Magnetic Fields and Cancer: Animal and Cellular Evidence—an Overview

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A few animal studies on the possible carcinogenic effect of magnetic fields have been published. They have been designed to reveal a possible tumor promotion obtained by applying continuous or pulsed alternating fields at flux densities varying between 0.5 μT and 30 mT on mice or rats initiated with different initiators. One study with 2 mT applied on DMBA-initiated mice may suggest a copromotive effect together with the promoter TPA. Another study on rats suggests an inihibitory effect by a magnetic field on rat liver foci formation, induced with DENA. Cell studies show that magnetic fields at some frequencies, amplitudes, and wave forms interact with biological systems. Thus effects have been seen, e.g., on enzymes related to growth regulation, on calcium balance in the cell, on gene expression, and on pineal metabolism and its excretion of the oncostatic melatonin. Cellular and physiologic studies thus suggest effects that may be related to cell multiplication and tumor promotion. — Environ Health Perspect 103(Suppl 2):63–67 (1995)

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Introduction

Carcinogenesis is a multistep and multifactorial phenomenon (*1*). Early animal experimental studies demonstrating the multistep character of tumorigenesis (*2, 3*) defined the two major steps as initiation and promotion by observing the development of tumors in mouse skin after local treatment with two types of carcinogens. The term promotion was originally an operational definition, associated with the particular two-phase experimental protocol used. Initiation has since been largely associated with genotoxic effects due to direct or indirect interactions between the carcinogen, or its metabolites, and DNA. The promotion step is responsible for the conversion of initiated cells to transformed cells. Promotion is associated with a number of cellular events, largely nongenotoxic in nature. Some animal studies also form the basis for a further division of the promotion stage into stage I (conversion) and stage II (propagation). A continuing cellular evolution into a fully invasive and metastasizing tumor cell tissue is termed progression. A chemical or physical factor capable to be effective in all biological steps is termed a complete carcinogen. It may be possible in series of animal experiments to define the activity of a factor for one or more of these (often overlapping) biological steps. The multistep nature of tumor development is assumed to be a general phenomenon and not restricted to certain tumors.

Two-phase experimental protocols have been established for mouse skin tumors and for rat liver tumors. In the mouse, the occurrence of benign tumors, papillomas, in the skin is analyzed and in the rat the formation of preneoplastic cell areas (foci) in the liver is determined. Two-phase protocols for other types of tumors, such as leukemia and brain tumors, have been less commonly used in animal models in the past. Such studies with magnetic fields are planned or ongoing with different initiator regimens.

Animal studies are essential to define the exposure parameters of magnetic fields responsible for an effect. The flux density, the frequency, the exposure duration, and exposure profile are among the important critical variables. Animal studies, as well as cell studies, are also essential in order to get an indication of the carcinogenic mechanism. The identification of the carcinogenic mechanism is important for a solid risk assessment.

So far no full-scale, long-term animal studies have been performed studying the possibility of magnetic fields acting as a complete carcinogen. Such studies are planned or already started in the United States (the NIEHS National Toxicology Program) and Italy. Data from these studies will appear within the next few years.

In some animal experiments designed primarily for studying possible tumor promotion by magnetic fields (summarized below), parallel series of animals have been included, which attempt to give an indication on whether magnetic fields also act as a complete carcinogen. As such parallel series consisted generally of small group numbers, only limited conclusions can be drawn from those observations in this context. With one exception (*4*), the other studies (*5,6*) seem not to reveal an effect of magnetic fields as a complete carcinogen. The Georgian study (*4*) showed around 30% mammary tumors in rats exposed to 20 μT 50 Hz daily for lifetime. Control animals had no tumors. Details of design, exposure regimen, and tumor observations are, however, lacking.

Animal Experiments

Tumor Promotion Studies

In a 2-year tumor promotion study with continuous 50-Hz magnetic fields, using 0.5-mT and 50-μT exposure on female NMRI mice (*5*), the skin tumors and other neoplastic lesions were observed after topical application of DMBA. The animals were exposed to a magnetic field for 19 or 21 hr a day. TPA was used as a positive control for skin tumor promotion. There was no difference in skin tumor development among DMBA and magnetic field-exposed animals compared to the DMBA-treated animals. This analysis was made with correction for survival and made for both cumulated tumor-bearing animals and cumulated number of skin tumors. Skin hyperplasia analyses did not reveal skin hyperplasia among DMBA + magnetic

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field-exposed mice related to magnetic field exposure.

A study (*6*) using female CBA/S mice and pulsed magnetic fields at 20 kHz with a saw-tooth shape and a flux density of 15μT (peak to peak) was designed to observe a possible enhancing effect of X-ray-induced lymphomas or of spontaneous lymphomas in this particular strain. Four X-ray doses of 1.31 Gy each were administered with a 4-day interval and the subsequent magnetic field exposure was performed 24 hr/day over the lifetime. In the X-ray-treated series a high lymphoma frequency was obtained. There was no statistical difference in lymphoma appearance between the X-irradiated animals and those also exposed to magnetic fields.

A large German study (*7*) using Sprague-Dawley rats involved four experiments and exposures to 15-mT DC fields or a gradient field of 0.31–1 μT, as well as a homogeneous field of 30-mT (continuous) 50-Hz AC fields, after initiation of mammary tumors with repeated (4×5 mg) oral administrations of DMBA. The exposure was performed 24 hr/day for 91 days. Magnetic fields did not alter the induced tumor frequency except in one experiment, where 30-mT AC fields increased the number of tumors per tumor-bearing animal. Fifteen-millitesla DC fields increased tumor weight but not tumor frequency in one experiment. The number of animals in the groups was small (18–36), limiting the sensitivity of the study. Also, the exposure and observation period was short. The experiment with 30-mT AC fields was repeated without the second time showing an increase in the number of tumors per tumor-bearing animal.

In a Georgian study (*4*) female rats (strain not specified) were initiated with NMU at a dose of 50 mg/kg bw administered iv to induce mammary tumors, which could be enhanced by subsequent 50 Hz magnetic field exposure. Two types of magnetic fields were used, variable (AC) fields and static (DC) fields with an intensity of 20 μT. The magnetic field exposure was 0.5 hr or 3 hr daily starting 2 days after NMU administration and possibly ongoing for the animal's lifetime (exposure details are not specified). Three hours of daily exposure to AC or DC fields increased the incidence of NMU-induced mammary tumors, while 0.5 hr of daily exposure did not. Also, the time-to-tumor appearance was shorter among the animals exposed for 3 hr daily. In the 3-hr groups, malignant tumors dominated among the histologic types, compared to the control group. The results obtained in these experimental series need to be confirmed.

The rat liver foci model has been used in a series of experiments (*8,9*). The exposure lasts for 12 weeks, when animals are sacrificed and liver samples are taken for staining for the enzyme markers, GSTp and GGT. In one study (*8*), 0.5-, 5-, 50-μT, and 0.5-mT continuous magnetic fields at 50 Hz were used in a tumor promotion protocol using Sprague-Dawley rats and DENA as initiator. This study did not show an enhancing effect of continuous magnetic fields on the development of preneoplastic foci induced by DENA.

Interaction Studies

In three papers on skin tumor promotion in SENCAR mice (*10–12*) 2 mT and 60 Hz continuous magnetic field-exposure was used during 6 hr/day, 5 days/week up to 21 to 23 weeks. In the investigation by McLean et al. (*11*) both promotion (above) and co-promotion of skin papillomas were studied in female SENCAR mice exposed to 2-mT, 60-Hz magnetic field. Using an initiating treatment of 2.56 μg DMBA (10 nmole) and a subsequent exposure to 1 μg TPA applied to the dorsal skin weekly, they tested whether a 21-week magnetic field exposure could modify tumor development. They found a slightly earlier development of tumors in the magnetic field-exposed animals, the difference in time to appearance of tumors was, however, not statistically significant. In a follow-up study (*12*) the same strain and sex was exposed under the same field conditions using a weekly dose of 0.3 mg of TPA. The rate of tumor development was found to be increased in the magnetic field-exposed group compared to a sham-exposed TPA group. A difference in the cumulated number of mice with tumors was observed, but this difference did not reach statistical significance at the end of the observation period (23 weeks). Splenomegaly (*11*) was observed among the TPA + magnetic field-exposed mice, and there was a greater number of mononuclear cells in the spleens of animals with combined exposure. There was also a depressed NK cell activity. This is suggestive of a suppression of the immune system, possibly related to a development of leukemia/lymphomas.

In one liver foci experiment (*9*), 50-Hz continuous magnetic field exposure at 0.5 μT and 0.5 mT was applied during both the hepatectomy and the initiation phase (with DENA), as well as during the promotion phase in combination with a phenobarbital (PB) treatment. The formation of preneoplastic foci was slightly inhibited in terms of foci area, frequency, and volume for both enzyme markers. This inhibition was statistically significant for 0.5 μT in terms of number of GGT-positive foci per cubic centimeter liver and for 0.5 mT in terms of mean area and percentage foci volume as estimated by the GSTp marker.

Hitherto published animal studies, using continuous 50- or 60-Hz magnetic fields, do not support the hypothesis of a tumor promotive effect of magnetic fields, as studied in mice and rats, with different protocols and initiators. Only one study reports a (surprisingly) high incidence of mammary tumors induced by NMU after 3 hr of daily exposure to variable or static magnetic fields. One other study in mice suggests a copromotional effect of 2-mT and 60-Hz magnetic fields obtained with the skin-specific control promoter. The suggestive information on mammary tumors and copromotion of skin tumors needs to be confirmed. Several animal experimental studies on tumor promotion with different magnetic field exposure regimens, initiators, tumor types under observation, and animal strains are ongoing or planned in Canada, Italy, Japan, Sweden, and the United States.

Physiologic Studies

One hypothesis, which has been forwarded (*13*) for magnetic field-related cancer development, is derived from physiologic studies on the hormone melatonin. Melatonin is excreted nightly from the pineal gland, and its formation and secretion are inhibited by periods of light or magnetic field exposure. Melatonin is oncostatic (*14*) via inhibition of the mitogenic activity of, e.g., estrogen, or by acting directly by blocking cell proliferation (*15*). Disturbances in the melatonin rhythm appear also to affect the function of the immune system (*16*). Pinealectomy increases chemically induced melanomas in Syrian hamsters (*17*) and mammary tumors in the rat (*14,18*). Injections of melatonin into rats induced with DMBA reduced tumor growth and incidence in some studies (*18–21*). Whether melatonin plays a regulating role for the development of other tumor types is not known.

Short, repeated exposures to 40-μT magnetic fields inhibit the conversion of serotonin to melatonin in the pineal gland in the rat (*22*), probably by eddy currents (*23,24*) induced by rapid alterations in the instantaneous inversion of the horizontal component of the geomagnetic field.

Cell Experiments

A few studies have been made on the possible genotoxicity of magnetic fields on cell systems (*25*), without finding mutations in *Salmonella* (*26,27*), strand breaks (*28*), or effects on DNA repair in human fibroblasts *in vitro* (*29*). In some of these studies there have been exposures to both electric and magnetic fields. Pulsed magnetic fields in some pulse widths, flux densities, and frequencies, but not in others, seem to increase the rate of DNA synthesis (*30*) of V79 cells and human fibroblasts (*31*) *in vitro*.

There seems to be general agreement (*25,32,33*) among reviewers on the issue of possible DNA injury related to magnetic field exposure that no such effects can be ascribed to magnetic fields.

Studies with cellular systems using different exposure setups, exposure durations, amplitudes, frequencies, and wave forms indicate that biological effects of magnetic fields on cellular systems are at hand (*34–44*), which may be related to cell multiplication or even tumor promotion.

Exposing human leukemia cells (*45–47*) or normal rat lymphocytes (*48*) to electromagnetic fields at various frequencies increases the transcripts of c-*myc* or histone. Transcriptional changes on the RNA level have also been observed with magnetic field in *Drosophila* and *Sciara* salivary gland cells (*49,50*) and in *Sacharomyces* of specific genes, genes responsible for the production of heat shock proteins (*51*).

In addition to effects on c-*myc* transcription, the expression of c-*fos*, c-*jun*, and protein kinase C in a lymphoblastoid cell line has been found to be altered by a magnetic field exposure (*52*) of short duration and of c-*fos* in a HeLa subline by a static magnetic field (*53*). Those genes are involved in the regulation of cell growth, and a change in the production of proteins resulting from a changed expression of those genes may influence the cellular proliferation in the tissue. Should such cells already be initiated, a tumor may result.

Effects on gene expression seem to depend on frequency, field strength, and exposure time (*39,46*). Thus the concept of exposure or dose "windows," where biological effects occur—like effects on calcium metabolism (*35,36,54*), or increases in the activity of certain enzymes (*55*) involved in cell growth—has been forwarded.

It seems to be well established that electromagnetic fields induce changes in the calcium metabolism of exposed cells. The calcium efflux has been increased (*37, 54–57*) in a number of studies; also, an increase in cytosolic calcium from extracellular sources in stimulated rat thymocytes exposed to 60-Hz sinusoidal magnetic field (*44*) and 3-Hz pulsed fields has been observed (*58*). Magnetic fields from an MRI unit (*59*) increase cytosolic calcium in human leukemia cells. Calcium is involved, e.g., in cellular processes (signal transduction) leading to mitogenesis; and the investigation of the magnetic field interaction with the calcium balance may be of great importance for the understanding of the molecular mechanism of magnetic field effects on different cell types. Transmembrane calcium signaling events may also be of importance (*57*) for the mediation of magnetic field effects on cells of the immune system. The effect of magnetic fields on calcium metabolism seems to be optimized when the ratio of the electromagnetic frequency to the DC field intensity equals the charge-to-mass ratio (cyclotrone resonance theory) of nonhydrated ions such as calcium, lithium, potassium, and magnesium (*60*).

The cell growth-related enzyme ornithine decarboxylase has been found to be increased (*61*) in mammalian tumor cells after exposure to electromagnetic fields. This increase was optimized (*62*) in mouse fibroblasts when the coherence of the time-varying magnetic field was maintained for a certain minimum period.

Exposure of mouse embryo cells *in vitro* to repeated 60-Hz electromagnetic fields enhances the colony formation of TPA-treated cells (*63*). This suggests that magnetic fields may act as a growth stimulator via membrane-related events. Also, studies using 72-Hz pulse trains and 15-Hz recurrent bursts (*64*) on osteoblasts *in vitro* indicate that magnetic fields affect membrane receptor function as observed by an inhibition of responses of cells to parathyroid hormone.

Thus studies on a variety of cellular systems, including mammalian and human cells, seem to indicate that biological effects on the cellular and subcellular level can be related to electromagnetic fields. The effects studied have some relevance to cell function and growth and, perhaps, tumor promotion. The exposure parameters are far from well characterized or uniform over the cellular systems studied. Furthermore, the possible magnetic field-related effects on cellular and subcellular phenomena need to be demonstrated as to their validity for whole animals (*41*) at long-term exposure conditions that can be related to human risk.

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