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MINIREVIEW

Effects of Magnetic Field Exposure on DNA: Research Needs

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Abstract. There is presently an intense discussion whether exposure to electromagnetic fields (EMF) causes any health effects. A large variety of experimental and epidemiological studies have been performed and conclusions drawn tend to be highly controversial. Since health effects cannot be excluded, extremely low frequency EMF has been considered as "possibly carcinogenic to humans". The high variability observed in experimental results may reflect complex interactions between several factors that have not been accounted for in previous studies. For example, it has been suggested that exposure to EMF, while not directly inducing DNA damage, may affect the cellular response to DNA damage generated by other processes. One of the recent fields of investigation aims the study of the cellular response to and repairs of a very deleterious type of DNA damage, the DNA double-strand break (DSB), under conditions of exposure to magnetic fields. In conclusion, additional research is needed to better understand the effects of EMF on human health.

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1. Introduction

Electromagnetic forces (one of four types of forces present in our physical world) play an important role in the constitution of matter (its elementary constituents, electron and proton, are equipped with electric charge), in its physical and chemical properties, and the laws of biology at the molecular level. From the scientific point of view the study deals well with the Classical Electromagnetic Theory of Maxwell or with the Quantum Theory of Electromagnetic Fields. Both are field theories. In the electromagnetic spectrum, the electromagnetic fields (EMF) are classified as a function of frequency. For frequencies below the ultraviolet these fields are non-ionizing. For the purposes of interest here, that Maxwell's is basically applied to elucidate the mechanisms of interaction between EMF and biological systems.

Two EMF frequency ranges of interest for its social impact are clearly differentiated: (***i***) Low power frequency (50 Hz) and frequencies for industrial and therapeutic use. (***ii***) High frequency (microwave and millimeter) related to mobile telephony and telecommunications applications in general.

It should be noted that power supply was an important development from the twentieth century and high frequency applications are being developed primarily from the second half of the twentieth century.

The effects of EMF in their interaction with biological systems are divided in thermal effects and nonthermal effects. The interaction mechanisms involved in thermal effects are well known and the recommendations and regulations are provided for and regulate the protection. Non-thermal effects, more subtle, is an active area of current research to: (i) To clarify the interaction mechanisms when the effect is confirmed. (ii) To ratify the effect unambiguously.

In this article we focus clearly on low frequency and non-thermal effects. It should be noted that in general, the EMF–interaction mechanisms with biological systems in relation to non–thermal effects are not known; being this circumstance one of the factors influencing the difficulty of replication of experiments in different laboratories.

One positive point has been the therapeutic use of low frequency magnetic fields during the last 40 years and in the not so positive, concerns about the impact of low frequency EMF on public health. Contemporary society has increased the use of electrical equipments. This increased dependence has caused the appearance of a great controversy about the possible negative health effects of EMF generated by such equipments. This controversy was further increased with the publication in 1979 of a study that showed a correlation between increased risk of acute lymphocytic leukemia and exposure to 60 Hz magnetic fields (MF) [1]. Since the publication of this study the dispute between magnetic fields and cancer has been present in the minds of the people and the work of researchers, in order to find a possible connection between them. There is currently no conclusive evidence that links exposure in vivo with the appearance of cancer. However, numerous other in vitro effects have been observed.

2. Current Biological Models for Magnetic Field Exposure

Epidemiological studies, difficult to perform, are inconclusive; being more active the laboratory studies both in vivo and in vitro. As the essential molecule for life and transmission of the genetic code is the DNA molecule, it is a fundamental molecule to study the possible effects that may arise from exposure to EMF alone or in presence of other agents to which biological systems may be exposed in controlled or accidental conditions.

One of the current fields of research is the cellular response and repair of a type of DNA damage very deleterious, the DNA double strand breaks (DSB), under conditions of

exposure to low frequency MF. The use of models based on genetically modified organisms (GMO) (i.e., *S. cerevisiae*) allows to investigate the efficiency and accuracy of DNA repair.

The study of such strains (GMO) subjected to MF alone or in combination with other agents has advantages in relation to the cell lines used by other researchers to study the effects on DNA.

Yeast genetically modified is a good model to study cellular and molecular functions similar to those that take place in higher organisms, and therefore it can be used as models for in vitro studies. In this way, there are models of *S. cerevisiae* produced on demand, by genetic engineering, which are capable of enzymatically self-induce two DNA DSB, with the advantage that the system avoids the confounding effects due to radical production associated with radiation exposure, certain clastogenic chemicals or ionizing radiation. The system allows to investigate the repair efficiency and accuracy, with a special emphasis on the intranuclear dynamics of chromatin damage.

3. DNA Damage

In recent years numerous papers have been published concerning the effects of MF on the DNA molecule. Most of them report that under different exposure protocols, the MF exposure produces DNA breaks and alterations in the repair of the damage. All these papers are related to in vitro studies where exposure conditions are, in each case, different and until now it is not clear the mechanism of interaction between MF and DNA.

Papers published in this way show a wide dispersion in terms of exposure protocols, cell lines and endpoints measured. The vast majority of these studies claim to have proven the existence of damage in the DNA molecule induced by the MF as well as alterations in the ability to repair them. To induce damage in the DNA molecule is generally used the exposure to ionizing radiation and/or chemical agents, which generates free radicals. This problem can be circumvented by the use of GMO that are capable of enzymatically self-induce two double strand breaks in the DNA chain without mediation of free radicals. In this way, the reliability of the damage reparation is higher. In this regard, the ideal cell lines are yeasts (i.e. *S. cerevisiae*) that allow obtaining mutants (GMO) in specific genes.

When we moved the study of the MF effects to a cellular level at controlled laboratory conditions, some authors have observed that exposure of tumor cells to pulsed electromagnetic fields (PEMF) can alter the effectiveness of anticancer drugs such as methotrexate, daunorubicin, etc. [2–5].

But what happens when the MF is combined with physical agents? In this regard it has been observed that low-frequency and intensity MF could potentiate the DNA strand breaks induced by X-rays [6]. On the other hand, it is well known the combined effect of MF and ultraviolet radiation. It appears that the MF could alter the cellular damage induced by ultraviolet light and / or the ability to repair this damage [7]. In this sense, the MF could be a potential radiosensitizer against the action of radiation, particularly ionizing radiation, for use in radiotherapy.

It should be noted that in some molecular systems (plasmids) and cellular (lymphocytes) exposed to static fields or sinusoidal 50 Hz, 7 mT, alterations and strand breaks in the DNA molecule have been observed only in the presence of metal ions ($SnCl_2$, $FeCl_2$, $FeCl_3$, Fe_2O_3) and not in their absence [8, 9].

Agents that in some way or another are associated with cancer are those who directly or indirectly induce DNA damage or disrupt the proper repair of damage induced by these agents or occurred spontaneously.

Among the authors who have observed enhancement of DNA damage after exposure of human and animal cells to MF include Reese et al., [10] and McNamee et al., [11], whose work has been performed with exposures to 60 Hz and

0.1 to 2 mT. By contrast, it has been observed in other studies that exposure to certain protocols (0.1-0.5 mT, 2-10 mT, 50 Hz) produce significant increase in DNA strand breaks, and an increase in DNA degradation [12, 13]. Other authors have observed the occurrence of breakage of double-stranded DNA when human fibroblasts were exposed to 50 Hz sinusoidal MF, 1 mT for 24 h [14]. In this regard, Jajte et al. [15] have observed a decrease in cell viability after simultaneous exposure to 7 mT static MF and Fe ions.

Low intensity and frequency MF do not exhibit a sufficient energy to cause breakage of a covalent bond and thus a direct breaking of the DNA strand. However, it appears that the indirect effect by free radicals may be the mechanism of production of cracks. Li and Chow [13] reported that MF may enhance the activity of free radicals. This statement justifies the need to investigate the effects of MF on the DNA molecule, but without the intervention of free radicals in the process, which could mask the result and the elucidation of interaction mechanisms.

4. Working Groups

Works on DNA damage by MF published by other authors focus on in vitro studies with different animal and human cell lines (both normal and tumor) and yeasts, and in vivo in small laboratory animals. It is important to mention several working groups:

(***i***) A first group of papers focuses on the study of the synergistic effect of MF, noting single and DSB after subjecting the cells to MF combined with different chemical agents [8, 13, 14, 16].

(***ii***) A second group refers to the MF as a stressor, resulting in cell protein synthesis of heat shock response but no appreciable rise in temperature in the cell [13, 17].

(***iii***) A third group focuses on studying the changes that the MF produced in the normal mechanism of repair of damage induced in the DNA molecule. It has been shown that low-frequency and intensity fields alter the fidelity of the repair of lesions in the genome, induced by ionizing radiation [18-20]. But have not been evaluated molecular markers associated with the repair of DNA damage, which could be altered by the action of MF. Markers such as *RAD52*, *RAD54*, *HDF1*, etc.

5. Future Considerations

Despite the results published up to now, it is needed at this time to perform further studies that could lead to identify interaction mechanisms of MF with living organisms at molecular level and that could establish the conditions under which the effects occur such as thresholds, dose-response relationships, frequency-dependence, and optimal waveforms. Some authors suggested the possibility that not all parameters are totally controlled and this circumstance may influence the observed effects. This is a general feature of non-thermal effects.

There are numerous articles that use cell strains of *S. cerevisiae*, but now we know to date no work using mutant yeast strains genetically modified, despite the obvious interest that has its use. Despite some authors found time and dose-response relationships [16] for DNA strand breaks of MF-treated fibroblasts, these results have not been replicated by other independent laboratories [21].

All these circumstances and the lack of clarity leads us to consider the need to investigate the effects of MF on the induction of DNA strand breaks and repair of these lesions, suggesting the advantages of the experimental model based on the exposure of GMO. In conclusion, it is needed additional research in this area to better understand the effects of EMF on human health.

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