Superimposition of an Incoherent Magnetic Field Eliminated the Inhibition of Hormone Secretion Induced by a 50-Hz Magnetic Field in Human Villous Trophoblasts *in vitro*

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Key Words

Noise/incoherent magnetic field • Hormone secretion • 50-Hz magnetic field • Human villous trophoblasts • Human chorionic gonadotropin (hCG) • Progesterone

Abstract

The effects of exposure to a sinusoidal 50-Hz magnetic field (MF) and an incoherent (noise) MF on hormone secretion in human first trimester villous trophoblasts were investigated. Trophoblasts were isolated from more than 30 first trimester human chorionic villi of 8–10 weeks gestation. They were cultured and exposed to MFs for different durations. The concentrations of human chorionic gonadotropin (hCG) and progesterone in culture medium were measured by electrochemiluminescence immunoassay. The results showed that exposure of the villous trophoblasts to a 50-Hz MF at 0.4 mT (milli Tesla) for 72 hrs could significantly inhibit the secretion of hCG and progesterone, whereas exposure to an incoherent MF (frequency range between 30 to 90 Hz) with the same conditions did not significantly affect the secretion. However, when the incoherent MF was superimposed on the 50-Hz MF and the cells were

exposed to both fields simultaneously, no significant change in hormone secretion was observed. Based on these results, we concluded that 50-Hz MF exposure for 72 hrs could inhibit the hormone secretion of trophoblasts, and an incoherent MF of equal intensity could completely eliminate the effects induced by the 50-Hz MF.

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Introduction

An extremely-low frequency electromagnetic field (ELF-EMF) is usually defined as an alternative electromagnetic field with frequency below 300 Hz. Electric power systems operate at frequencies of either 50 or 60 Hz. Thus, power frequency electromagnetic field falls into the ELF range of the spectrum. Most devices used in residential and occupational settings that have electrical wires are potential sources of power-frequency electric and magnetic fields (EMFs). Thus, use of electricity has significantly increased exposure of humans to

environmental levels of ELF-EMF.

There are many epidemiological results indicating that exposure to ELF-EMF during pregnancy could increase the risk of spontaneous abortion [1-4], induce fetal congenital anomalies [5] and birth defects [6]. Some animal studies [7-9] also indicated deleterious reproductive effects of ELF-EMF exposure. The potential adverse effects of ELF-EMF on reproductive health/outcomes are of increasing concern. There are epidemiological [10] and animal studies [11] that showed negative effects. However, the evidence for reproductive effects of ELF-EMF has been inconclusive and inconsistent so far. The topic requires further studies. Theoretically, epidemiological studies can provide direct evidence. Because of the limitations of epidemiological studies, it has not been possible to draw conclusions concerning adverse effects of ELF magnetic fields on pregnancy outcome [12]. Thus, finding a plausible mechanism of ELF magnetic fields that could affect pregnancy outcomes would help explain these epidemiological results. Trophoblast is one of the main components of the placenta and plays critical roles in normal pregnancy. Dysfunction of trophoblasts usually leads to spontaneous abortion [13, 14]. In order to explore the possible mechanism of ELF-EMF in relation to adverse pregnancy outcomes, in the present study, we investigated the effect of 50-Hz MF exposure on secretions of human chorionic gonadotropin (hCG) and progesterone in primary cultured human first trimester villous trophoblasts *in vitro*.

It is now clear that exogenous ELF-MF can cause biological effects. But, how organisms or cells respond to exogenous EMF, which is 100–1000 times weaker than the random thermal noise fields generated by thermal motion of ions in and around the cells is still a puzzle. In order to explain the phenomenon, Litovitz et al. [15, 16] have proposed the temporally and spatially coherent hypothesis of EMF. It states that living cells distinguish thermal noise fields from external EMF because thermal noise fields are temporally and spatially incoherent whereas external EMF is coherent. When exogenous fields are both spatially and temporally coherent, they would induce biological effects. However, effects of a spatially and temporally coherent MF would be interfered by superimposing a spatially coherent but temporally random incoherent ('noise') MF. In the present experiment, we also investigated whether incoherent MF could interfere the effects of a 50-Hz MF on secretion of human chorionic gonadotropin (hCG) and progesterone.

Materials and Methods

Isolation and culture of trophoblasts

Placentas were obtained from healthy nonsmoking women undergoing elective pregnancy termination at 8-10 weeks gestation immediately after artificial abortion. Informed consent was obtained from each woman involved in this study. Collection of placenta was performed with the approval of the Human Subject Ethic Committee, Women's Hospital, Zhejiang University School of Medicine. Trophoblasts were isolated and cultured according to a method described by Dong et al. [17]. Briefly, a placenta was washed with ice-cold Hanks' balanced salt solution without calcium and magnesium. Coagulates, connective tissue and vessels were removed. The chorionic villus tissue was coarsely minced, transferred to 50 ml of warm (37 °C) calcium and magnesium-free Hanks' solution containing 0.125% trypsin (Sigma, St Louis, MO, USA) and 0.2 mg/ml DNase I (Sigma, St Louis, MO, USA 1,500 Kunitz units/mg), pH7.4, and then incubated at 37 °C with shaking for 15 min. Tissue fragments were then allowed to settle for 1 min. The aliquot supernatant was collected and equal volume of Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Grand Island, NY, USA) containing 15 % heat-inactivated fetal calf serum (FCS) (Sijiqing Biotech, Hangzhou, China) was added to stop trypsinization. Cell suspension was centrifuged at 1200 x g for 10 min at room temperature. The pellets were re-suspended in 6 ml DMEM containing 25 mM HEPES and 25 mM glucose. The remaining villi tissue fragment was subjected to the same digestion procedure again with addition of 50 ml warm fresh trypsin-DNase solution. Finally, the two resultant cell suspensions were pooled, filtered using a 100-mesh screen sieve, and centrifuged at 1200 x g for 10 min. The pellets were re-suspended in ice-cold NH₄Cl (0.155 M in water) and incubated at 0 °C for 10 min to lyse the erythrocytes, then an equal volume of DMEM was added. The cells were washed and resuspended in DMEM containing 15% FCS, 100 U/ml penicillin, and 100 µg/ml streptomycin. The trophoblast cells were adjusted to a concentration of 5-8×10⁵ cells/ml and planted into 4-multiwell plates (Nunc, Roskilde, Denmark) with 1ml per well. Ten wells of cells were prepared for each chorionic villus. Cells were incubated in a humidified atmosphere of 5% CO₂ and 95% air at 37 °C. The growth state of cells was observed using an inverted microscope.

Magnetic field exposure system

The same MF exposure system used in our previous experiments [18] was used in this experiment. It consists of three groups of square copper coils (36×36 cm²) placed inside an incubator (Model 3164, Forma, Marietta, GA, USA). The upper, middle, and lower coils (that consist of 168, 60, 168 turns, respectively) are connected in series and spaced 8 cm apart from each other. The coils are placed in an iron metal container with many ventilation holes to shield cells from stray MF. A 50-Hz sinusoidal magnetic field was generated by feeding a line current to the coils. Two power regulators were used to control the flux density. The flux density within the coils can be set from 0 to 0.8 mT. Magnetic flux densities were measured using an EFA-300 EM Field Analyzer (Narda Safety Test Solutions,

GmbH, Pfullingen, Germany). When energized, a very uniform magnetic field can be generated within the coils ($10 \times 10 \times 10 \text{ cm}^3$), where cell culture dishes were placed.

For incoherent and combined (sinusoidal and incoherent) MF exposure, cells were exposed in another identical incubator, in which three groups of square coils ($36 \times 36 \text{ cm}^2$) are double-wrapped with two lines of copper wire. A '30-90 Hz' white-noise signal (provided by Dr. Miguel Penafiel, Catholic University of America, Washington, DC, USA) was sent to one of the double-wrapped wires after magnifying through a power amplifier (CROWN 1400CSL, Crown International Inc., Elkhart, IN, USA). The other copper wire coil was fed by a sinusoidal 50-Hz current during combined MF exposure. The amplitude of the sinusoidal and 'noise' MF could be adjusted to produce a magnetic field strength (rms) according to the experimental requirement.

For sham exposure, the condition was the same as exposure but without current or signal input to the coils. Temperature in all the incubators was monitored with a thermocouple probe (sensitivity $\pm 0.1^\circ \text{C}$) attached to the plates near the dishes. During exposure, the incubators were aired with humidified 95% air and 5% CO_2 , and all the dishes were kept at $37.0 \pm 0.2^\circ \text{C}$ throughout the entire experiment. The exposure system was turned on at least 2 hrs before an experiment. After exposure, dishes were removed from the chambers while the magnetic field was still on. The waveforms of different MFs were monitored by an oscilloscope (Fig. 1). The alternating current (AC) background MF fields in the incubators were $1\text{--}2 \mu\text{T}$ and the total static MF was $18.5 \mu\text{T}$ with a $14.1 \mu\text{T}$ horizontal and $12.0 \mu\text{T}$ vertical components.

Human chorionic gonadotropin (β -hCG) and progesterone measurement

The hormone secretion level of trophoblasts from different villus (placenta) showed a large variation. In order to normalize the data, we designed multiple parallel controls in the experiment, i.e. each exposure sample (each time point) was set up a parallel control sample which cells came from the same villus. After culturing for 24 hrs, trophoblasts were changed with fresh culture medium. Then the total ten wells of trophoblasts, which were prepared from the same chorionic villus, were divided into two groups. Each group contained five wells of cells. One group of cells was cultured in the MF exposure system and the other group of cells was cultured in the sham exposure system. Except for the MF, which was on in one of the systems, the culture conditions in the two systems were the same. In the present experiment, cells were exposed to a 50-Hz sinusoidal MF, an incoherent MF ('noise' MF) or a combined MF (superimposition of 'noise' and 50-Hz sinusoidal MFs) for 6, 12, 24, 48, or 72 hrs. The flux density of each MF component was 0.4 mT . After the cells had been exposed for a specific time, one well of cells each from the exposure group and sham exposure (parallel control) group were harvested at the same time. The culture medium of cells was collected and frozen at -80°C . After all groups were collected, β -hCG and progesterone concentrations in the culture medium were measured by the Elecsys 2010 System (Roche Diagnostics, Indianapolis, IN, USA) with electrochemiluminescence

Fig. 1. MF-signal waveform oscillographs. The upper, middle and lower waveforms show the 50-Hz sinusoidal MF, incoherent ('noise') MF, and combined MF, respectively.

Fig. 2. Levels of β -hCG and progesterone in trophoblasts cultures. After trophoblasts were cultured for different durations in vitro, the culture media were collected and both the concentrations of β -hCG and progesterone were assayed. Based on the level of the 6-hr group, folds of change were calculated. $n=6$. The error bars represent SD.

immunoassay. The operation process was blinded, such that the researchers who did the biochemical assays were not aware of the treatments of the samples. Folds of the change in concentration were calculated (each of parallel control was taken as 1 to compare to the respective exposed group). At least six independent experiments for each MF exposure condition were performed.

Statistical analysis

Data were presented as folds of change in concentrations of β -hCG and progesterone after exposure to MF relative to corresponding parallel controls (i.e., sham exposed samples for the same period of time in the same experiment). The data were analyzed by one-way analysis of variance (ANOVA) followed by Dunnett-t test. A $p < 0.05$ was considered statistically significant.

Results

Analysis of hormone secretion of trophoblasts in vitro

In a separate control experiment, trophoblasts were cultured for 6, 12, 24, 48 or 72 hrs without MF exposure. The culture media were collected and concentrations of β -hCG and progesterone were measured by electrochemiluminescence immunoassay. The results showed that both concentrations of β -hCG and progesterone in the medium increased significantly according to the culture times (Fig. 2). This indicated that the trophoblasts cultured *in vitro* had viable hormone secretion functions.

Effects of MF exposure on hormone secretion of trophoblasts

The results showed that, although exposure of trophoblasts to a 50-Hz MF at 0.4 mT for up to 48 hrs did not significantly affect the secretion levels of β -hCG and progesterone (compared with respective parallel controls, $p > 0.05$), it indicated the trend for the inhibition of the hormone secretion. However, exposure to the field for 72 hrs significantly inhibited β -hCG and progesterone secretions of trophoblasts (compared with parallel controls, $p < 0.05$ and $p < 0.01$, respectively) (Fig. 3).

Incoherent MF eliminated the inhibition of hormone secretion caused by a 50-Hz MF

Unlike the 50-Hz MF, results presented in Fig. 4 showed that exposure to an incoherent MF alone at 0.4 mT for 72 hrs did not cause a significant change of secretion levels of β -hCG and progesterone (compared with respective parallel controls, $p > 0.05$). However, superimposition of the incoherent MF could completely eliminate the inhibition of β -hCG and progesterone secretions caused by 50-Hz MF at 0.4 mT (Fig. 5).

Discussion

Trophoblasts are not only the main composition of maternal-fetal placenta barrier, but also secrete the hormones hCG [19] and progesterone [20], which play crucial roles during pregnancy, such as the process of implantation [21], angiogenesis and placentation [22, 23], preventing immunological feto-maternal rejection [24], increasing the exciting threshold of uterus muscle cells, decreasing the stress ability of uterus, and induction of immune tolerance to the fetus [25, 26]. It means that any

Fig. 3. Effects of exposure to a 50-Hz MF on β -hCG and progesterone secretions of trophoblasts *in vitro*. The 0.4 mT MF exposure for 72 hrs could inhibit significantly β -hCG and progesterone secretion of trophoblasts, $n=8$. The data for the respective parallel control groups were taken as 1. The error bars represent SD. (* $p < 0.05$, and $\Delta p < 0.01$, compared with respective parallel controls).

Fig. 4. Effects of exposure to an incoherent MF on β -hCG and progesterone secretions of trophoblasts *in vitro*. $n=7$. The data for the respective parallel control groups were taken as 1. The error bars represent SD. ($p > 0.05$, compared with respective parallel controls).

Fig. 5. Effects of superimposing an incoherent MF on a 50-Hz MF on β -hCG and progesterone secretions of trophoblasts *in vitro*. $n=6$. The data for the respective parallel control groups were taken as 1. The error bars represent SD. ($p > 0.05$, compared with respective parallel controls).

exogenous factors, which could destroy the integrity of the maternal-fetal placenta barrier and/or affect hormone secretion of trophoblasts, could finally affect the normal pregnancy and possibly cause spontaneous abortion.

Results of the present study showed that exposure for 72 hrs to a 50-Hz MF at 0.4 mT could significantly inhibit hormone secretions of trophoblasts. This indicated that MF exposure could disturb secretion functions of trophoblasts. We have also found that a 50-Hz MF at 0.4 mT did not significantly affect the apoptosis-related gene expression (unpublished data). It suggested that the mechanism of hormone-secretion inhibition caused by MF does not involve apoptosis. Using the dual-sided perfusions method, Lopucki et al. [27, 28] investigated the effects of 50-Hz MF exposure on human placenta cotyledon, and the results showed that 2 and 5 mT MFs could disturb the ultrastructure of the nuclei and cytoplasm, increase the density of the vascular-epithelial membrane of villi cells of human placenta [27], and affect the electrolyte balance of human placenta *in vitro*, which in turn could result in a disorder of trophoblasts metabolic and transport functions [28]. However, MF at the same intensity did not increase the concentration of 8-hydroxy-2'-deoxyguanosine (8-OH-dG) in cellular DNA of cotyledons, which is often taken as a marker of oxidative DNA damage in tissues [29]. Their data indicated that exposure of human placenta cotyledon to a 50-Hz MF could affect normal cellular functions. Their results and the results of this present experiment suggested that exposure to ELF-MF for hours could produce potential harmful reproductive effects. But the detailed mechanisms need further exploring.

Based on their studies [15, 16, 30], Litovitz et al. proposed a hypotheses that cells distinguish between external EMF and thermal noise fields because they exhibit a distinct difference in spatial behaviors. Thus, thermal noise fields are ignored by cells. Because external electromagnetic 'noise' fields are temporally incoherent in time, they fail to satisfy temporal coherent criterion and cannot induce biological effects. However, since externally imposed electromagnetic 'noise' is spatially coherent, cells are unable to discriminate against it, so it is capable of confusing the biological EMF detection

mechanism and inhibits the biological effects induced by applied coherent EMFs. Since then, the 'temporal and spatial coherence hypothesis' of EMF has been supported by many *in vitro* and *in vivo* studies [31-37]. In the present experiment, we found that exposure to a 50-Hz MF for 72 hrs could inhibit the hormone secretion of trophoblasts, while an incoherent ('noise') MF with the same intensity did not. When the incoherent MF was superimposed, the inhibitory effects on hormone secretion induced by the 50-Hz MF were eliminated. Our previous studies also found that superposition of an incoherent MF with the same intensity could inhibit 50-Hz MF-induced gap junction intercellular communication suppression [38], EGF receptor clustering and phosphorylation [18], and Ras protein activation [39]. The present result further confirmed the hypothesis with a different cell model and biological endpoint. Litovitz et al. [15] presumed that the plausible mechanism of the coherent EMF interacting with cells is that the field affects the binding of ligands to receptors and consequently modifies the transduction of the extracellular signal into cells. However, it was not clear whether the present result involves the mechanism of receptors. Lopucki et al. [28] speculated that ELF-MF leads to dysfunction of placenta through molecular interactions. Our previous study showed that without ligand, a 50-Hz MF alone also could induce biological effects [39]. Thus, it does not exclude the possibility that 50-Hz and 'noise' MFs could act at other sites and other mechanisms. Although the detailed mechanisms need to be investigated further, results from the present experiment support the 'temporal and spatial coherence hypothesis'. The hypothesis may provide a new approach to prevent the possible deleterious effects of ELF-EMF exposure.

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