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The Effect of Electromagnetic Fields with the Mg^{2+} Cyclotron Frequency on Mouse Reproductive Performance

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Abstract

The present study is aimed to test whether exposure to electromagnetic fields of very weak intensity (≤1 mT) and low frequency (≤100 Hz) may influence reproductive performance and induce teratogenesis in mice. We speculate that a resonant effect occur when the applied frequency matches the cyclotron frequency of Mg^{2+} (≈60 Hz) involved in the cell duplication. Four groups of mice (four dams and one male each) were exposed to ≅50 μT electromagnetic field continuous irradiation of for 100 days. A control group (four dams and one male) was also examined. The exposed dams exhibited a significantly lower number of offspring *per* birth than the control ones (11.0 vs. 11.6; $P = 0.006$). A significantly lower average daily gain of body weight *per* mouse was observed (0.74 vs. 0.77 g/d; $P = 0.002$), resulting in a reduction of the average body weight *per* nest at 11 days of age (404 vs. 463 g; $P = 0.048$). *Post mortem* examinations revealed a significant increase in mild chronic hepatic inflammatory findings (28 vs. 0%; $P = 0.001$) in the offspring and myocardial hypertrophy (25 vs. 0%; $P = 0.023$) in the dams. The exposure of mice to an electromagnetic field with the cyclotron frequency of Mg^{2+} during pregnancy caused a measurable effect on the reproductive performance in terms of offspring *per* birth. This finding may be considered as a warning about the environmental effects of the electromagnetic fields on the stability of individual species and ecosystems.

Keywords

ELF-EMF, Cyclotron Frequency, Mouse, Birth-Rate, Postnatal Growth, Histological Findings

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1. Introduction

The effects of exposure to external non-ionising electromagnetic fields and their ability to induce carcinogenesis, teratogenesis and mutagenesis-related effects are of specific importance to human health. This is especially true in industrialised societies, in which individuals are continuously exposed to increasingly high levels of electromagnetic fields (EMFs) that are emitted by various electrical installations and telecommunication systems. Therefore, a wide body of literature has been produced regarding this subject. The 3 kHz - 300 GHz range of electromagnetic radiation has been focused on; this range is referred to, for convenience, as radiofrequency electromagnetic fields (RF EMFs) [1]-[5]. Even if the existence of a clear and strong effect on embryonic development has not been widely accepted by the scientific community for RF [2] or extremely low frequency (ELF) (<300 Hz) magnetic fields with non-thermal intensities [4], several studies have shown that relatively low intensity EMFs are capable of interacting with molecular, cellular and systemic processes [6]-[9]. The primary issue that confronts this field is the lack of a conclusive understanding of the mechanism of interaction between EMFs and living organisms. This lack of data creates limits with respect to both the design and the critical evaluation of different experiments. Among the available evidence, two experiments [10] [11] point towards the existence of a resonance-based mechanism that relies on the coupling of the electric charge of biologically relevant ions and the applied magnetic field. It was observed that very weak magnetic fields, when applied to living organisms, produce variations in intracellular ionic concentrations when the frequency of the applied field matches the characteristic frequency of the involved ion species. This frequency is referred to as the ion cyclotron frequency (ICR), which can be defined as $f_c = (1/2\pi) \times (q/m) \times B_0$, where q and m are the electrical charge and the mass of the ion, respectively, and B_0 is a constant magnetic field. Another mechanism that is quoted in the literature is the ionic parametric resonance model [12], for which the amplitude of the field is a critical parameter in explaining both the non-thermal effect and the so called "window effect", *i.e.* the amplitude range in which an effect is observed. The main results that were observed in such experiments include the modification of ionic flux through cell membranes. These models suggest a novel approach for experiments that are based on animal exposure to EMFs. Specifically, ions that are involved in cell division, such as Mg^{2+}, can be targeted using a resonant frequency that is chosen according to the q/m ratio and the static ambient magnetic field.

The aim of this study was to compare an experimental and a control group of mice, the first one exposed to a magnetic field with a frequency that was based on the cyclotron frequency of Mg^{2+} (derived using the above formula), during gestation, birth and the first 11 postnatal days. The overall experimental trial lasted 100 days.

2. Animals

All of the animal handling, anaesthesia and euthanasia procedures were performed in accordance with the Italian and European codes of ethics. All of the animal procedures conformed to the Italian D.L. no. 116 of 27 January 1992 and the associated guidelines in the European Communities Council Directive of 24 November 1986 (86/609/ECC). Furthermore, this study was supported by a grant from the Ministero dell'Istruzione, dell'Università e della Ricerca, Italy (registration number 60A08-5987/10).

Twenty female and five male (8 weeks old) CD1 SPF (Specific Pathogen Free)/VAF (Virus and Antibody Free) mice from Charles River Laboratories Italia (Calco-LC) were used for this study. The animals were kept in the following controlled conditions over the duration of the experiment: environmental temperature of 21˚C ± 1˚C; humidity between 40% and 70%; air change per hour equal to 8 to 12 volumes; nyctohemeral cycle of 12/12 h; lighting intensity of 300 to 600 lux, with the light suspended 1 m over the floor; noise < 60 db. The bases of the cages were made of polypropylene, and the ceilings were made of a meshed stainless steel. A complete maintenance dry diet for mice (Standard Diet GLP - 4 RF 21; Charles River, Italy) was administered ad libitum. Water was also available ad libitum. Following 15 days of adaptation, 4 groups, each of which consisted of 1 male mouse and 4 female mice, were exposed to low intensity and low frequency electromagnetic fields (ELF-EMF groups). Another group, which consisted of 1 male mouse and 4 female mice, was used as a control (Control group). Each group was housed in a single cage.

3. Materials and Methods

3.1. Exposure System

To create a uniform exposure zone, we used 6 coils with radii of 380 mm and which were spaced 380 mm apart

in a Helmholtz configuration (**Figure 1**). Each of the coils was made of glass fibre, with copper wire windings wrapped within the carbon fibre. An alternating magnetic field was generated using a waveform generator mod. AFG310 by Tektronix (Beaverton, OR 97077, USA) with 2 Volt peak-to-peak with a 10 Ohm resistance, compensated using an external resistor. The environmental, static, magnetic field and the alternating magnetic field that was produced inside of the cage were measured over the entire exposure period using a F.W. Bell gauss metre (F.W. Bell, Orlando, FL, USA) Mod. 7010. The gauss metre was equipped with a low-field Hall sensor that had a resolution of 0.1 μT. The static magnetic field that was measured at the plane of the cages was B_0 = 47.4 μT. The amplitude of the alternating field that was produced by the coils was therefore set to a range of 38 - 47 μT. The measured amplitude of the static field was used to calculate the sinusoidal field frequency according to the cyclotron frequency of Mg^{2+}, namely $f_c = 1.26 \cdot B_0$. Both the intensity and frequency of the employed ELF-EMFs were monitored daily throughout the trial. During the exposure, the temperature inside of the cages was at room temperature (21˚C ± 1˚C).

3.2. Reproductive Performance and Blood Analysis

During the 100-day trial, the reproductive variables of the dams (gestations, births, offspring) were recorded and used to evaluate the effect of ELF-EMFs on fertility. Moreover, mice were weighed and data were used to calculate the average body weight (ABW) and average daily gain (ADG) of the offspring as indicators of the ELF-EMFs influence on growth and feed efficiency. The presence or absence of macroscopic alterations in the adults and the offspring, as well as the amount of food that was consumed by the adults, was also monitored.

As described above, on the 100th day of trial, blood samples were intracardially obtained from all 25 of the adult mice, which had not been subjected to any food restrictions. The blood samples were treated with K_2-EDTA and were used to examine the following haematological parameters: haematocrit percentage, haemoglobin concentration, erythrocyte count, mean corpuscular volume, mean corpuscular haemoglobin levels, mean corpuscular haemoglobin concentrations, platelet count, leukocyte count. A differential leukocyte count was also performed for neutrophils, lymphocytes, monocytes, eosinophils and basophils. All of these analyses were performed with the same commercial system (ADVIA 120 Haematology System-BAYER Corp. Diagnostic Division, Tarrytown, NY, USA). The morphological evaluation of the blood cells was microscopically performed on blood smears that were stained with Wright-Giemsa. Furthermore, the plasma that was obtained following the centrifugation of the blood samples was treated with K_2-EDTA and used to measure the following clinical chemistry parameters: total cholesterol, triglycerides, blood glucose, total protein, albumin, calcium, inorganic phosphorus, creatinine, blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine kinase, sodium, potassium, and chloride (automatic analyser ROCHE Hitachi 912 Plus-ROCHE Diagnostic Corp., Indianapolis, USA).

Figure 1. The exposure apparatus consisted of six coils in a Helmholtz configuration. Each coil, having a radius of 0.38 m, was made out of glass fibre, in which was embedded the copper wire. Coils are spaced 0.38 m, the total length of the exposure space was 1.9 m. Magnetic fields are generated by currents induced in the coils by a waveform generator.

3.3. Post Mortem Examination

All of the newborn mice were euthanised 11 days after birth. According to a random selection method, one offspring per birth (72 exposed and 19 control, respectively), together with all of the dams and adult males, were submitted to a complete post mortem examination to assess any morphologic or topographic abnormalities. The entire body was fixed in 10% buffered formalin, and main organs and tissues (i.e., brain, thymus, spleen, lungs, heart, liver, pancreas, stomach, intestine, kidneys, skin, muscles and bone marrow) were sampled. All sampled organs and tissues were then formalin-fixed, paraffin-embedded, routinely processed and stained with haematoxilin and eosin.

Microscopic examination were performed by the same pathologist who performed *post mortem* examination using a camera (Eclipse E100, Nikon) in a blinded fashion: three slide per each organs were observed reporting any pathological changes according to standard diagnosis (UNI EN ISO 10993-10, 2004). Specifically, the vertebrae of the mouse pups were counted to assess the effect of ELF-EMF exposure on bone formation. Changes in haematopoietic activity were evaluated by counting the splenic megakaryocytes in 10 random high-magnification fields (40×).

3.4. Statistical Analysis

The average daily gain (ADG) was calculated by performing linear regression analysis of the body weights that were measured on the 3rd, 7th and 11th postnatal days. The assumption of normality and variance homogeneity of the following variables was tested using the Shapiro-Wilk test (PROC UNIVARIATE): the number of gestations, the number of births, the number of offspring per dam, the average number of offspring per birth, the average body weight (ABW) per nest, the ADG per mouse and nest, the food consumption of each group per day and the haematological profile. Because these variables were normally distributed, the data were submitted to a one-way ANOVA (PROC GLM) to assess the effect of the ELF-EMF. The histological data (in percentages) were not normally distributed. These data were therefore analysed by performing a multiple proportions test using the Marascuillo procedure. Bonferroni adjustments were performed to verify the effects of the ELF-EMFs on the offsprings and dams. For the histological variables that exhibited significantly ($P \leq 0.01$) different k-proportions between the groups, the risk ratios and the 95% confidence intervals were calculated in terms of the ratio between the exposed and unexposed animals. The Marascuillo procedure was also used to analyse the histological findings of the treated dams and their offsprings.

All the statistical analysis were performed using SAS software (2010; release 9.3), except for the Marascuillo parametric test that was carried out by using XL-Stat software (Version 2015.2.02, Addinsoft, GMSL, Milano, Italy).

4. Results

4.1. Reproductive Performance and Haematological Profile

The number of gestations, births and total offspring for each dam were not affected by ELF-EMF exposure (**Table 1**). However, the average number of offspring *per* birth was significantly ($P = 0.006$) lower in the exposed dams. As reported in **Table 1**, the ELF-EMFs produced a significantly lower ABW in the offspring at 7 ($P = 0.044$) and 11 ($P = 0.048$) postnatal days; this result was confirmed by the observed lower ADG, which was determined by performing a linear regression analysis of the BW of the pups over time. The amount of food that was consumed did not differ between the groups (4 exposed and 1 control) of adult mice during the trial (31.3 vs. 32.7 g *per* day; $P = 0.589$).

The haematological and clinical chemistry parameters in the adult animals were not affected by the exposure. However, a moderate decrease in the white blood cell count (4.0 vs. 5.7 × 10^9/L; $P = 0.071$) was observed in the exposed mice. Furthermore, a reduction in the number of both neutrophils (20.7 vs. 27.9 × 10^9/L; $P = 0.034$) and lymphocytes (2.7 vs. 4.0 × 10^9/L; $P = 0.028$) in the exposed mice were also detected.

4.2. Histological Findings

Neither the offspring, the dams nor the adult males exhibited any gross changes, although hydrocephalus was observed in one exposed pup. The *post mortem* examination of the offspring revealed no significant differences

Table 1. The effect of ELF-EMFs on gestations, births, offspring number, average body weight (ABW) *per* nest at 3, 7 and 11 postnatal days, and average daily gain (ADG) *per* mouse and nest.

	Treatment		ANOVA	
	ELF-EMF	Control	*P-value*	RMSE
Number of gestations, n°	4.44	4.75	0.288	0.51
Number of births, n°	4.44	4.75	0.288	0.51
Average number of offspring *per* birth, n°	11.0	11.6	0.006	0.35
Average number of deaths *per* birth, n°	0.20	0.19	0.942	0.18
Total number of offspring *per* dam, n°	48.9	55.2	0.103	6.6
ABW *per* nest at 3 days, g	112	123	0.107	12
ABW *per* nest at 7 days, g	257	294	0.044	30
ABW *per* nest at 11 days, g	404	463	0.048	51
ADG *per* mouse, g/d	0.74	0.77	0.002	0.01
ADG *per* nest, g/d	36.5	42.5	0.045	5.0

RMSE, root mean square error.

for any of the histological findings. However, it was observed a mild mononucleated inflammatory population in hepatic portal spaces, a condition for which there was a significantly (P = 0.001) higher k-proportion in the exposed mice and a relative risk ratio of 2.53 (**Table 2**). As reported in **Table 3**, the *post mortem* analyses of exposed adult females revealed that the ELF-EMF induced a significantly (P = 0.0023) higher incidence of myocardial hypertrophy. Moreover, splenic follicular hyperplasia was significantly higher in the control group (12 vs. 75%; P = 0.008), although the risk ratio was very low (0.18).

The *post mortem* analysis of the adult males revealed a higher incidence of mild hepatic degeneration, splenic follicular hyperplasia, mild multifocal acute splenitis and chronic interstitial pneumonia in the exposed groups, although these effects were not statistically significant given the very low number of examined animals. Lastly, no difference was observed in the adult animals with respect to the number of splenic megakaryocytes (data not tabulated for brevity).

5. Discussion

5.1. Reproductive Performance and Haematological Profile

In the present study, extremely low frequency fields of a specific resonant frequency, namely the cyclotron frequency of Mg^{2+}, were applied to test their effects on mouse reproduction. The importance of Mg^{2+} in the duplication process of cells is well established [13] [14]. Thus, the effect of electromagnetic fields on Mg^{2+} may be enhanced during embryogenesis. With respect to the birth rate data, the ELF-EMF exposure elicited a mild effect, which was limited to a significant reduction of the offspring number *per* birth; although the total offspring during the entire period of the trial did not change. In agreement with the literature [15]-[18], EMF exposure did not cause adverse effects on reproductive performance.

The ELF-EMFs significantly affected the growth of the offspring after 3 postnatal days as a consequence of altering lactation and/or their metabolism. These data are in agreement with other authors [19], who reported that the mean BW of exposed offspring at postnatal day 7 days was significantly lower than the weight of the unexposed pups. Moreover, a negative influence on BW increase seems to persist into the second and third weeks of age [18]-[20]. Because it was recorded that food consumption was the same between the two groups of dams, a result that was also observed [16], it could be hypothesised that the lower ADG of the exposed offspring was the consequence of a change in the efficiency with which dams converted dietary gross energy to net energy of lactation.

The results of the haematological and blood chemistry analyses in the dams revealed no reproducible alterations due to ELF-EMF exposure. Consistent with reports in the literature, the observed changes were sporadic and did not affect organogenesis in the offspring [17]-[22].

Table 2. The effect of ELF-EMFs on the histological parameters that were examined in the offspring (n = 72 exposed; n = 19 control).

	Treatment		*P-value*
	ELF-EMF	Control	
Mild multifocal interstitial pneumonia, %	47[a]	22	0.133
Mild centro-lobular hepatosis, %	31[ab]	58	0.188
Mild chronic aspecific reactive hepatitis, %	28[abc]	0	0.001
Chronic enteritis, %	3[bc]	0	0.310
Splenic follicular hyperplasia, %	3[bc]	0	0.310
Mild chronic rhinitis, %	0[c]	11	0.289
Mild chronic pleuritis, %	0[c]	11	0.289

P-value indicates the significance of the *k*-proportion based on the Marascuillo test (Bonferroni adjustment). In the case of mild chronic aspecific reactive hepatitis, a risk ratio of 2.53 was estimated, and the 95% confidence interval was 1 - 17.4. [a,b,c]The column proportions differ significantly ($P \leq 0.01$; $\chi^2 = 51.6$); the analysis was performed using treated offspring.

Table 3. The effect of ELF-EMFs on the histological parameters that were examined in the dams (n = 16 exposed; n = 4 control).

	Treatment		*P-value*
	ELF-EMF	Control	
Mild hepatic degeneration, %	81[a]	75	0.835
Mild multifocal acute splenitis, %	31[ab]	25	0.737
Myocardial hypertrophy, %	25[ab]	0	0.023
Mild multifocal interstial nephritis, %	12[b]	0	0.129
Renal tubules degeneration/ectasia, %	12[b]	25	0.618
Splenic erythrocatheresis, %	12[b]	0	0.129
Splenic follicular hyperplasia, %	12[b]	75	0.008
Chronic interstial pneumonia, %	12[b]	0	0.129
Apoptotic findings, %	12[b]	0	0.129
Splenic congestion, %	6[b]	25	0.417
Chronic enteritis, %	0[b]	25	0.248

P-value indicates the significance of the *k*-proportion comparison based on the Marascuillo test (Bonferroni adjustment). With respect to splenic follicular hyperplasia, a risk ratio of 0.18 was estimated, and the 95% confidence interval was 0.04 - 0.73. With respect to the observed myocardial hypertrophy, the risk ratio was not estimable. [a,b]The column proportions differ significantly ($P \leq 0.01$; $\chi^2 = 42.8$); the analysis was performed using treated dams.

5.2. Histological Findings

In the present study, *post mortem* examinations of postnatal day 11 pups verified the absence of any changes in either organ or vertebrae genesis or development. These results confirm the results of previous studies that have been performed on rats and mice that were chronically exposed to electromagnetic fields [3]-[23]. The only noticeable histological finding among the offspring was an instance of hydrocephalus, which was observed in one exposed pup. Congenital hydrocephalus can be experimentally induced by numerous insults, such as radiation, infections, chemicals and nutritional deficiencies [24]-[27]; however, in all these studies, the incidences of the resulting hydrocephalus was not sufficiently high to allow for an explanation of its primary causes.

The absence of gross changes in the exposed dams is in agreement with the studies of other authors [16] [17],

which reported that were no significant macroscopic alterations between EMF-exposed and control dams. A higher observation of mild hepatic chronic inflammatory population, without other associated changes, indicated a slight influence of ELF-EMF on offspring pathologies. Similar results were also observed in literature [21], who reported that the pathological changes observed in 21-day-old mice that were exposed to fields of different intensities and frequencies were not specific to EMF exposure.

In the present study, the only statistically significant observations in the dams were myocardial hypertrophy in the exposed and splenic erythrocatheresis in the control ones. This result confirms that the majority of the observed microscopic findings are primarily due to spontaneous pathologic conditions. These changes are not related to specific pathogen but they could be spontaneous or secondary to opportunistic biological agents exposure not revealed by microscopic observation [28]. Furthermore, the observed mild hepatic degeneration was the most significant histological finding for both the exposed and control dams. This effect was a likely consequence of the repeated pregnancies and/or lactation rather than of the ELF-EMF exposure.

Summarising the results of this study and of the current literature, it can be noticed that the epidemiological evidence of the effects of non-thermal electromagnetic fields on living organisms is still weak and inconclusive, primarily due to inaccurate assessment of the intensity and frequency of the exposure, which makes difficult to compare different experimental trials. Alternatively, there is a wide body of evidence that electromagnetic field exposure induces noteworthy effects *in vitro* [29], including specific outcomes on processes that are related to embryogenesis [30]. With respect to *in vivo* studies, there are many reports on high frequency field exposure; however, fewer data are available regarding exposure to low frequency fields even though many positive reports are available [7]. Particularly, it was previously reported [31] that long-term exposure to the Ca^{2+} cyclotron frequency affects the growth and metabolism of rats.

6. Conclusion

The present experimental protocol was designed on the basis of the hypothesis that embryogenesis is the life stage ideal for studying the effects of EMF exposure. However, the effect of the fields on a very multifaceted system, such as a living organism, involves highly complex interactions between multiple parameters and it is not plain to relate an effect to a single cause or a sequence of external agents. The exposure of mice to a magnetic field with the cyclotron frequency of Mg^{2+} during pregnancy appears to weakly perturb the reproduction of the exposed animals in terms of the average number of offspring per birth. Such a fact together as the minor anomalies observed in adult mice during 100 days of exposure may be considered as a warning about the importance of environmental magnetic fields on the stability of individual species or even eco-systems. The present data confirm the need for a conceptual bio-physical model that allows for the clear identification of how electromagnetic fields exert their biological effects even at non-thermal intensities and very low frequencies.

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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