 10% FCS, at a concentration of 1×10^6 cells/mL, and were seeded at 37°C in test tubes (Falcon, Becton and Dickinson, Lincoln Park, NJ).

Cell Viability and Protein Content

Cell viability was determined by the trypan blue exclusion test, and by lactate dehydrogenase (LDH) concentration in culture supernatants after centrifugation. LDH is

a stable cytoplasmic enzyme present in all cells, and is rapidly released into the cell culture supernatant after the plasma membrane is damaged. Protein content was measured by the Folin phenol reagent.[30]

Chemiluminescence

Chemiluminescence was measured using a low noise-count-rate photomultiplier (model 9214B, EMI, Middlesex, England) as previously described.[29] The light was measured in 2.5-mL tubes, with a sample volume of 1.0 mL. The reactions were initiated by aliquots of luminol solution (0.10 μmol/L) to the J774.2 murine macrophages (10^6/test tube). The resting intensity of the chemiluminescence was recorded 5 min after adding the luminol. PMA solution was then added to the test tubes, in order to obtain a final concentration of 0.3 μmol/L. The light emitted was then recorded continuously for 15 min. The intensity of the chemiluminescence was determined by

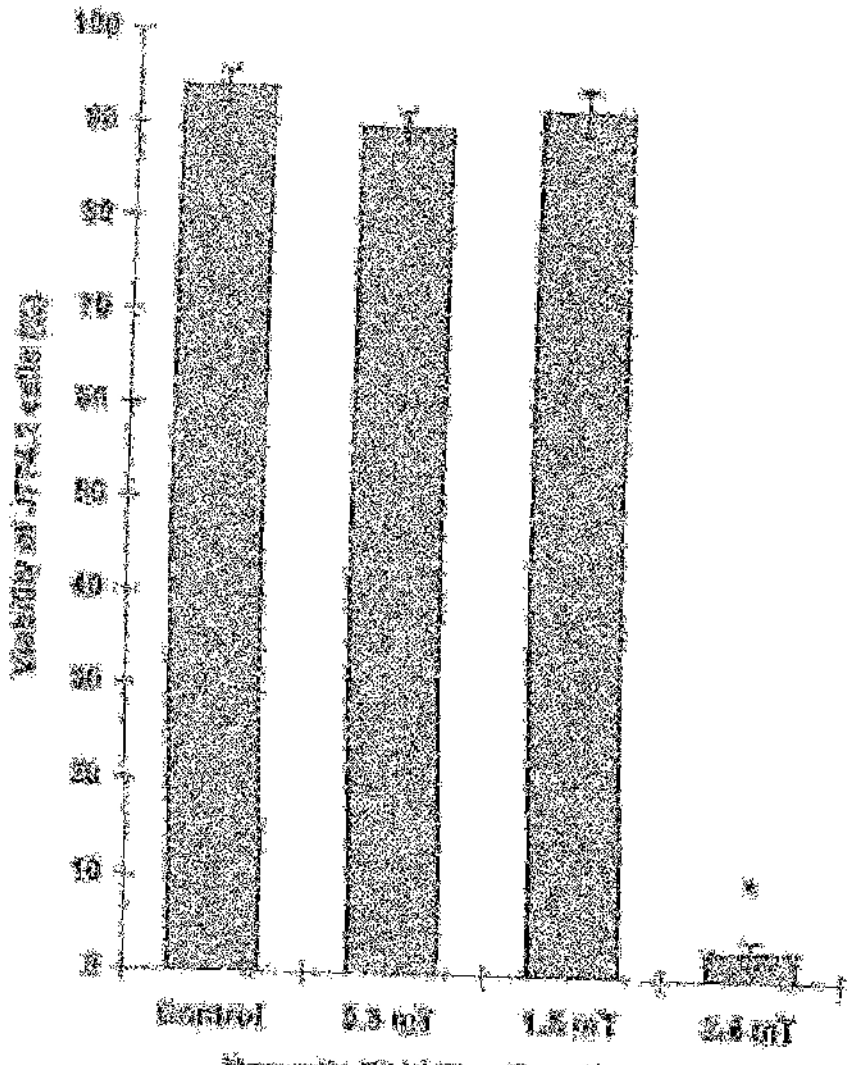

Figure 1. Viability of macrophages J774.2 exposed to a range of ELF magnetic field flux densities as evaluated by the trypan blue exclusion test (mean ± SEM, $n = 3$). $p < 0.001$ as compared to all lower flux densities.

measuring counts per minute (cpm), and by calculating the area under the chemiluminescence intensity curve (integral chemiluminescence). This assay evaluates luminol-dependent chemiluminescence of cells, using PMA as a stimulant of respiratory bursts through activation of protein kinase C (PKC).

Nitrite Assay

The accumulated nitrite, as a stable end product of nitric oxide (NO), was determined colorimetrically by the diazotization reaction, using the standard Griess reagent,[27] as we have previously described.[28] The absorbency of culture medium and Griess reagent at 550 nm was determined with an automated microplate reader EIA800 (Bio-Tec Instruments, Winooski, VT). Nitrite content was determined by using sodium nitrite as a standard.

TNF-α and PGE_2

TNF-α and PGE_2 concentrations were determined by the ELISA method, using the Factor-Test-X™ and the PGE_2 Caymen Chem. kits, respectively.

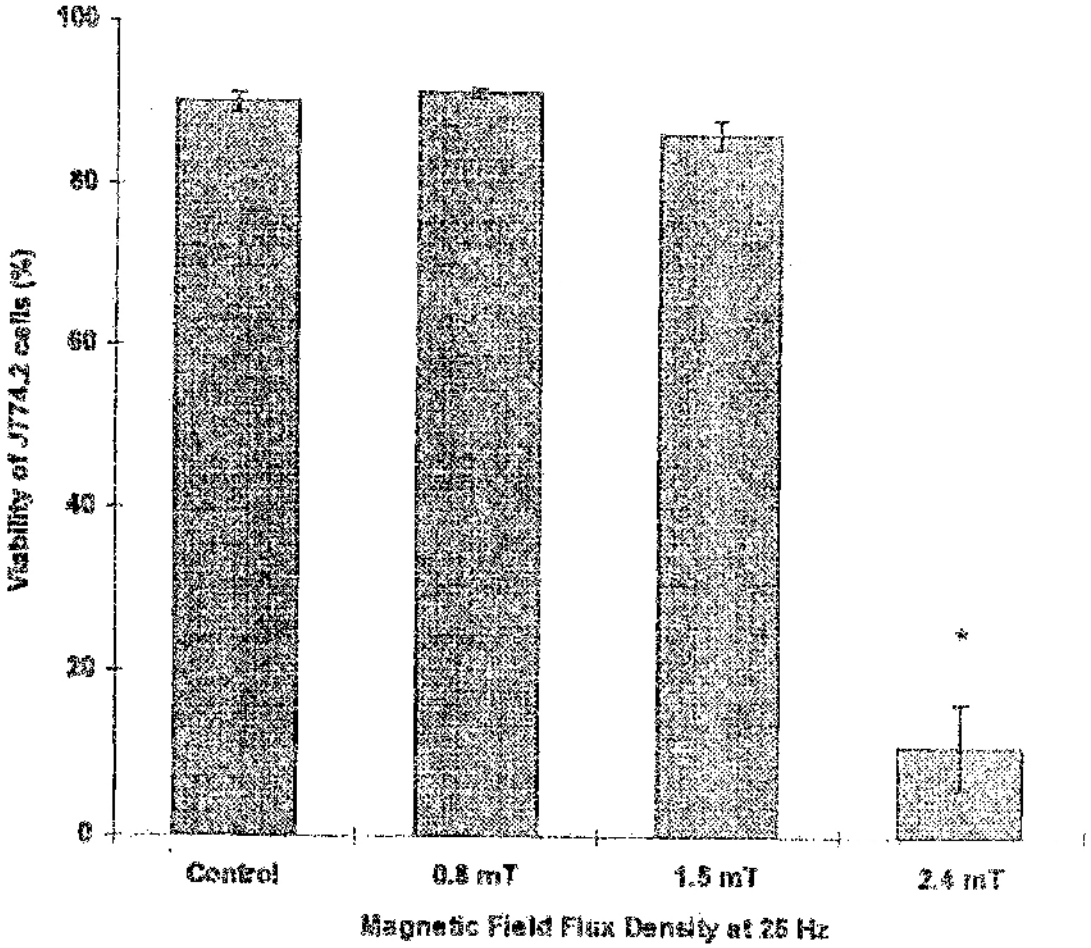

Figure 2. Viability of macrophages J774.2, preexposed to a range of ELF-MF flux densities, as evaluated by LDH concentration in their supernatants (mean ± SEM, $n = 3$). $^{*}p < 0.001$ as compared to all lower flux densities.

Magnetic Field Exposure

For viability studies, cultures of isolated cells were exposed to 25 Hz sinusoidal ELF-MF for 24 hr, and three intensities of magnetic fields were evaluated: 0.8, 1.5, and 2.4 mT. We limited our test samples to exposures at 0.8 mT because exposure at higher levels produced undesirable effects on cell viability. At 0.8 mT, viability was comparable to controls. Magnetic field generator Flora 02 was constructed by Duscan Dajca Elcotrade (Preshov, The Czech Republic). Coils were constructed of copper wire bundles, 16 cm in diameter wound around plastic forms. Before initiating the present studies, operation of the generator was independently validated by the Institute of Physics of the Silesian University in Katowice, Poland. The magnetic field was generated by a magnetic core, which was placed in a CO_2 incubator (Assab Kebo Lab., Spanga, Sweden), and kept at 37°C. Cell cultures were set up in polystyrene tubes 55 × 11 mm (10^6 cell/mL), which were placed in a Styrofoam form, placed in turn inside an 8-cm inner diameter circular coil. The incubator was equipped with a fan. There was no significant effect of the magnetic field from the coil on the control samples. The flux densities of magnetic fields in

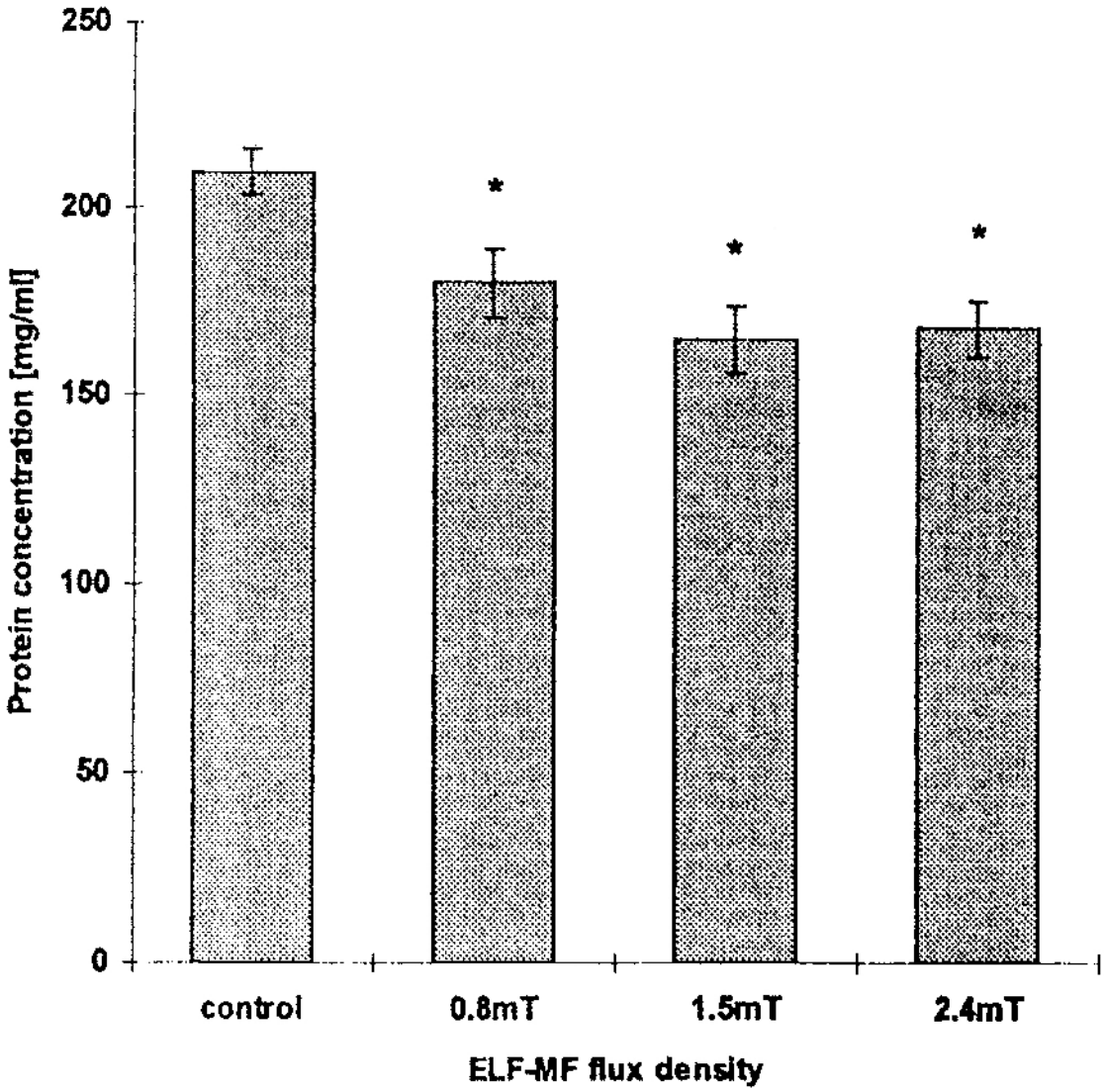

Figure 3. Protein concentrations in the J774.2 macrophages, preexposed to a range of ELF-MF flux densities (mean ± SEM, $n = 5$). $^*p < 0.001$ as compared to nonexposed (control) cells.

the site of the control samples were near zero. The external coil diameter was 16 cm. Unstimulated cells were placed in the same incubator, 30 cm distant from the edge of the coil. The J774.2 cell line was exposed to ELF-MF for a specified length of time in each field, and then both the stimulated and control cells were removed from the magnetic field.

For statistical evaluation of the data, Mann–Whitney *U*-test and the Student's *t*-test were used on all triplicates.

RESULTS

Cell Viability and Protein Content

Viability of the control (unstimulated) macrophages was 90±2% by the LDH test and 94±3% by the trypan blue exclusion test. Two magnetic induction-dependent effects were observed: viability and LDH levels. No significant differences in cell viability were detected at the 0.8 mT/25 Hz and the 1.5 mT/25 Hz between the

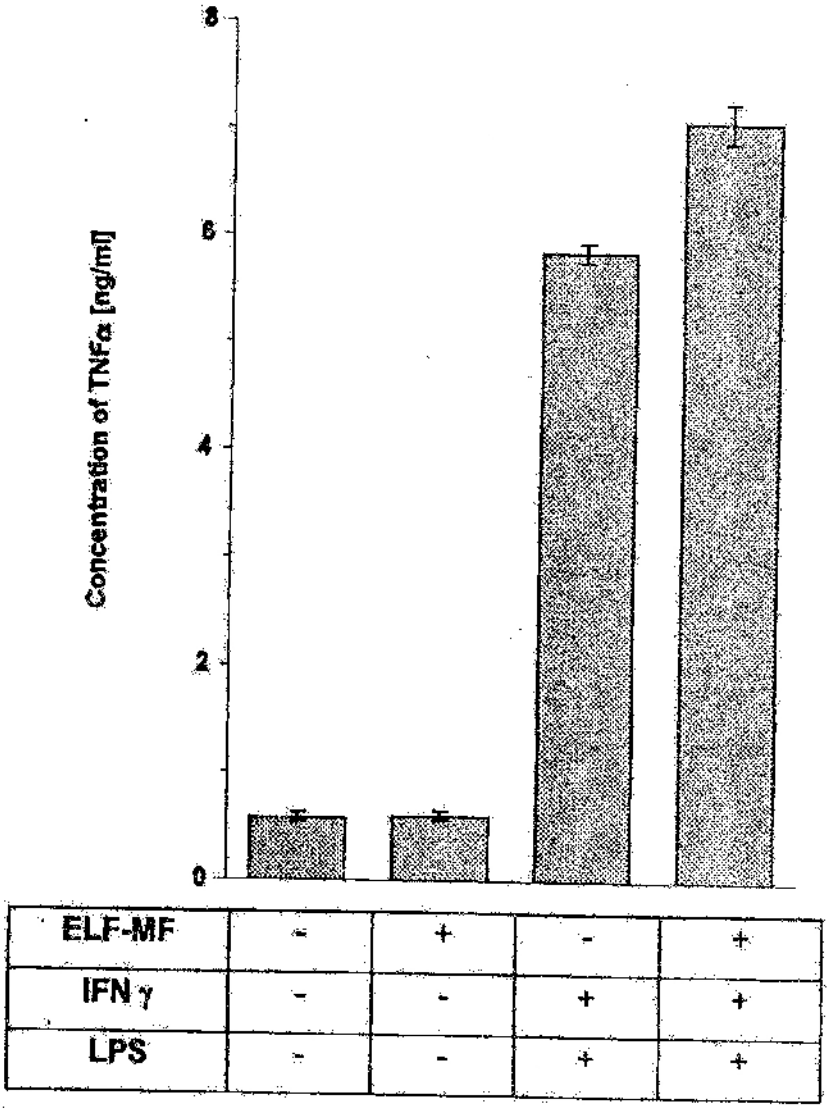

Figure 4. TNF-α production by one or more of the following stimulators: ELF-MF (0.8 mT/25 Hz), IFN-γ (25 IU/mL) and LPS (100 ng/mL) (mean ± SEM, $n = 5$).

control and ELF-MF exposed cells, but at the higher flux density (2.4 mT/25 Hz), the viability of the cells was significantly impaired. Cell viability as recorded by both methods is presented in Figures 1 and 2, respectively. Significant differences were also detected between the control and any of the three experimental cell groups (exposed to flux densities 0.8, 1.5, or 2.4 mT) in regard to their protein concentration (Figure 3).

TNF-α and PGE_2

Significant increase in TNF-α production by the J774.2 cell line was observed after 24 hr of exposure to 0.8 mT/25 Hz ELF-MF. Concentrations of TNF-α in these cells are presented in Figure 4, as a function of their LPS/IFN-γ stimulation. No significant differences in PGE_2 concentrations were detected between the control cells and those exposed to 0.8 mT/25 Hz ELF-MF.

Nitrite Concentrations

Production of nitrite by the J774.2 cells was achieved after their stimulation by both LPS and IFN-γ. This production was gradually increased with time. When the same cells were exposed to 0.8 mT/25 Hz ELF-MF, an additional release of nitrite from them was recorded (Table 1).

Chemiluminescence

Exposure of the J774.2 cells for 24 hr to 0.8 mT/25 Hz ELF-MF resulted in an increase in their count rate, as recorded for 15 min after adding PMA. The levels of their chemiluminescence are presented in Figure 5.

Table 1. Effects of Extremely Low-Frequency Magnetic Field (0.8 mT/25 Hz) on Production of Nitrite (NO_2^-) by Murine J774.2 Macrophages in Culture ($n=3$)

Lipopolysaccharide (LPS) (200 ng/mL)	Interferon-γ (IFN-γ) (25 IU/mL)	Extremely Low-Frequency Magnetic Fields (ELF-MF)	Concentration of Nitrite [NO_2^-] (μM)
−	−	−	0.2±0.1
−	−	+	0.2±0.1
+	−	−	0.6±0.4
+	−	+	0.7±0.4
−	+	−	12±1
−	+	+	12±1
+	+	−	32±2
+	+	+	30±1

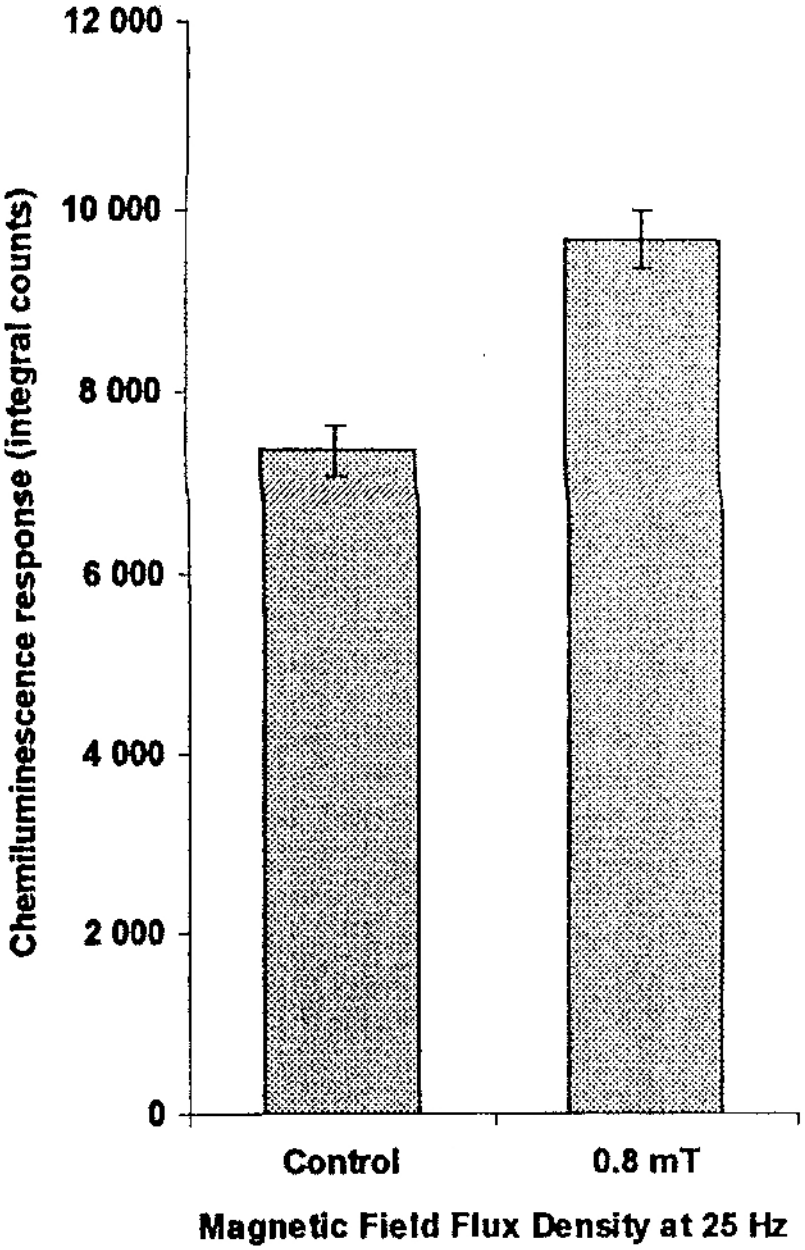

Figure 5. Chemiluminescence emitted from J774.2 macrophages stimulated with 0.16 μM of PMA (without exposure to a magnetic field) and from cells exposed to ELF-MF of 0.8 mT/25 Hz (mean ± SEM, $n = 15$).

DISCUSSION

The purpose of the present study was to determine the effect of extremely low-frequency magnetic field on viability and release of cytotoxic mediators from murine J774.2 macrophages. Earlier studies on a cellular level have demonstrated various biological effects that result from exposure of the cells to ELF-MF. Such cell cultures seem to give a better insight into the effects evoked by ELF-MF within a single cell, as well as enabling measuring the production and release of protective mediators in subcellular organelles.

Studies with different cellular systems, using a variety of exposure setups, exposure durations, amplitudes, frequencies, and wave forms, indicate that ELF-MF affects cell viability.[6,20–22] It also affects multiplication of the cells,[9] mediator sec-

retion,[29] and even tumor promotion.[5,17] There are many reports about biological effects of ELF-MF on healthy and cancerous cells, in vitro and in vivo, and the present study reiterates such studies by demonstrating that exposure of mammalian macrophages to 2.4 mT/25 Hz affects their viability.

Recent studies also demonstrate that ELF-MF can affect cellular viability and proliferation. Schimmelpfeng and Dertinger[6] suggest that exposure of cultured mammalian cells to 2H-mT/50-Hz magnetic field decreases the number of cells and their DNA content. Liboff et al.[7] reported that exposure of fibroblasts to ELF-MF (16 μT/76 Hz) increased ^{3}H-thymidine uptake by these cells in culture. While Kwee and Raskmark[30] reported an increased number of transformed human epithelial amnion cells after 30 min of exposure to an 80 μT/50 Hz magnetic field, it was also recently reported that a magnetic field of 0.3 and 0.7 T for 60 min decreased the colony-forming ability of cultured mammalian cells, and affected the cell cycle.[22]

There are various possible mechanisms causing side effects following exposure of mammalian cells to magnetic fields. The locus of this activity is believed to be in the cell membrane, its nucleus, or some of its macromolecules.

Host immune response includes humoral and cell-mediated immunity. Recent studies have demonstrated crucial roles of free radicals, nitric oxide, TNF-α, and PGE_2 in this process. In the present study, cell-mediated immunity was assessed by measuring production of free radicals, as well as levels of TNF-α and PGE_2, 24 hr after exposure of murine macrophages to 0.8H-mT/25H-Hz magnetic field.

It has been established that free radicals, especially NO, are major mediators of the microbicidal and tumoricidal activities of macrophages. In the present study, a 0.8-mT/25H-Hz magnetic field activates chemiluminescence, but does not alter the synthesis of NO_2^-. Our results confirm reports that a 0.1 mT/60H-Hz magnetic field induces respiratory bursts in primed rat peritoneal neutrophils, by using the dye 2′,7′-dichlorofluoresceine, which reacts with free radical-derived oxidants such as H_2O_2 to form 2′,7′-dichlorofluoresceine in real time.[31] It was also shown that a 0.1H-mT/60H-Hz magnetic field stimulates production of free radicals by human peripheral neutrophils.[32]

TNF-α is a cytokine, mainly produced by activated macrophages, and has a massive lethal effect on some tumors, causing hemorrhagic necrosis, which results in their regression. The TNF-α also plays a major role in apoptosis and necrosis of cancer cells.[33] In the present study, a magnetic field of 0.8 mT/25 Hz activates TNF-α production by the J774.2 murine macrophages. While a magnetic field of 30 mT/50 Hz decreases IFN-γ production and increases IL-1 production, no significant difference was detected between the control and the ELF-MF-exposed cells in the production of other cytokines, by human peripheral blood mononuclear cells.[29] It should also be noted that while some investigators (e.g., Ref. [34]) suggested that PGE_2 is an important regulator of the expression of nonspecific tumor cell killing by murine macrophages, our present results demonstrate that there is no significant difference between the control and the exposed cells in production of this prostaglandin at the exposure level used.

CONCLUSION

In conclusion, our results demonstrate that exposure of murine J774.2 macrophages to extremely low-frequency magnetic field, at 25 Hz and at certain flux

densities, decrease cell viability, and may have biological significance in the anti-microbial effect of static magnetic fields.

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