

# Electromagnetic fields and autoimmune diseases

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## Summary

**Introduction:** experimental studies demonstrated that electromagnetic fields (EMFs) modify ion calcium fluxes in the membranes of blood mononuclear cells and induce changes in metabolism and surface marker expression. There is also evidence of autoimmune diseases in subjects with genetic predisposition, following exposure to physical, chemical or biological noxious agents or perception of stressful situations. The aim of this systematic review is to evaluate the effects of electromagnetic fields (EMFs) on onset and progression of autoimmune diseases.

**Materials and Methods:** all papers published in scientific journal from 1979 to 2013 were examined for inclusion in the systematic review. The research was conducted using the following key-words: electromagnetic fields, immune response, autoimmunity, Systemic Lupus Erythematosus. 37 studies were included in this article.

**Results:** there is clear evidence that exposure to EMFs produced by radiotelevision broadcasting stations, radars, or electricity induces changes (within the physiological range) in number and percentage of circulating immune cells as well as in the immune response.

Experimental studies on rats demonstrated that exposure to electricity induces metabolic effects similar to those of stress. Women resident near high power lines showed reduced melatonin production as in workers performing stressful night shifts. Employees with prolonged conversation time on mobile phone showed lower levels of serum TSH (index of increased thyroid metabolism) as in situations of stress.

**Discussion:** it is demonstrated that there is absorption of energy in organisms exposed to EMFs; the effects of the EMFs (more elevated on the immune and nervous systems) are similar to those induced by stress stimulations. We suggest that the adaptation of tissues to the EMFs, in genetically predisposed subjects, may stimulate the onset and progression of autoimmune diseases.

KEY WORDS: *electromagnetic fields, immune response, autoimmunity, Systemic Lupus Erythematosus*

## Introduction

Electromagnetic fields (EMFs) are produced by geomagnetic and environmental activities, industrial, domestic and therapeutic uses as well as by cell metabolism. Most of the research on the biological effects of EMFs do not present reproducible results and clear relationships between cause and effect. However, it is evident that the effects of EMFs depend on dose, time of exposure and on cellular excitability, greater in nervous and immune cells. Moreover, the biological effects of EMFs may not be simply explained by the increase of temperature inside the cells (thermal effects).

There is evidence of autoimmune diseases in subjects with a genetic predisposition, following exposure to physical, chemical or biological noxious agents or perception of stressful situations; Systemic Lupus Erythematosus (SLE) represents the prototype of autoimmune disorders because of its abundance of clinical manifestations.

The aim of this systematic review is to evaluate the effects of electromagnetic fields on autoimmune diseases.

## Materials and methods

All papers, published in scientific journals from 1979 to 2013, were examined for inclusion in the systematic review. Papers suitable for inclusion were identified by a systematic research in the following databases: MEDLINE/ PubMed, MEDLINE/ National Library of Medicine (NLM), MedlinePlus, Biomedcentral, Scopus, Cochrane Library. All articles references were examined in order to find further papers useful for the systematic review.

The research was conducted using the following key-words: electromagnetic fields, immune response, autoimmunity, Systemic Lupus Erythematosus. 37 investigations were included in this study.

## Results

### Ethiopathogenesis of autoimmune diseases

One of the features of the immune system is the capacity to distinguish self-antigens from a vast array of antigens of foreign materials. Recognition of self-antigens plays an important role in shaping both T and B cell repertoires of immune receptors in order to preclude harmful autoimmune responses. With regard to this, autoimmunity represents the end result of the breakdown of one or more mechanisms regulating the immune tolerance.

No single mechanism can explain all the different manifestations of autoimmunity (1, 2). The clonal selection theory of immune tolerance includes the idea that interaction of lymphoid cells with specific antigens during fetal or early postnatal life could lead to the elimination of "forbidden clones" able to respond to autoantigens. Loss of immunologic tolerance to self-antigens may also be induced by specific disorders in the immune response of T or B cells (3, 4) as well as by impairment of regulatory modulation of the immune mechanisms (5, 6). With regard to this, decreased apoptosis or a diminished production of immunoregulatory cytokines (such as IL-10) are reported to be associated with the development of autoimmunity (7).

Evidence in humans of genes susceptible to autoimmunity comes from family studies and especially from studies on twins; moreover, genetic mapping has begun to identify chromosomal regions with abnormalities that give a predisposition for specific autoimmune diseases (1, 8): particular alleles of the major histocompatibility complex (MHC) have been identified, but there is evidence that several other genes are important in increasing this susceptibility; e.g. inherited homozygous deficiency of the early proteins of the classic pathway of complement is very strongly associated with the development of SLE (9).

Genetic abnormalities of normal immune processes may suggest a predisposition for the development of abnormal responses related to stimulation by noxious agents (chemical, physical, bacterial or viral) or stressful situations induced by life events.

Additional factors that appear crucial in the induction of autoimmunity include age and hormonal status: many autoimmune diseases, such as SLE, are far more common in women (1, 10, 11).

**Systemic Lupus Erythematosus.** Autoimmune diseases range from those specifically affecting a single organ to systemic disorders with involvement of many organs. Systemic Lupus Erythematosus (SLE) represents the prototype of the autoimmune disorders because of its abundance of genetic alterations and clinical manifestations (8-11). Moreover, SLE is associated with a vast array of autoantibodies whose production appears to be a part of a generalized immune hyper-reactivity (10).

Environmental noxious agents play a crucial role in triggering or aggravating SLE; these agents include ultraviolet light and drugs; the list of drugs that may induce SLE-like diseases is long (10). There is also evidence that stressful situations may trigger the onset of SLE.

Severity of SLE varies from mild and intermittent to severe forms (10, 11). Most patients experience exacerbations following periods of relative quiescence; however, permanent complete remissions are rare. Systemic symptoms, particularly fatigue and myalgias/artralgias, are present most of the time. Most patients have polyarthritis, in some cases with areas of necrosis and/or myositis. Cutaneous manifestations include discoid lesions and systemic rash which may disfigure the face, particularly the cheeks and the nose ("butterfly rash"); the patients with these symptoms are extremely photosensitive. Serious manifestations of the disease are nephritis, with proliferative glomerular form, and vasculitis; generalized vasculitis may explain the increased prevalence of transient ischemia attacks, stroke and myocardial infarction. Cardiac involvement includes myocarditis and fibrinous endocarditis, while the pulmonary manifestation may be pleuritis, interstitial inflammation and intra-alveolar hemorrhage. Hematologic disorders include anemia, lymphopenia and thrombocytopenia. Ocular manifestations, such as Sjogren's congiuntivitis sicca, retinal vasculitis and optical neuritis, may occur. SLE affects the central and peripheral nervous systems; this is the major cause of morbidity and mortality, in partly due to occlusive vasculitis. The most common manifestation is cognitive impairment, in particular, difficulty with memory and reasoning. Psychosis can be the dominant manifestation. SLE may cause headaches and seizures of any type.

Fertility in women suffering from SLE may be normal; however, a high incidence of premature delivery, fetal sufferance and abortion was observed (10, 11).

### Effects of electromagnetic fields on the immune system

Electromagnetic fields (EMFs), produced by geomagnetic and atmospheric activities, contribute to the existence of living beings since they are used by species of insects, birds and reptiles for spatial orientation and migration (12). Moreover, metabolic activities and body functions produce EMFs.

It must also be mentioned that EMFs are utilized for diagnostic purpose (magnetic nuclear resonance imaging) or for therapeutic purposes for providing additional energy to the tissues to repair damages or to enhance metabolism.

EMFs today play a great and indispensable role in industrial, economic and social activities. EMFs are produced by power stations to transport electricity (frequency 50 or 60 Hz) through wires; EMFs are also produced by radio-television stations (frequency KHz and MHz), by radars (MHz and GHz), cellular telephones and satellites (MHz and GHz); they are also utilized in industrial and home activities (e.g. for eating foods).

Most of the research on the biological effects of EMFs do not present reproducible results and clear relationships between cause and effect. It is also difficult, to analyze the differences among the effects of EMFs with different frequencies. For this reason, today there is agreement mainly on the results of studies on the bi-

ological effects of EMFs induced by the increase of temperature inside the cells ("thermal effects"). However, it is clear that the biological effects of EMFs may not be simply explained by the "thermal effects" only. The biological effects of EMFs depend on dose, time of exposure and frequency or wavelength (13). The energy of environmental EMFs absorbed by cells induces changes in metabolism; the effects of this interaction depend on the characteristic and excitability of the cells; it is known that environmental EMFs mainly affect the metabolic activities of nervous and immune cells (13). In this review, we examine the results of studies on the effects of EMFs on immune and neuroendocrine systems which may exert integrated responses to environmental stimulations.

In "vitro" studies. Peripheral blood mononuclear cell (PBMC) stimulation is a model for the study of "in vitro" blastogenesis, proliferation and transcription and translocation of many proteins. Using this method it was shown that low frequency EMFs modify calcium fluxes in membranes acting on the release of thromboxane B<sub>2</sub> and interleukin 1 (14). PBMCs of humans exposed "in vitro" to low frequency EMFs showed inhibited proliferative response to mitogens and changes in lymphocyte metabolism and surface marker expression (15, 16); the EMF exposure was shown to influence CD4<sup>+</sup>, CD14<sup>+</sup> and CD16<sup>+</sup> expression, production and/or localisation (17).

Experimental studies on animals. Static magnetic fields, locally applied to different brain areas of rats modified the immune response depending on time of exposure and region of the brain exposed (18). Mice chronically exposed to 50 Hz EMFs in the same conditions as humans showed reduction of the total number of lymphocytes, leukocytes, polymorphonuclear neutrophil, CD4<sup>+</sup> and NK cells (19). Subchronic exposure with scalar flux density to 60 Hz EMF suppressed NK cell activity in both young and mature mice without increasing the incidence of neoplasia (20).

It should be pointed out that the EU promotes the adoption of "in vitro studies" as preliminary steps for investigating unknown noxious agents. This procedure was adopted either for ethical reasons in order to reduce the number of sacrificed animals or to reduce the expenses for experiments. The procedures previously adopted in Soviet Union and eastern countries utilized a large number of animals with lower ethical restrictions. In Soviet Union, experimental studies on long-term low level exposure of rats to radiofrequency EMFs, showed autoimmune and reproductive effects (21). These investigations were recently repeated showing the same general trend of the earlier studies evidencing that EMF exposure reduces the formation of antibodies in brain tissue with possible stimulation of autoimmune mechanisms; possible adverse effects on fetal development were also confirmed (21).

Studies on humans. After the first study on the incidence of childhood leukemia induced by electricity (22), several epidemiological investigations did not show any associations between residential exposure to EMF and leukemia (23, 24). However, pooled analysis of data from epidemiological studies on the risk of

childhood leukemia was the basis for the classification of 50 or 60 Hz EMF as possible carcinogens by the International Agency for Research on Cancer (IARC) (25); recently, a higher incidence of childhood and adult leukaemia was reported near a power radio transmitter located in the suburbs of Rome. However, no casual implication was thereafter drawn by the same authors of this report because of the small number of cases and the lack of exposure data (26). Increased incidence of glioma and acoustic neurinoma induced by the use of mobile phones was reported (27). With regard to this, IARC recently classified RF-EMF in category 2B as possible human cancerogenic. While the scientific community is still discussing this subject, preliminary measures to reduce the risk deriving from the use of mobile phones have been introduced by some countries.

It was demonstrated that temporary or prolonged EMF exposure of humans modifies blood leukocytes. Patients and volunteers showed decreased % of total blood lymphocytes and cytotoxic T cells and increased helper lymphocytes immediately following the static EMF of magnetic resonance imaging (28). Radar operators (exposed to EMFs ranging from 390 MHz to 10.96 GHz) showed reduced blood cytotoxic CD8<sup>+</sup> lymphocytes and increased serum IgM (29). 60 electric utility workers showed a negative correlation between EMF exposure and blood ornithine decarboxylase (ODC) activity (related to the metabolism of melatonin) and NK cell number; the alteration of these hematologic parameters was stronger among workers with reduced melatonin production (30). Moreover, reduced 6-sulfatoxymelatonin excretion was not observed in groups of women resident near high power electricity lines (31).

We also investigated 19 women with prolonged exposure to EMFs emitted by radio-television broadcasting stations in their residential area in the year 2000; 12 of them were examined five years later (32, 33). The EMFs on the balconies of the homes were (mean  $\pm$  S.D.) 4.3  $\pm$  1.4 V/m in the first determination and 3.7  $\pm$  1.3 V/m in the follow up monitoring, while the residential exposure of the control women was <2.0 V/m in the year 2000. The EMF exposed group showed reduced blood NK lymphocytes as well as PHA stimulated PBMC proliferation and IL-2 and IFN-release. Moreover, in the follow up study, blood NK activity of the EMF exposed women was significantly lower (within the physiological limits) than that of a control group ( $p < 0.01$ ).

### Stress-like stimulations induced by EMFs

Current evidence indicates increased incidence of autoimmune diseases, including SLE, in genetically predisposed individuals, mainly women, exposed to environmental agents or experiencing stressful situations (34, 35); an association was also shown between the incidence of SLE and shift work and healthcare work with patient contact (36).

Exposure to electricity may induce a stress-like situation. Adult male Sprague-Dawley rats were exposed to

50 Hz EMFs (0.5 mT) for a period ranging from 5 days to 4-6 weeks; at the end of the exposure, they showed thymus involution, adrenal gland hypertrophy, hyperglycemia, promelanocortin elevated production and depressive-like behaviour (37).

Melatonin is a hormone with a supposed oncostatic action, mainly secreted by the pineal gland during the dark phase of the light-dark cycle; it is reported that melatonin regulates the efficiency of natural immunity, including NK activity, which defends from infections as well as onset and progression of cancer diseases; reduced production of melatonin was observed in workers with the stressful situation of working night shifts (38). Reduced 6-sulfatoxymelatonin excretion was observed not only in groups of women resident near high power lines (30) but also in workers occupationally exposed to electricity (29).

The effects of the use of mobile phones on thyroid function was evaluated in 2598 employees (men and women) divided into three groups on the basis of personal use of a mobile phone (39). The group of employees with more prolonged conversation time showed lower levels of serum TSH, an index of increased thyroid function, as occurs in stressful situations. The authors were unable to establish whether these results were determined by EMF exposure from mobile phones or by the stress of using these instruments.

### Limits of exposure

Limit values of exposure to environmental and occupational noxious agents were determined by several international organizations in the United States and western countries. These limits were mainly established by evaluating the results of experimental and/or epidemiological studies demonstrating initial and/or pre-clinical physiological and/or biochemical alterations induced by exposure. Following mainly the analysis of the results of epidemiological researches, decisions could be achieved too late, as in the case of benzene exposure (today with the limit of exposure about 20 times lower than 40 years ago).

With regard to EMF exposure, in the United States and Western countries, the degenerative effects (such as for testicles and crystalline) induced by the heat produced by the EMFs were previously taken into account, while there was lower consideration for the results of the studies on the biological "non thermal" effects of the EMFs, including those of experimental researches. The Italian law (DLgs 81/08) relates the Italian limit values to those of the European Directives, which are in agreement with those of the ICNIRP (International Commission on Non-Ionizing Radiation Protection). With regard to the exposure of the population, in absence of an agreement of the scientific community on the long-term effects of the EMFs, preventive prudential limit values were adopted. However, it remains to be established if the guideline for the average population may address the requirements of a minority of potentially sensitive subjects as in the case of air pollution guidelines which are not based on the special needs of the asthmatics.

### Discussion

Since most of the research on the biological effects of EMFs do not present reproducible results and clear relationships between cause and effect, there may not be sufficient reliable data to analyze the differences among the effects of EMFs in relation to the frequency. Specific experimental and epidemiological studies in this field have to be carried taking into account the additive effects of electricity, mobile phones and domestic devices.

The biological effects of EMFs may not be simply explained by those induced by the increase of temperature inside the cells. Since it is clear that EMFs induce absorption of energy by biological tissues, this additional energy may modify a large number of metabolic activities in different cellular compartments. It is also clear that the cells which are more affected by EMF exposure are those of the immune and nervous systems and that EMFs may affect DNA metabolism.

With regard to the therapeutic use of EMFs, EMF exposure could be beneficial or dangerous depending on dose, frequency, as well as time and site of exposure. It is known that EMF exposure acts as a stress-like stimulation; there is evidence of increased incidence of autoimmune diseases in genetically predisposed individuals exposed to environmental agents or experiencing stressful situations; with regard to this, the effects of EMFs may be additional to those of other stressors such as noise (40), chemical pollution (41) or life and occupational events (34, 35).

An organism exposed to EMFs may adopt mechanisms which provide adaptation for the absorbed energy of the EMFs. Whenever there is genetic predisposition to autoimmunity disorders, in particular to SLE, the organism, during the phase of adaptation to the EMF exposure, may develop autoimmunity mechanisms which may reduce the immune tolerance versus its own cells.

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