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Electromagnetic fields, the modulation of brain tissue functions — A possible paradigm shift in biology

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All life on earth is bathed in a sea of natural low-frequency electromagnetic (EM) fields from conception to death. Generated principally by thunderstorm activity in equatorial zones, these fields exhibit peaks in the ELF spectrum between 8 and 32 Hz – the [Schumann (1957)] resonances. Their energy is measured in billions of coulombs. They are ducted worldwide between the earth's surface and the ionosphere approximately 140 km above the earth. With a circumference of 41,000 km, the earth may act as a cavity resonator in this ducted propagation, with a resonant frequency around 8 Hz for waves moving at the velocity of light (300,000 km/s). Schumann fields are weak, with electric components of about 0.01 V/m, and magnetic fields of 1–10 nanotesla. We may contrast these weak extremely-low-frequency (ELF, with frequencies below 300 Hz) fields with the earth's much larger static geomagnetic field, typically around 50 microtesla (μT).

Over the last century, steadily increasing use of electric power in all industrialized societies has sharply increased the EM environment and modified its spectral content. In U.S. urban environments, typical 60 Hz domestic ambient fields may be in the range 0.03–0.3 μT, but substantially higher near washing machines, hair dryers, electric shavers, etc. There is great and growing use of microwave devices, thus extending utilization of the EM spectrum many octaves, from a few cycles/sec (Hz), with corresponding wavelengths of 10,000 km or more, to millimeter waves and the far-infrared region.

[Bullock (1991)] has defined induced brain rhythms as "oscillations caused or modulated by stimuli or state changes that do not directly drive successive cycles". This perspective directs attention to two sets of related but inverse problems. There are tonic central nervous responses to rhythmic stimuli, responses that extend beyond a brief epoch of rhythmic stimulation. There are also phasic responses to continuing rhythmic stimuli. Aspects of their significance in brain functions has been revealed through imposition of EM fields as tools that induce brain tissue fields mimicking in varying degrees components of intrinsic brain electrical rhythms.

Initial studies with imposed EM fields in the nervous system centered on modulation of brain ionic mechanisms ([Adey, 1981a] [Adey, 1981b][Bawin and Adey, 1976]; [Bawin et al., 1975][Bawin et al., 1978]; Blackman et al., 1979][Blackman et al., 1985]) and behavioral responses [Gavalas et al., 1970]; [Gavalas-Medici and Day-Magdaleno, 1976]; [Kalmijn, 1974]); Embryonic exposure of the developing vertebrate nervous system to EM fields at specific frequencies (50 or 60 Hz) may establish thereafter lasting frequency-dependent sensitivities in cerebral calcium binding ([Blackman et al., 1988]) Initial studies on ionic mechanisms were followed by investigations of developmental modifications and behavioral teratology following embryonic and fetal exposures ([Delgado et al., 1982]; [Juutilainen et al., 1986]a, 1986b; [McGivern et al., 1990]; [Sikov et al., 1987]). More recent epidemiological studies have reported developmental defects in motor skills, memory and attention in children exposed throughout life to high intensity radar fields pulsed at EEG frequencies ([Kolodynski and Kolodynska, 1996]). An association between occupational exposure to power frequency magnetic fields and Alzheimer's disease has been reported in joint studies of two series of patients in California and one in Finland ([Sobel et al., 1995]).
These studies in brain tissue have led to investigation of the possibility of similar phenomena in non-nervous tissue, with the conclusion that sensitivity to weak low-frequency EM fields may be a more general property of cells in tissue (for reviews, see [Adey, 1992a][Adey, 1992b] [Adey, 1999]). They point to a private language of intrinsic communication by which cells may "whisper together" in activities such as metabolic cooperation and growth regulation ([Adey, 2003a).

Intracellular enzymes mediating metabolic, messenger and growth functions have been used as molecular markers of transductive coupling of EM fields in cell surface receptor mechanisms. Representative studies in each of three membrane-related enzyme groups include adenylate cyclase ([Luben et al., 1982]; [Luben and Cain, 1984]), guanylate cyclase ([Bawin et al., 1994][Bawin et al., 1996]), protein kinases ([Byus et al., 1984]; [Uckun et al., 1995]), and ornithine decarboxylase ([Byus et al., 1987][Byus et al., 1988]; [Litovitz et al., 1993]). In addition, low frequency magnetic fields induce rapid transitory intracellular expression of heat-shock proteins that mediate a wide range of cellular stress responses ([Lin et al., 1997]; Lin et al., 1998]).

1. Bioelectromagnetics: developments towards a physical biology

The emergent field of bioelectromagnetics encompasses two important scientific frontiers. On the one hand, it addresses studies in the physics of matter; and on the other, the search for essential bioenergetics of living systems. To carry this joint endeavor forward in future research, mainstream biological science is coming to recognize the essential significance of nonequilibrium processes and long range interactions ([Frohlich, 1988]). Historically, biology has been steeped in the chemistry of equilibrium thermodynamics. Heating and heat exchange have been viewed as measures of essential processes in the brain and other living tissues, and intrinsic thermal energy has been seen as setting an immutable threshold for external stimulation ([Adair, 1994]). Through the use of EM fields as tools, it is clear that heating is not the basis of a broad spectrum of biological phenomena incompatible with this concept. They are consistent with processes in nonequilibrium thermodynamics ([Adey and Lawrence, 1984]; [Binhi, 2002];[Scott, 1999]). .

With the emergence of new knowledge on quasiparticles, solitonic waves and cooperative processes, many earlier postulates on the biological role of equilibrium thermodynamics have undergone extensive reappraisal ([Adey, 1992a][Adey, 1993]). Experimental evidence of biological effects of weak ELF magnetic fields is supported by theoretical models involving quantum-interference effects on protein-bound substrate ions. This ion-interference mechanism predicts specific magnetic-field frequency and amplitude "windows" within which the biological effect would occur, using the principles of gyroscopic motion ([Binhi, 2002]; [Binhi and Savin, 2002]

1.1 Evidence for role of free radicals in electromagnetic field bioeffects

Beyond the chemistry of molecules forming the fabric of living tissues, this experimental evidence suggests a biological organization based in far finer physical processes at the atomic level, rather than in chemical reactions between biomolecules ([Adey, 1997]). Physical actions of EM fields may regulate the rate and the amount of product of biochemical reactions, possibly through *free radical mechanisms* ([McLauchlan and Steiner, 1991];[Till et al., 1998]; [Timmel et al., 1998];), including direct influences on enzyme action ([Grissom, 1995]). Chemical bonds are magnetic bonds, formed between adjacent atoms through paired electrons having opposite spins and thus attracted magnetically.

When chemical bonds are broken in chemical reactions, each atomic partner reclaims its electron and moves away as a *free radical* to seek another partner with an opposite electron spin. The brief lifetime of a free radical is about a nanosecond or less. McLauchlan points out that this model predicts a potentially "enormous effect" on the *rate* and *amount of product* of chemical reactions for static fields in the low mT range. For oscillating fields, the evidence is less clear on their possible role as direct mediators in detection of ELF frequency-dependent bioeffects. The highest levels of free radical sensitivities to imposed magnetic fields may reside in *spin-mixing* of orbital electron spins with nuclear spins in adjacent nuclei, where potential sensitivities may exist down to zero magnetic field levels. However, as a practical consequence, this sensitivity would hold only if occurring before diffusion reduced the probability of radical re-encounter to negligible levels (see [Adey, 2003a] for review)..

Lander (1997) has emphasized that we are at an early stage of understanding free radical signal transduction. "Future work may place free radical signaling beside classical intra- and intercellular

messengers and uncover a woven fabric of communication that has evolved to yield exquisite specificity," but not necessarily through "lock and key" mechanisms. Lander speculates that certain amino acids on cell surface proteins may act as selective targets for oxygen and nitrogen free radicals, thus setting the *redox* potential of this target protein molecule as the critical determinant of its highly specific interactions with antibodies, hormones, etc. Magnetochemistry studies ([Grundler et al., 1992]) have suggested a form of cooperative behavior in populations of free radicals that remain *spin-correlated* after initial separation from a singlet pair. As discussed below, magnetic fields at 1 and 60 Hz destabilize rhythmic oscillations in brain hippocampal slices via as yet unidentified nitric oxide mechanisms (Bawin et al., 1996).

In a general biological context, these are some of the unanswered questions that limit free radical models as general descriptors of threshold events..

2.Observed effects of environmental fields in the central nervous system

Reported central nervous system interactions with environmental fields have tested both electric and magnetic ELF fields, and a range of radio-frequency (RF) and microwave fields. These RF/microwave fields have examined both thermal and nonthermal exposures, with either unmodulated fields or with various ELF amplitude-, pulse- and frequency-modulations. At tissue electric gradients in the range 10^{-7}–10^{-1} V/cm and concomitant ELF magnetic fields in the range 1.2–10 μT, a spectrum of physiological and behavioral sensitivities have been reported, They were first reported in neurobehavioral studies ranging from marine vertebrates to man ([Adey, 1981a][Adey, 1981b]), and in later laboratory studies at the cellular level ([Adey, 1992a][Adey, 1992b][Adey, 1997]; [Liburdy, 1995]). Many of these observations have been independently replicated. The level of these sensitivities has raised important questions about how detection occurs in the face of much larger focal energies at cell surfaces attributable to molecular and atomic thermal collision energies (kT), and in the face of presumably much larger background electrical "noise" generated in the brain as a whole ([Bialek, 1983]; [Bialek and Wit, 1984]).

None of these sensitivities to such weak signals appears related to a brief, punctate EM stimulus generated by a single transient event. Effective stimuli are coherent ([Adey, 1993]), presenting a train of regularly recurring signals that must be present for a certain minimum duration ([Litovitz et al., 1993]). Thus, these sensitivities were initially reported to be *windowed* with respect to field frequency in EEG studies in the cat ([Bawin et al., 1973]) and monkey ([Gavalas et al., 1970]; [Gavalas-Medici and Day-Magdaleno, 1976]). Later studies reported similar frequency windowing at cell and molecular levels in cerebral tissue ([Bawin et al., 1975]; [Blackman et al., 1985]; [Kolomytkin et al., 1994]) and in non-neural cells ([Byus et al., 1987]; [Walleczek, 1994]). These are highly cooperative processes. They may be modeled biophysically in a hierarchy of energetic and temporal steps. For example, they may commence with spin-correlated free radical interactions ([Grundler et al., 1992]), extending to ion parametric resonance phenomena ([Blanchard and Blackman, 1994]; [Lednev, 1991]), and to solitonic conduction in transmembrane signaling across phospholipid-protein energetic domains, established by joint states of intramembranous proteins and surrounding phospholipid molecules ([Adey, 1992a]). By their nature, these systems are likely to be insensitive to incoherent oscillations representing the aggregate process of large tissue domains.

2.1 Tissue detection of low frequency fields and RF/microwave fields amplitude-modulated at low frequencies

In early studies, similarities were noted in certain responses of tissues, cells and subcellular fractions exposed to environmental fields in the ELF spectrum, or to RF/microwave fields amplitude-modulated at similar ELF frequencies. The findings suggest, but do not yet establish unequivocally, that this frequency dependence may be a system property in a sequence beyond the first transductive step.

2.1.1 Detection of extremely low frequency fields

For ELF fields, models based on joint static-oscillating magnetic fields have been proposed. They include ion cyclotron resonance (Liboff, 1992), where mono- and divalent cations, such as potassium and calcium, abundant in the cellular environment, may exhibit cyclotron resonance at ELF frequencies in the presence of ambient static fields of less than 100 μT, such as the geomagnetic field. Other models describing ELF frequency dependence have considered phase transitions ([Lednev, 1991]) and ion paramagnetic resonance ([Blanchard and Blackman, 1994]), but interpretation of this frequency dependence based on ion paramagnetic resonance remains unclear ([Adair, 1998]).

2.1.2 Detection of amplitude- or pulse-modulated RF/microwave fields

For amplitude- or pulse-modulated RF/microwave fields, there is the implication that some form of *envelope demodulation* occurs in brain tissue recognition of ELF modulation components, but the tissue may remain essentially transparent to the same signal presented as an unmodulated (CW) carrier wave ([Adey, 1981a]; [Adey, 1999]). However, it should also be emphasized that bioeffects of CW microwave fields have also been reported in both neural and non-neural systems in the absence of thermal stress. For example, in the nematode *Caenorhabditis elegans*, 700-1000MHz , 0.5W CW fields elicited a heat-shock protein response, an increased growth rate and an increased proportion of egg-bearing adults ([di Pomerai et al., 2002]). Rat hippocampal slices exposed to 700 MHz CW fields at extremely low Specific Energy Absorption Rates (SARs) in the range 0.0016 – 0.0044W/kg for 5 – 15 min showed a 20% potentiation in evoked population potentials in the lower range of stimulus intensities, but increased or decreased evoked potentials at higher intensities ([Tattersall et al., 2002]).

However, crucial questions remain unanswered. It is not known whether biological low-frequency dependence is established at the transductive step in the first tissue detection of the field, or whether it resides in an hierarchical sequence of signal coupling to the biological detection system ([Engstrom, 1997]). For ELF magnetic fields, experimental evidence points to a slow time scale in inhibition of tamoxifen's antiproliferative action in human breast cancer cells ([Harland et al., 1999]).

In accordance with principles of radio physics, extraction of ELF modulation information from an amplitude-modulated signal requires a *nonlinear element* in the detection system ([Adey, 2003a]). Such a required nonlinearity in tissues may exist in several ways:

1) A spatial component, as in the changing directions and cross sections of the preferred tissue conduction pathways in the intercellular spaces.
2) nonlinearities related to the intensely anionic electric charge distribution on strands of glycoproteins that form the cell surface glycocalyx. They attract a surrounding cationic atmosphere mainly of calcium and hydrogen ions, with this charge separation creating a Debye layer having a large and probably nonlinear virtual surface capacitance at low frequencies ([Einolf and Carstensen, 1971]). Displacement currents induced in this region by ELF modulation of an RF field may then result in demodulation.
3) Extreme functional nonlinearity within the cell membrane associated transmembrane charge tunneling ([DeVault and Chance, 1966]). These early experimental studies by Chance and colleagues have been extended theoretically ([Moser et al., 1992]) in modeling a cell membrane with a transverse dimension of 40 A^o, with the conclusion that a variation of 20 A^o in the distance between donors and acceptors in a protein molecule changes the electron transfer rate by 10^{12}-fold. Concurrently, in the time domain, the electron transfer rate is pushed from seconds to days, or a 10-fold change in rate for a 1.7 A^o change in distance.

2.3 Cell membranes as primary sites in detection, amplification and transmembrane coupling of interactions with environmental EM fields: modulation of brain tissue calcium binding

Concepts of a cell emphasize the role of a bounding membrane, surrounding an organized interior that participates in essential chemical processes. This enclosing membrane is thus the organism's window on the world around it. Cellular aggregates that form tissues of higher animals are separated by narrow fluid channels that are of special importance in signaling from cell to cell. These tiny :"gutters" form the *intercellular space* (ICS) , typically not more than 150 A^o wide. It is the pathway for biomolecules to binding sites on cell membrane receptors. Its lower electrical impedance makes it a preferred pathway over transmembrane paths for induced currents of intrinsic and environmental electromagnetic fields ([Adey, 1992a]). Although occupying only ~10% of the tissue cross-section, it carries at least 90%of any imposed or intrinsic current, directing it along cell membrane surfaces. Whereas the ICS may have a typical impedance of ~ 4-50 ohm.cm^{-1}, transmembrane impedances are ~ 10^4 –10^6ohm.cm^2.

From within the cell, electrochemical "antennae" protrude as glycoprotein strands into these gutters, forming a *glycocalyx.* They offer an anatomical substrate for the first detection of weak electrochemical oscillations in pericellular fluid, including field potentials arising in activity of adjoining cells, or as tissue components of environmental fields. There is increasing evidence for direct communication between cells due to their mutual proximity. Bands.of *connexin* proteins form *gap-junctions* directly uniting adjoining cell membranes. Experimental evidence supports their role in intercellular signaling (Zhou et al., 2001). Beyond a possible initial role in weak EM field transduction, they may be involved in cell surface signal amplification through a highly cooperative binding or release of calcium ions ([Bawin et al., 1975]; [Bawin and Adey, 1976]; [Blackman et al., 1979][Blackman et al., 1985]); a sensitivity that also exists in preparations of sub-micron sized cerebral synaptosomes ([Lin-Liu and Adey, 1982]). Calcium ions are attracted to numerous negatively charged anionic sites on the glycoprotein strands. Charge sites on these strands may exhibit coherent states between adjoining charge sites for periods extending into the millisec range ([Schwarz, 1970]). This signal amplification along cell surfaces is followed by transmembrane coupling of calcium-mediated signals through the glycoprotein strands to the cell

interior ([Lindstrom et al., 1995]). This influx of calcium into cells is also modulated by weak ELF magnetic fields in a frequency-dependent manner ([Walleczek, 1994]).

Electrostatic factors, rather than chemical interactions, have been identified experimentally in regulation of fluxes of potassium and other cations through transmembrane ion channels ([Lopez, 2003]). These findings offer support for cell membranes as a site of intrinsic and environmental EM field bioeffects. A subset of ion channels known as inward rectifier channels (IRK) are preferred pathways for inward conduction of K^+ ions. A highly hydrophobic negatively charged pore at the inner end of this channel attracts complementary positively charged spermine and other polyamine molecules into the cytoplasmic pore. Polyamines have the highest charge/mass ratio of any biomolecule. They "forcibly herd and queue" K^+ ions towards the transmembrane exit ([Nishida and MacKinnon, 2002; [Matsuda et al., 2003]). Polyamines are synthesized from ornithine in response to both ELF field exposures([Byus et al., 1987]) and to microwave fields amplitude-modulated at low frequencies [Byus et al., 1988]).

3. Calcium-dependent neuroregulatory mechanisms modulated by EM fields

3.1. Sensitivity of cerebral neurotransmitter receptors

Binding of neurotransmitters to their specific receptor sites is sensitive to weak modulated microwave fields. [Kolomytkin et al. (1994)] studied specific receptor binding to rat brain synaptosomes of three neurotransmitters, GABA, acetyl choline and glutamate, using 880 or 915 MHz fields at power densities of 10–1500 uW/cm2. Incident fields of 1500 μW/cm2 decreased GABA binding 30% at 16 pulses/s, but differences were not significant at 3, 5, 7, or 30 pulses/s. Conversely, 16 pulse/sec modulation significantly increased glutamate binding. For acetyl choline receptors, binding decreased 25% at 16 pulses/s, with similar trends at higher and lower frequencies. As a function of field intensity, sensitivities of GABA and glutamate receptors persisted for field densities as low as 50 μW/cm2 at 16 pulses/s with 915 MHz fields.

3.2. The glutamate receptor and normal/pathological synthesis of nitric oxide; sensitivity to magnetic fields

An enzymatic cascade is initiated within cells when glutamate receptors are activated, leading to the synthesis of nitric oxide (NO). Receptor activation initiates an influx of calcium, triggering the enzyme nitric oxide synthase to produce nitric oxide from the amino acid arginine. As a gaseous molecule, NO readily diffuses into cells surrounding its cell of origin. It has been identified as a widely distributed neuroregulator and neurotransmitter in many body tissues ([Izumi and Zorumski, 1993]). Its chemical actions in brain appear to involve production of cGMP (cyclic-guanosine monophosphate) from GTP (guanosine triphosphate). The pathophysiology of NO links its free radical molecular configuration to oxidative stress, with a possible role in Alzheimer's and Parkinson's disease, and in certain types of epilepsy. Magnetic resonance spectroscopy (MRS) has suggested decreased levels of N-methylaspartate, an activator of the glutamate receptor, in the striatum of brains of patients with Parkinson's disease ([Holshouser et al., 1995]).

Studies of the role of NO in controlling the regularity of EEG waves in rat brain hippocampal tissue have shown that inhibition of its synthesis is associated with shorter and more stable intervals

between successive bursts of rhythmic waves. Conversely, donors of NO and cGMP analogs applied during blockade of NO synthesis lengthen and destabilize intervals between successive rhythmic wave bursts ([Bawin et al., 1994]).

The rate of occurrence of these rhythmic EEG wave bursts in rat brain hippocampal tissue is also disrupted by exposure to weak (peak amplitudes 0.08 and 0.8 mT) 1 Hz sinusoidal magnetic fields ([Bawin et al., 1996]; Figure 1). These field effects depend on synthesis of NO in the tissue. They are consistent with reports of altered EEG patterns in man and laboratory animals by ELF magnetic fields ([Bell et al., 1992]; [Lyskov et al., 1993]).

A sequence of functional steps have been described in mechanisms mediating this regulatory role of NO. The synthetic enzyme nitric oxide synthase is localized in the dendritic spines of hippocampal CA1 pyramidal cells ([Barette et al., 2002]} Long-term potentiation (LTP) in the hippocampus following electrical stimulation involves sequential activation by NO of soluble guanylate cyclase, cGMP-dependent protein kinase, and cGMP-degrading phosphodiesterase ([Monfort et al., 2002]). The post-stimulus time interval during which NO operated was restricted to less than 15 min, suggesting that NO does not function simply as an acute signaling molecule in induction of LTP, but may have an equally important role outside this phase(([Bon and Garthwaite, 2002]).

4. Neuroendocrine sensitivities

4.1 Effects of environmental EM fields on melatonin cycling in animals and man

Brain neuroendocrine sensitivities to ELF fields have centered around the pineal gland, where synthesis and secretion of the hormone melatonin exhibits a strong circadian rhythm. There is a nocturnal peak around 2.0 a.m. in man and animals ([Reiter and Richardson, 1990]). The cycle is variably sensitive to the day/night ratio of light exposure in different species. Its possible susceptibility to a changing EM environment has been the subject of intense study ([Semm, 1983]; [Wilson et al., 1986][Wilson et al., 1990]). Evidence for modulation of human melatonin cycling by environmental EM field exposure remains unclear ([Juutilainen et al., 2000];[Stevens et al., 1997]), and although aspects of these studies remain unclear within and between species, the most consistent findings in animal models have been in the Djungarian hamster ([Yellon, 1994]). Acute exposure of long-day (16 h light/8 h dark) animals to a 60 Hz magnetic field (0.1 mT, 15 min) 2h before light off suppresses the night-time rise in melatonin in the pineal gland and in the blood. In short-day (8 h light/16 h dark) animals, acute exposures produced similar results, but daily exposures for as long as 3 weeks had no effect.

Beyond diurnal activity rhythms, melatonin is key to a broad range of regulatory mechanisms ([Reiter, 1992]), including the immune system, reducing incidence of certain cancers in mice, and inhibiting growth of breast cancer cells ([Hill and Blask, 1988]; [Liburdy et al., 1993]). This inhibitory action of melatonin is reported to be blocked by 60 Hz magnetic fields at a 1.2 μT threshold level in MCF-7 human breast cancer cells ([Liburdy et al., 1993]; [Blackman et al., 1996]). Further studies ([Ishido et al., 2001]) have confirmed the original observation of an oncostatic action of melatonin on MCF-7 cells at physiological concentrations. Also, this oncostatic action was inhibited by exposures to 50 Hz magnetic field at 1.2 μT through an action on melatonin

type 1A receptors on the cell membranes. Since other enzymes involved in the melatonin signaling pathway, such as GTPase and adenylyl cyclase, were unaffected by the exposures, it is hypothesized that the magnetic fields may uncouple signal transduction from melatonin receptors to adenylyl cyclase.

Patients with estrogen receptor-positive breast cancer have lower nocturnal plasma melatonin levels ([Tamarkin et al., 1982]). Epidemiological studies also suggest a relationship between occupational exposure to environmental EM fields and breast cancer in women and men ([Stevens et al., 1992]). Women in electrical occupations have a 40% higher risk of breast cancer than other women in the workplace ([Loomis et al., 1994]). An increased incidence of breast cancer has also been reported in men in a variety of electrical occupations ([Demers et al., 1991]; [Matanoski et al., 1991]).

4.2. Behavioral teratology associated with EM field exposure in animals and man

In animal models, periods have been delineated in early development when hormones most readily affect long-lasting changes in sexual and other behaviors. In the rat, for example, the time of greatest susceptibility to the organizational action of the gonadal steroids occurs during the last week of gestation and continues for 4 or 5 days after parturition. Complete masculinization of the brain during this period is dependent on normal secretory patterns of testosterone, as well as on normal ontogenic development of brain regions sensitive to steroid action, such as the amygdala and hypothalamus.

Prenatal exposure of rats to an ELF magnetic field has been reported to demasculinize adult scent marking behavior and to increase accessory sex organ weights ([McGivern et al., 1990]). Pregnant Sprague–Dawley rats were exposed to a pulsed magnetic field (15 Hz, 0.3 ms, peak intensity 0.8 mT) for 15 min twice daily on days 15–20 of gestation. No differences in litter size, number of stillborns, or body weight were observed in offspring from field-exposed dams. At 120 days of age, field-exposed male offspring exhibited significantly less scent marking behavior than controls. Accessory sex organ weights, including epididymis, seminal vesicles and prostate, were significantly higher in field-exposed subjects at this age. However, circulating levels of testosterone, luteininizing hormone, and follicle-stimulating hormone, as well as sperm counts, were normal. Defective glycosaminoglycan formation at cell surfaces in the developing chick brain has been proposed as a mechanism of action of weak magnetic fields ([Ubeda et al., 1983]).

Subtle defects in behavioral and motor performances have been reported in children exposed to high intensity pulsed radar fields from conception through adolescence ([Kolodynski and Kolodynska, 1996]). For more than 25 years, a Latvian early warning radar has operated in a populated area, at frequencies of 154–162 MHz (pulse repetition frequency 24.5/s, pulse width 0.8 ms). The study involved 966 children (425 M, 541 F), aged 9–18 years, all born in farming communities, and many living under conditions of chronic radiofrequency exposure. A computer-based psychological test battery evaluated neuromuscular coordination, reaction time, attention and recent memory. As compared with unexposed controls, and with children living at the margins of the antenna beam, children exposed to the main lobe of the radar beam had less developed memory and attention, slower reaction times, and less sustained neuromuscular performance.

5. Influence of EM fields on brain tumor incidence in man and in animal models

5.1. Epidemiological studies

Environmental EM fields may act jointly with exposure to environmental chemicals with known cancer-promoting actions in enhancing occupational brain tumor risks. Experimental evidence supports cell membranes as a site for joint actions of many chemical cancer promoters with EM fields ([Adey, 1992b]). The latter include pesticides, weedicides and electrical solvents. A case-control study by the U.S. National Cancer Institute of brain tumor incidence in RF/microwave occupational exposures ([Thomas et al., 1987]) in the states of New Jersey, Pennsylvania and Louisiana concluded that all excess risk for primary brain tumors in white males aged over 30 years derived from jobs involving design, manufacture, installation and repair of electronic equipment (Risk Ratio=2.3, 95% CI=1.3,4.2). Cases were divided into cohorts with 5, 10, 15 and 20+ years of exposure. Risks of astrocytomas increased to ten-fold for those employed 20 years or more, when concurrent exposure to electrical and electronic solvents was involved. RRs were not increased in men exposed to RF/microwave fields, but who never worked in electrical or electronics jobs; leading the authors to emphasize concurrent exposures to soldering fumes, solvents and a variety of chemicals as possible co-factors with RF/microwave fields in tumor promotion.

In a case-control study of risk factors for gliomas and meningiomas in males in Los Angeles County, involving 272 men aged 25–69 with primary brain tumors and 272 matched neighbor controls ([Preston-Martin et al., 1989]), glioma (but not meningioma) risk related to prior employment in jobs likely to involve high exposure to electric and magnetic fields ($P<0.05$). The risk was greatest for astrocytoma (OR for employment in such jobs for >5 years=4.3; CI=1.2–15.6). As in the study of microwave workers cited above, there was evidence of concurrent action of chemical factors. More glioma cases had worked in the rubber industry (discordant pairs 6/1), and more worked in hot processes using plastics (9/1).

[Savitz and Loomis (1995)] have linked work site magnetic field measurements to individual work histories in a cohort mortality study (138,905 men) at 5 large American electric power companies over a period of 36 years. Brain cancer risk increased by a factor of 1.94 per microtesla-year of magnetic field exposure in the previous 2–10 years, with a mortality rate ratio of 2.6 in the highest exposure category.

In a series of studies, Hardell and colleagues have examined the relationship between the side of the head habitually used in operation of cellular and cordless phones and a possible relationship to the site of brain tumors ([Hardell et al., 2003]). The risk for ipsilateral use significantly increased the risk for astrocytoma for all types of phones, but use of the phone on the opposite side of the head was not associated with significantly increased risk. Overall, use of FM (analog) phones gave an increased risk, whereas digital and cordless phones did not increase risks significantly.

5.2. Animal models of brain tumor promotion

There are few accepted animal models of spontaneous malignant central nervous system (CNS) tumors, although there has been increasing use of the Fischer 344 rat, with a reported incidence of spontaneous malignant tumors as high as 11%. Two life term studies using this rat model have compared exposures to the North American Digital Standard (NADC) digital phone field using

Time Division Multiple Access (TDMA) modulation pulsed at 50 "packets"/sec, with comparable exposures to the older type of FM (analog) phone fields ([Adey et al., 1999]; [Adey et al., 2000]). Rats were exposed in utero to a single dose of the short-lived neurocarcinogen ethylnitrosourea (ENU), and thereafter, exposed intermittently to either TDMA or FM fields for 23 months.

In the TDMA study, when compared with rats receiving ENU but unexposed, rats that died from a primary CNS tumor before termination of the study showed a significant reduction in tumor incidence ($P<0.015$). A similar but non-significant reduction in spontaneous tumor incidence occurred in rats field-exposed but not receiving ENU ($P<0.08$). In the balanced design of this experiment, consistent non-significant differences in survival rates were noted between the four rat groups, with higher death rates in a progression: sham/field:sham/sham:ENU/field:ENU/sham. By contrast in the FM study, no field-related effects were observed in number, incidence or types of either spontaneous or ENU-induced CNS tumors.

These observations of an apparent protective effect against ENU-induced and spontaneous CNS tumors are not isolated. Low dosage of X-rays in fetal rats at the time of ENU dosage sharply reduce subsequent incidence of induced tumors ([Warkany et al., 1976]), through activation of AT (alkylguanine-DNA-alkyltransferase) enzymes that participate in DNA repair ([Stammberger et al., 1990]). Other studies with nonionizing (microwave) fields also suggest their actions in mechanisms of DNA repair. Modulation of levels of single-strand breaks in brain cell DNA has been reported following low-level, long-term microwave exposure in mice ([Sarkar et al., 1994]) and in acute experiments in rats ([Lai and Singh, 1995]).

6. Summary: intrinsic and induced electric fields as threshold determinants in central nervous tissue; the potential role of cell ensembles

The intact nervous system might be expected to be more sensitive to induced electric fields and currents than *in vitro* preparations, due to a higher level of spontaneous activity and a greater number of interacting neurons. However, these fields induced in the body are almost always much lower than those capable of stimulating peripheral nerve tissue ([Saunders and Jefferys, 2002]). Weak electric field effects, below action potential thresholds, have been demonstrated in *in vitro* brain slice preparations ([Faber and Korn; 1989]; [Jefferys, 1995]}.Behavioral sensitivities in sharks and rays may be as low as 0.5 nV/mm for tissue components of electrical fields in the surrounding ocean ([Kalmijn, 1971]), or 100 times below measurable thresholds of individual electroreceptor organs ([Valberg et al., 1997]).

Research in sensory physiology supports the concept that some threshold properties in excitable tissues may reside in highly cooperative properties of a population elements, rather than in a single detector ([Adey,1998, 2003a, 2003b]). Seminal observations in the human auditory system point to a receptor vibrational displacement of 10^{-11}m, or approximately the diameter of a single hydrogen atom ([Bialek, 1983]; [Bialek and Wit, 1984]). It is notable that suppression of intrinsic thermal noise allows the ear to function as though close to 0^{o} K, suggesting system properties inherent in the detection sequence. Human olfactory thresholds for musk occur at 10^{-11} M, with odorant molecules distributed over 240 mm^2 ([Adey, 1959]). Human detection of single photons of blue-green light occurs at energies of 2.5 eV ([Hagins, 1979]). In another context, pathogenic bacteria, long thought to function independently, exhibit ensemble properties by a system recognizing

colony numbers as an essential step preceding release of toxins. These *quorum sensing* systems may control expression of virulence factors in the lungs of patients with cystic fibrosis ([Erickson et al., 2002]).

Although far from a consensus on mechanisms mediating these low-level EMF sensitivities, appropriate models are based in nonequilibrium thermodynamics, with nonlinear electrodynamics as an integral feature. Heating models, based in equilibrium thermodynamics, fail to explain a wide spectrum of observed nonthermal EMF bioeffects in central nervous tissue. The findings suggest a biological organization based in physical processes at the atomic level, beyond the realm of chemical reactions between biomolecules. Much of this signaling within and between cells may be mediated by free radicals of the oxygen and nitrogen species. Emergent concepts of tissue thresholds to EMF sensitivities address ensemble or domain functions of populations of cells, cooperatively "whispering together " in intercellular communication, and organized hierarchically at atomic and molecular levels.

7. See Also

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Examples of rhythmic slow activity (RSA) and magnetic field exposure in a hippocampal slice. *a*: Chart recording of one episode of RSA. *b*: Chart recording at lower speed showing several RSA episodes. The arrow above the trace indicates the event displayed in *a*. The hatched bar under the trace indicates exposure to a 1 Hz field at 560 μT. *c*: Playback of the interval marked with an asterisk in *b* at a faster chart speed to show the first disruption of the RSA intervals. The arrow under the trace indicates the onset time (T) of the destabilization of the intervals. *d*: Successive RSA intervals are plotted on the vertical axis (in seconds) against time (horizontal axis, minutes). The ticks on the horizontal axis define 10 min epochs. The hatched bar indicates field exposure. The onset time of destabilization occurred 3.1 min after the beginning of the exposure. Horizontal scale bars=1 s in *a*, 60 s in *b*, 20 s in *c*; vertical scale bars=2 mV. (From [Bawin et al., 1996], with authors' permission.)