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Acute exposure to 50-Hz magnetic fields increases Interleukin-6 in young healthy men.

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Running head: *Magnetic field and cytokines evaluation*

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Abstract

Some epidemiologic studies have suggested that extremely low frequency magnetic fields might affect human health, and, in particular, that the incidence of certain types of cancer might increase among individuals living or working in environments exposed to such fields. This study is part of a broad study we conducted in humans. The study presented here was designed to look for possible effects of acute exposure to 50-Hz magnetic fields (10 μT) on the interleukin 1 beta (IL-1β), interleukin 2 (IL-2), interleukin 6 (IL-6), interleukin-1 receptor antagonist (IL-1RA), and the interleukin-2 receptor (IL-2R) production. Thirty-two young men (20–30 years old) were divided into two groups (sham-exposed or control group, and exposed group) of 16 subjects each. All subjects participated in two 24-hour experiments to evaluate the effects of both continuous and intermittent (one hour "off" and one hour "on" with the field switched "on" and "off" every 15 seconds) exposure to linearly polarized magnetic fields. The subjects were exposed to the magnetic field from 2300 to 0800 while recumbent. Blood samples were collected during each session at 11:00, 17:00, 22:00, 01:00, 04:00, 06:00 and 08:00. Results showed that exposure to 50-Hz magnetic fields (10 μT) significantly increases IL-6 when subjects were exposed to an intermittently magnetic field. However no effect has been observed on interleukin IL-1β, IL-2, IL-1RA, and IL-2R.

Key words*: Cytokines, Magnetic Field.*

Introduction

It is well known that overhead transmission lines, transformers, and household appliances are major sources of electromagnetic field (EMF) exposure. For this reason a concern regarding the potential effect of extremely low frequency magnetic fields (ELF-EMF) on human health has been widely debated, the main concerns focusing on their carcinogenic potential and relationship with immune system functions. This debate was stimulated by some epidemiological studies suggesting that exposure to 50–60Hz MFs may be associated with an increased incidence of various types of cancer (1-11).

As the immune system is involved in the control of cancer development and other diseases, it is important to know whether or not immunological functions are affected by the exposure to ELF-MF. Several studies have examined various immune cell parameters but with conflicting findings. ELF-MF were reported to produce changes in the activity or the number of circulating natural killer (NK) cells (12-17). However, no changes were observed in other studies (18- 22).

Cytokines which are produced by a variety of cells were also investigated. Exposure to low frequency pulsed electromagnetic fields increased interleukin-1 and interleukin-6 production by human peripheral blood mononuclear cells (23). It has been shown that exposure to 50 Hz sinusoidal MFs decreased TNF-α production, while no effect was found on IFN-γ production (24). Another study has also reported that 50 Hz electromagnetic fields decreased TNF-α and IFN-γ production and increased IL-1β production (25). It is to note that all these studies on cytokine production have been conducted in vitro. Overall, the possible effects of ELF magnetic fields have been investigated in different types of cell cultures. On the other hand, there are only a limited number of human studies that are dedicated to the investigation of effects of ELF on the immune system. The study presented here was designed to look for

possible effects of acute exposure to 50-Hz magnetic fields (10 μT) on the IL-1β, IL-2, IL-6, IL-1RA, IL-2R production in humans.

Materials and Methods

Human subjects

Thirty-two healthy subjects volunteered for this study and provided written consent. All were men aged 20 to 30 years. They were selected after routine clinical and laboratory examinations. Selection criteria included: regular sleep habits, no medication, no chronic disease or disability, no recent acute illness, no smoking. Those selected were instructed to eat balanced meals and to abstain from consuming alcohol and coffee for 24 hours before and during each experimental session. They were synchronized with a diurnal activity from 08:00 to 23:00 and nocturnal rest.

Exposure facility

The experimental unit consisted of three independent rooms and a shared bathroom. The exposed subjects slept in the first room (2 beds), and the sham-exposed in the second (2 beds). We did not inform subjects of their exposure status. The wooden beds were arranged parallel to each other in each room. Before setting up the exposure materials and beds, we used "Linda Wheel and EMDEX II dosimetry systems" to evaluate the noise of the background magnetic field. Its' level was less than 40 nanotesla in both bedrooms. In the area immediately surrounding the experimental site, the flux density of the geomagnetic field was approximately 46 μT. Since a minimum distance of 6 m between exposed and sham-exposed beds is required to prevent the generated field from affecting the sham-exposed group, we spaced them 7 m apart. The devices for generation, calibration, and continuous monitoring of the magnetic field were located in the third room (26).

Magnetic field generation

A linearly polarized magnetic field (10 µT) was generated by a system based on Helmholtz coils. Three rectangular coils (120 x 140 cm) spaced 80 cm apart were used for each bed. They were wrapped in wood and look like normal wooden stems attached to the bed and allowed subjects to feel comfortable towards the device. The coils were positioned at the level of the head, groin and ankles. When energized the coils did not produce any vibration. The device was able to generate both continuous and intermittent exposure conditions. In the intermittent exposure, the device was turned “on” for one hour and “off” for the next hour. Whenever the device was turned “on”, the magnetic field was on a 15-second “on-off” cycle. Since “on-off” switching operations induce high frequency transient electric fields that can have a biological effect, the signal generator was monitored by computer and synchronized with passages at zero of the current wave to avoid any transient fields. The magnetic field was generated by a Tollner generator and amplified by a Kepco amplifier, all under a computer controled system developed by Electricité de France, Research and Development Department engineers. A "Positron" dosimeter system was attached to the subject's body at the height of the pelvis, to control the exposure quality and to verify that the device was working. The 10 µT intensity was chosen as representative of the average level of exposure in occupational settings or near transmission lines for electrical workers after a dosimetry survey.

Experimental procedure

This experiment studied four subjects per day (2 exposed and 2 sham exposed), and each subject participated in three 24-hour sessions. They arrived at the laboratory at 09:30. Catheters were placed in antecubital vein for the 24-hour period, and the first blood sample was obtained at 11:00. They slept in darkness between 23:00 and 08:00 and spent their waking time in the laboratory (diurnal activity from 08:00 to 23:00 and nocturnal rest). Blood

samples (tubes without anticoagulant) were taken from 11:00 to 08:00 of the following day (11:00, 17:00, 22:00, 01:00, 04:00, 08:00). During the day, 15 minutes before each sampling, subjects were asked to lie down in semi recumbent position until sampling time. From 01:00 to 08:00, the samples were obtained under dim light (less than 50 Lux) without waking the subjects, who slept with eye-mask from 23:00 to 08:00. Exposure to magnetic field lasted from 23:00 until 08:00.

The first 24h session was performed before starting the experiment and leads subjects to be acclimated to the environment and devices.. We studied two groups: the first, sham-exposed, i.e., control (N = 12 - 16), and the other, exposed (N = 12-16). During the second session, two weeks after the first, a continuous 50-Hz magnetic field of 10 µT was applied. In the third session, a month after the second, the same subjects previously exposed to a continuous magnetic field were exposed to an intermittent 50-Hz magnetic field of 10 µT. The same subjects served as sham contols in both sessions. No one has reported an auditory or tactile cue that could be produced by the coils when energized. This protocol was approved by the local ethics committee.

Cytokine assay

IL-1RA (R&D System, Minneapolis, MN, USA), IL-2R (Genzyme Corporation, Cambridge, MA, USA), IL-1β, IL-2, IL-6 (Biosource, Europe S.A., Fleurus Belgium), were assayed by ELISA in duplicate using serum samples drawn during the two 24h study days. Sampling occurred at 11:00, 17:00, 22:00, 01:00, 04:00, 06:00, and 08:00. For inter- assay coefficients of variation (see Table I).

Statistical analysis

The data are expressed as means ± SEM. Data were analyzed with 2- way ANOVA repeated-measures (GraphPad v5.02). The main effects of field, time factor and their interaction were tested (Table 2). Post-test Bonferroni was applied. The significance level was set at $p < 0.05$.

Results

Significant changes in the concentration of IL-6 were observed in the subjects exposed to intermittent MF. Bonferroni post-tests analysis showed an elevation in serum IL-6 was statistically significant at 06:00 and 08:00 with $p < 0.01$. However, exposure to continuous or intermittent magnetic fields of 10 μT did not affect or modify the cytokine production levels of IL-1β, IL-2, IL-1RA or IL-2R. No significant interaction between the field and the time of sampling was found (Table II). There was also no statistical significance of the main effects of the field (Table II). Data are presented in Figures 1 and 2.

Discussion

Epidemiological studies have shown an association between ELF exposure above approximately 0.3-0.4 μT and an increased risk of childhood leukemia (27, 28). However, despite several years of work, evidence from experimental studies to support a causal relationship between ELF exposure and leukemia is lacking and argues against causality. Thus ELF-MF exposure continues to generate a debate about its possible effects on health. In addition, there is no identified mechanism by which ELF-MF exposure in doses below 5 μT might affect the incidence of cancer or any other disease in the human population (29). As the immune system is involved in several types of cancers it is worthwhile to explore the effect of ELF-MF exposure on the immune system.

Our present controlled study was conducted in humans who were exposed for one night to 50Hz MF of 10 μT from 23:00 to 08:00. Results showed that IL-6 production significantly increased in subjects exposed to intermittent but not with continuous exposure. Bonferroni post test showed that the significance is more observed in the last part of the night (06:00 and 08:00). Since IL-6 shows a circadian rhythm with peak in the morning hours (30), the data presented may suggest a circadian stage depending stimulation of IL-6 production by the intermittent MF. The increase of IL-6 production during that time was approximately 4 to 5 fold higher than control group. Even if non-significant, the upward trend for IL-6 was observed from 01:00 just after the onset of exposure time (23:00). IL-6 is a cytokine secreted predominantly by T-cells and macrophages with both pro- and anti-inflammatory effects. IL-6 stimulates the immune response to trauma and other tissue damage leading to inflammation (31). Its role as an anti-inflammatory cytokine is mediated through its inhibitory effects on tumor necrosis factor alpha (TNFα) and IL-1 and activation of IL-1 RA and IL-10. IL-6 is a regulator of body temperature and fever and mediator of the acute phase response (32). It

crosses the blood brain barrier and plays a role in neuroinflammation and some types of dementia (33). IL-6 is relevant to many disease processes such as diabetes (34), atherosclerosis (35), depression (36), autoimmune diseases (37, 38, 39), and some forms of cancer (40, 41, 42, 43). High levels of IL-6 and IL-6R have been reported in several chronic inflammatory and autoimmune diseases as well as in cancer (44, 45, 46). However, the cytokine production levels of IL-1β, IL-2, IL-1RA and IL-2R were not affected by the MF exposure neither in the continuous mode nor in the intermitten mode.

To date, and to our knowledge, information regarding the effects of extremely low frequency MF on human cytokines is scarce. Most studies were carried out in *in vitro* models. These studies on the peripheral blood mononuclear cell~~s~~ cultures (PBMC) have shown conflicting results. Some authors reported an increase of cytokine production such as IFN-γ and IL-4, IL-1, and IL-6 (23, 25, 47) after exposure to ELF-MF or a decrease in TNF-α and IFN-γ production (25) while others did not find any effect on IL-1β, IL-8, IFN-γ, TNF-α, IL-10, IL-6 and IL-2 production (24, 48, 47, 22, 49). This inconsistency in the results might be due to the difference in the type of the magnetic field and/or the intensities used.

In our study, the effect observed on IL-6 was obtained with intermittent and not with continuous exposure. It is to note that a similar effect *in vitro* (an increase of IL-6) in the literature has been reported with pulsed magnetic field (23), while no effect was found with static or continuous alternating magnetic field (47, 49). It is likely that the type of MF applied may be of importance and could have a different impact on the production of IL-6. Further confirmation of these findings in human subjects are desirable.

In animal studies, only a few studies have investigated cytokine production in immune cells after exposure to ELF EMFs. Some authors have reported that exposure of sheep to EMF had no effect on the activity of IL-1 or IL-2 (50). A reduction in IL-1 activity was observed in their previous studies (51). The authors concluded that the difference observed in the results might be attributed to magnetic field strength and/or the age of the animals used which could be important variables in determining whether EMF exposure will affect IL-1 activity. Another study has reported that exposure to 1 mT ELF-MF increased IL-1β at transcriptional and translational level in rat cortical neurons (52). IL-1β release was also reported to increase in macrophages after 24 h exposure to 1 mT of 50Hz MF (53)

Conclusions:

The results obtained for IL-6 in the present study should be interpreted with caution and require further studies and confirmation to ascertain if the effect observed is due to MF exposure and reproducible. It is also important to stress the potential clinical significance of this increase of IL-6 concentration particularly since its receptor (IL-6R) had been found to be increased under exposure to MF (54).

Overall, the lack of effect observed in the present study on IL-1beta, IL-2, IL-1RA and IL-2R supports our previous findings in which acute exposure (9 hours) to 50-Hz magnetic fields (10 μT) did not affect the immunologic and hematologic systems (19), melatonin secretion (26), hormones of the hypothalamo-pituitary-thyroid and adrenal axis (55), and a large number of clinical chemistry variables (56) including biogenic amines (57). Even our chronic study on workers exposed daily to magnetic fields for a period of 1–20 yr in their workplace and at home showed that this exposure does not lead to alterations in the melatonin secretion (58).

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Table I. Coefficients of variation for low and high controls for the measured variables

Variables	Units	Control I (Low values)				Control II (High values)		
		Range	Mean	CV		Range	Mean	CV
Interleukin-1 Beta	pg/ml	79 - 129	105.3	9.7%		380 - 580	514.5	9.8%
Interleukin-1 RA [Receptor Antagonist]	pg/ml	66.7 - 73.7	72.5	19.0%		534.8 - 591.2	547.1	5.4%
Interleukin-2	U/ml	3.9 - 6.5	5.0	17.6%		10.0 - 15.0	14.2	11.6%
Interleukin-2R [Receptor]	pg/ml	1002 - 1502	1247.7	9.4%		3187 - 4781	3784.8	17.5%
Interleukin-6	pg/ml	91 - 137	120.9	8.2%		200 - 300	297.1	4.7%

Table II: Repeated-measures 2-way ANOVA: comparison between exposed and sham exposed by examining the main effects of the field (continuous or intermittent), the time factor and their interaction.

Variables/factors	Continuous exposure *P*	Intermittent exposure *P*
IL-6		
Field	0.2878	**0.0186**
Time	0.1156	< 0.0001
Field X Time interaction	0.5635	0.0032
IL-1RA		
Field	0.5198	0.3455
Time	0.0012	0.0042
Field X Time interaction	0.7975	0.3022
IL-1 Beta		
Field	0.5556	0.6382
Time	0.7566	0.6379
Field X Time interaction	0.2267	0.4402
IL-2		
Field	0.7220	0.3851
Time	0.0962	0.5906
Field X Time interaction	0.5663	0.1425
IL-2R		
Field	0.0768	0.1441
Time	0.0584	< 0.0001
Field X Time interaction	0.9721	0.9587