Review Article

A NEUROBIOLOGICAL BASIS FOR ELF GUIDELINES

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Abstract—**It is well understood that electric currents applied directly to the body can stimulate peripheral nerve and muscle tissue; such effects can be fatal if breathing is inhibited or ventricular fibrillation is induced. Exposure to extremely low frequency electric and magnetic fields will also induce electric fields and currents within the body, but these are almost always much lower than those that can stimulate peripheral nerve tissue. Guidance on exposure to such fields is based on the avoidance of acute effects in the central nervous system. This paper reviews the physiological processes involved in nerve cell excitability in the peripheral and central nervous system, and the experimental evidence for physiologically weak electric field effects. It is concluded that the integrative properties of the synapses and neural networks of the central nervous system render cognitive function sensitive to the effects of physiologically weak electric fields, below the threshold for peripheral nerve stimulation. However, the only direct evidence of these weak field interactions within the central nervous system is the induction of phosphenes in humans—the perception of faint flickering light in the periphery of the visual field, by magnetic field exposure. Other tissues are potentially sensitive to induced electric fields through effects on voltage-gated ion channels, but the sensitivity of these ion channels is likely to be lower than those of nerve and muscle cells specialized for rapid electrical signaling. In addition, such tissues lack the integrative properties of synapses and neuronal networks that render the central nervous system potentially more vulnerable.**

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Key words: electromagnetic fields; radiation, non-ionizing; health effects; radiation protection

INTRODUCTION

It is well understood that electric currents applied directly to the body can stimulate peripheral nerve and muscle tissue; such effects can be fatal if breathing is inhibited or ventricular fibrillation is induced. There is an established literature describing these effects (reviewed, for example, by Reilly 1998), mostly in relation to electric current passing through the body as a result of inadvertent contact with a "live" conductor. Regulations which seek to prevent or minimize the effects of such contact have long been accepted world-wide. Exposure to extremely low frequency (ELF) electric and magnetic fields will also induce electric fields and currents within the body, but these are almost always much lower than those that can stimulate peripheral nerve tissue. Guidance on exposure to such fields is published by ICNIRP (1998) and IEEE (2002) and is based on the avoidance of acute effects in the central nervous system (CNS). This review briefly describes the physiological processes involved in nerve cell excitability in the peripheral and central nervous system and the experimental evidence for physiologically weak electric field effects, reviewed at an ICNIRP/WHO workshop (McKinlay and Repacholi 2003), along with data from more recent studies. The evidence for other possible health effects resulting from EMF exposure have been reviewed elsewhere (e.g., ICNIRP 2003; McKinlay et al. 2004; WHO in press) and are not considered here.

VOLTAGE-GATED ION CHANNELS

Voltage-gated ion channels in cell membranes allow passage of particular ionic species across the cell membrane in response to the opening of a "gate," which is sensitive to the transmembrane voltage (e.g., Catterall 1995; Bezanilla 2000; Hille 2001; Mathie et al. 2003). It is well established that electric fields induced in the body either by direct contact with external electrodes, or by exposure to low frequency magnetic fields, will, if of sufficient magnitude, excite nerve tissue through their interaction with these voltage-gated ion channels. The probability of an ion channel being open is regulated by the transmembrane voltage or membrane potential. This is achieved through the action of a voltage sensor, an electric dipole reorientation or charge movement within the ion channel protein, which induces a conformational change in the ion channel molecule favoring an open conformation or two distinct closed conformations, one

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capable of opening and the other being inactivated. Sensitivity is therefore primarily to the transmembrane electric field but varies widely between different ion channels (Hille 2001; Saunders and Jefferys 2002; Mathie et al. 2003). Many voltage-gated ion channels are associated with electrical excitability and electrical signaling. Such electrically excitable cells not only comprise neurons, glial and muscle cells, but also gametes and endocrine cells of the anterior pituitary, adrenal medulla, and pancreas (Hille 2001).

All these cells generally express voltage-gated sodium and calcium channels. Both of these ion channels are involved in electrical signaling and calcium ions activate a number of crucial cellular processes including neurotransmitter release, excitation-contraction coupling in muscle cells and gene expression (Catterall 2000; Hille 2001). Some ion channels, for example voltage-gated potassium and chloride ion channels, also exist in other, non-excitable tissues such as those in the kidney and liver and show slow electric potential changes, but their voltage sensitivity is likely to be lower (e.g., Jan and Jan 1989; Begenisich and Melvin 1998; Catterall 2000; Cahalan et al. 2001; Nilius and Droogmans 2001).

PERIPHERAL NERVOUS SYSTEM

Peripheral nerves comprise neurons whose cell bodies are located within the CNS with extended processes (axons) that lie outside the CNS. They conduct action potentials (impulses) towards (sensory nerves) or from (motor nerves) the spinal cord, and nerve stimulation shows an all-or-nothing threshold behavior. An action potential is a brief, self-sustaining wave of electrical depolarization that passes along the nerve axon and is caused by an influx of sodium ions following the opening of transient voltage-gated sodium channels. This is rapidly followed by a slower, longer lasting increase in potassium ion conductance, which repolarizes the nerve membrane and results in a short refractory period during which further stimulation is either not possible or is difficult. At power frequencies (50/60 Hz) for example, excitation results from a membrane depolarization of between 10–20 mV, corresponding to an electric field across the tissue of 5–25[‡] V m^{-1}, depending on orientation (McKinlay et al. 2004).

Large, rapidly changing, pulsed magnetic fields used in various specialized medical applications such as magnetic resonance imaging (MRI) can induce electric fields large enough to stimulate peripheral nervous tissue in humans. Reilly (1998, 1999) calculated induced electric field threshold values for peripheral nerve stimulation based on the changes in sodium and potassium conductance originally described by Hodgkin and Huxley (1952) and Frankenhaeuser and Huxley (1964). Minimum, orientation-dependent stimulus thresholds for large diameter (20 μm) myelinated nerve axons were estimated to lie around $6_{pk\text{-}pk}$ V m^{-1} at frequencies up to about 1–3 kHz. Electric field thresholds were estimated to be larger for smaller diameter neurons. Above this range, thresholds rise as the effective stimulus becomes shorter than the membrane time-constant. The time-constant results from the structure of biological membranes: the thin lipid membrane behaves as a capacitance while the ion channels provide a parallel resistance. At frequencies below around 10 Hz, accommodation to a slowly changing stimulus, which results from the slow inactivation of sodium channels, will also raise thresholds. In MRI, nerve stimulation is an unwanted side effect of a procedure used to derive cross-sectional images of the body for clinical diagnosis. Threshold rates of change of the switched gradient magnetic fields used in MRI for perception, discomfort, and pain resulting from peripheral nerve stimulation have been extensively reviewed by Nyenhuis et al. (2001). Generally, median, minimum threshold rates of change of magnetic field (during periods of <1 ms) for perception were 15–25 T s^{-1} depending on orientation and showed considerable individual variation (Bourland et al. 1999). These values were somewhat lower than previously estimated by Reilly (1998, 1999), possibly due to the constriction of eddy current flow by high impedance tissue such as bone (Nyenhuis et al. 2001). Thresholds rose as the pulse width of the current induced by the switched gradient field decreased; the median pulse width (the chronaxie) corresponding to a doubling of the minimum threshold (the rheobase) ranged between 360 and 380 μs but again showing considerable individual variation (Bourland et al. 1999). Numerical calculations of the electric field induced by pulses in the 84 subjects tested by Nyenhuis et al. (2001) have been used to estimate the median threshold for peripheral nerve stimulation at 60 Hz as 48 mT (Bailey and Nyenhuis 2005).

CENTRAL NERVOUS SYSTEM

A major function of the neurons of the brain and spinal cord is the integration of the often very large number of synaptic inputs received from other neurons and the projection of this information, either locally or distally within the CNS, or in the case of motor neurons, whose cell bodies are situated within the spinal cord, along peripheral motor nerve fibers to muscles. Each

[‡] All values expresses as root mean square (rms) unless otherwise stated.

neuron may receive tens of thousands of excitatory and/or inhibitory synapses. For example, Purkinje cells, which form the main output of the cerebellum, a region of the brain concerned with motor coordination, each receive as many as 200,000 synapses (Llinás and Walton 1998) whereas pyramidal cells in the hippocampus, concerned with spatial and short-term working memory, each receive about 25,000 synapses (Johnston and Amaral 1998).

Integration in an individual neuron takes place post-synaptically over the branched processes or dendrites emanating from the soma (cell body) and very often over the soma itself and involves the graded, electrotonic spread and summation of the small excitatory or inhibitory post-synaptic potentials over this region. Impulse initiation usually takes place in the initial segment of the nerve axon (axon hillock) where there is often a higher density of transient, voltage-gated sodium channels. Integration and summation in the nerve cells of the CNS thus involve graded, non-threshold post-synaptic responses in the dendrites and soma as well as the propagation of action potentials down nerve fiber tracts (e.g., Schmitt et al. 1976; Bullock 1997). In addition, many nerve cells in the awake animal are spontaneously active; soma and dendrite (soma-dendrite complex) membrane potentials are therefore likely to fluctuate continually. Induced electric fields and currents will add to the total synaptic input suggesting that thresholds for impulse initiation by externally induced fields will be lower than those necessary for the direct stimulation of peripheral nerves. The overall effect could, however, be excitatory or inhibitory, depending on the functional properties of the neuron(s) involved.

These and other long-term changes in synaptic behavior such as long-term potentiation or depression involved in learning and memory processes depend on the activity of a variety of different ionic currents, of which about a dozen, mostly different types of sodium, potassium, or calcium currents, have been described so far (McCormick 1998). Some of these are activated by transmembrane voltages below the threshold for impulse initiation and include persistent sodium currents, which induce long lasting increases in excitability; low threshold calcium currents, which are often involved in the generation of rhythmic bursts; and muscarine-sensitive potassium currents, which contribute to the modulation of neuronal excitability and to the slow adaptation of spike frequency seen during a maintained depolarization.

Much of the normal cognitive function of the brain depends on the collective activity of very large numbers of neurons; neural networks are thought to have complex non-linear dynamics that can be very sensitive to small voltages applied diffusely across the elements of the network (Adair 2001; ICNIRP 2003; Jefferys et al. 2003). Interacting groups or networks of nerve cells exposed to weak spatially and temporally coherent electrical signals would be expected on theoretical grounds to show increased sensitivity through improved signal-to-noise ratios compared with the response of individual cells (Valberg et al. 1997; Sterling 1998; Adair 2001). Making simple assumptions, in a neural network in which a number of neurons converge (i.e., make synaptic connections) onto a single neuron, the signal-to-noise ratio in the latter should increase in proportion to the square root of the number of converging neurons. An extensive theoretical description is given by Adair (2001) in which the signal-to-noise ratio is enhanced in secondary "coincidence" neurons that fire on the simultaneous receipt of sufficiently large sets of input impulses from primary sets of neurons.

The integrative properties of neural networks are characteristic of CNS function and account, for example, for a behavioral sensitivity to various environmental stimuli that greatly exceeds that of individual sensory receptors. This topic has been discussed by many authors for a number of sensory modalities including the warmth-cold detection in mammals (Adair 1999), geomagnetic field variation by honey bees (Adair 2001), and electroreception in several aquatic vertebrates, including sharks and rays (Murray 1965; Pickard 1988; Adair et al. 1998; Adair 2001), the North American paddlefish (Neiman and Russell 2004) and the platypus, an egg-laying mammal (Pettigrew et al. 1998; Pettigrew 1999). Detailed quantitative arguments are presented by Adair (2001) supporting the view that sensory integration of the output from several thousand primary receptor cells through convergent neural networks can adequately account for the sensitivity of sharks to electric fields as low as 0.5 μV m^{-1}, which are estimated to induce a change in the transmembrane potential of individual receptor cells of only ~100–200 nV.

Localized nerve tissue stimulation in the CNS

In transcranial magnetic stimulation (TMS), parts of the brain are deliberately stimulated in order to produce a transient, functional impairment for use in the study of cognitive processes (Reilly 1998; Walsh and Cowey 1998; Ueno 1999). Brief, localized, suprathreshold stimuli are given, typically by discharging a capacitor through a coil situated over the surface of the head, in order to stimulate neurons in a small volume (a few cubic centimeters) of underlying cortical tissue (Reilly 1998). The induced current causes the neurons within that volume to depolarize synchronously, followed by a period of inhibition (Fitzpatrick and Rothman 2000). When the pulsed field is applied to a part of the brain

thought to be necessary for the performance of a cognitive task, the resulting depolarization interferes with the ability to perform the task. In principle then, TMS provides cognitive neuroscientists with the capability to induce highly specific, temporally and spatially precise interruptions in cognitive processing—sometimes known as "virtual lesions." Reilly (1998) calculated induced electric field thresholds for smaller diameter (10 μm) nerve fiber stimulation in the brain to be of the order of $12_{pk\text{-}pk}$ V m^{-1}. However, Walsh and Cowey (1998) cite typical rates of change of magnetic field of 30 kT s^{-1} over a 100 μs period transiently inducing an electric field of $500_{pk\text{-}pk}$ V m^{-1} in brain tissue.

There is a slight risk with some TMS procedures of inducing an epileptic seizure in susceptible people. Epileptic syndromes are characterized by increased neuronal excitability and synchronicity (Engelborghs et al. 2000); seizures arise from an excessively synchronous and sustained discharge of a group of neurons (Jefferys 1994; Engelborghs et al. 2000). TMS is widely used, apparently without adverse effects, but repetitive TMS has been observed to trigger epileptic seizure in some susceptible subjects (Wassermann 1998; Fitzpatrick and Rothman 2000). These authors also reported short- to medium-term memory impairments and noted the possibility of long-term cognitive effects from altered synaptic activity or neurotransmitter balance. Contraindications for TMS use agreed at an international workshop on repetitive TMS safety (Wassermann 1998) include epilepsy, a family history of seizure, the use of tricyclic antidepressants, neuroleptic agents and other drugs that lower seizure threshold.

Weak electric field effects in the CNS

CNS function is also considered to be sensitive to electric fields induced in the body by exposure to ELF magnetic fields at levels that are below threshold for impulse initiation in nerve axons (Jefferys 1995; Saunders and Jefferys 2002; Jefferys et al. 2003; Saunders 2003). Three separate strands of evidence are discussed below: data from in vitro studies, EMF cognitive studies, and EMF effects on retinal function.

In vitro CNS studies. Physiologically weak electric field interactions have been shown in experimental studies to have physiological relevance mostly using isolated animal brain tissue. These interactions result from the extracellular voltage gradients generated by the synchronous activity of a number of neurons or from those generated by applying pulsed or alternating electric fields directly through electrodes placed on either side of the tissue. Jefferys and colleagues (Jefferys 1995; Jefferys et al. 2003) identified in vitro electric field thresholds of around $4–5_{pk\text{-}pk}$ V m^{-1}. Essentially, the potential gradient in the extracellular space alters the potential difference across the neuronal membrane with opposite polarities at either end of the neuron. The ability of an extracellular field to affect membrane potential depends on the strength of the field, the geometry of the neuron in relation to the field, and the neuron length-constant, the latter being a measure of the ability of the current to enter and leave the neuron across the neuronal membrane. The relationship between the two is linear for gradients below a few tens of volts per meter, with about 0.1 mV change at the soma membrane potential for every 1 V m^{-1} of the extracellular field gradient (Bikson et al. 2004). This relationship is likely to be weaker than that found in myelinated fibers such as those of the peripheral nervous system (see above; McKinlay et al. 2004), and is probably is due to the different geometry and shorter length-constants of the soma-dendrite complexes of CNS grey matter.

Another important factor is the membrane time-constant, which is the product of the nerve membrane resistance and capacitance, although this is further complicated by the detailed anatomy of central neurons. The time-constant of the soma-dendrite complex is a few tens of milliseconds (Bikson et al. 2004) and indicates a limited frequency response. Similar arguments concerning the limited frequency response of weak electric field effects due to the long time-constants (25 ms) arising from cell membrane capacitance have been given by Reilly (2002). Further preliminary evidence from one of our laboratories[§] suggests that the effects of time varying (AC) fields on membrane potential fall off rapidly as frequencies increase from 10 to 100 Hz. Most cortical neurons cannot sustain firing at these rates. The majority, termed regular spiking and intrinsic burster neurons, have relatively slow potassium currents that stop them from firing rapidly for long periods (>few tens of milliseconds). In contrast, the fast spiking neurons can sustain firing at the kinds of rates (>100 Hz) found in some of the fast EEG rhythms. However, even the neurons that cannot fire on every cycle of the AC fields could be entrained onto particular phases and this could theoretically affect network functions that depend on precise timing.

Recent experimental work by Francis et al. (2003) reported a neural network threshold of around 140 mV m^{-1}, more sensitive than the modulation of single neuron activity of 185 mV m^{-1} found in their study. In this

[§] Deans JK, Powell AD, Jefferys JGR. Personal communication. Department of Neurophysiology, Division of Neuroscience, Medical School, University of Birmingham, Birmingham, B15 2TT, United Kingdom; December 2005.

study, the spontaneous neuronal population activity exhibited by hippocampal slices in the presence of elevated potassium ion concentrations could be more readily entrained by a 1–2 Hz electric field stimulus applied across the preparation than could single neurons. Elsewhere, on theoretical grounds, a lower limit on neural network sensitivity to physiologically weak induced electric fields has been considered to be around 1 mV m^{-1} (Adair et al. 1998; Veyret 2003).

EMF studies and cognitive function. Possible EMF effects on cognitive function were reviewed at the ICNIRP/WHO workshop by Crasson (2003). Generally, these studies examined the effects of exposure mostly to power frequency magnetic fields of between about 1 μT–1 mT. Crasson (2003) concluded that, overall, laboratory studies that have investigated the acute effects of power frequency fields on cognitive functioning in humans are heterogeneous, not only in terms of electric and magnetic field exposure but also in terms of experimental design and the cognitive measures used. Results are rather inconsistent and difficult to interpret with regard to their functional relevance for possible human health risks. Statistically significant differences between field and control exposure, when they are found, are small, subtle, transitory, without any clear dose-response relationship, and they are difficult to reproduce.

EMF studies and retinal function. The retina is a part of the brain, having been derived embryologically as an outgrowth of the forebrain (e.g., Dowling 1987). The effects of exposure to weak low frequency magnetic fields on human retinal function are well established. Exposure of the head to magnetic flux densities above about 5 mT at 20 Hz, rising with decreasing or increasing frequencies (to about 15 mT at 50 Hz), will reliably induce faint flickering visual sensations, called magnetic phosphenes, in the periphery of the visual field (Sienkiewicz et al. 1991; Attwell 2003). It is generally agreed that phosphenes result from the interaction of the induced electric fields and currents with electrically sensitive cells in the retina (Attwell 2003). Several lines of evidence suggest the production of phosphenes by a weak induced electric field does not involve the initial transduction of light into an electrical signal. Firstly, the amplification of the initial signal generated by the absorption of light takes place primarily through an intracellular "second-messenger cascade" of metabolic reactions prior to any change in ion channel conductivity (Hille 2001). Secondly, the phosphene threshold appears unaffected by "dark" adaptation to low light levels (Carpenter 1972). In addition, phosphenes have been induced in a patient with retinitis pigmentosa, a degenerative illness primarily affecting the pigment epithelium and photoreceptors (Lövsund et al. 1980).

Retinal circuitry can be viewed as an appropriate, albeit conservative, model for induced electric field effects on CNS neuronal circuitry in general (Attwell 2003). Firstly, the retina displays all the processes present in other CNS areas, such as graded voltage signaling and action potentials, and has a similar biochemistry. Secondly, in contrast to more subtle cognitive effects, phosphenes represent a direct and reproducible perception of field interaction. A clear distinction can be made in this context between the detection of a normal visual stimulus and the abnormal induction of a visual signal by non-visual means; the latter suggests the possibility of direct effects on cognitive processes elsewhere in the CNS. Attwell (2003) further notes that the occurrence of phosphenes in the periphery rather than the center of the visual field may partly reflect the greater degree of synaptic convergence that occurs here from the photoreceptors to the ganglion cell axons that form the optic nerve. The rod photoreceptors, which predominate in this region, mediate vision under low light levels such as those that occur at dusk; several stages of synaptic convergence, from as many as 1,000 rods to 1 ganglion cell, increase signal gain but with a concomitant loss in visual acuity (Taylor and Smith 2004).

Thresholds for electrically induced phosphenes have been estimated to be about 10–14 mA m^{-2} at 20 Hz (Adrian 1977; Carstensen et al. 1985). A similar value (10 mA m^{-2} at 20 Hz), based on studies of magnetically induced phosphenes, has been derived by Wake et al. (1998). The equivalent electric field threshold can be estimated as around 100–140 mV m^{-1} using a tissue conductivity for brain tissue of about 0.1 S m^{-1} (Gabriel et al. 1996). More recently, Reilly (2002) has calculated an approximate 20 Hz electric field threshold in the retina of 53 mV m^{-1} for phosphene production. A similar value (60 mV m^{-1}) has been reported elsewhere (see Saunders 2003).

More detailed calculation by Attwell (2003) based on neuroanatomical and physiological considerations suggests that the phosphene electric field threshold in the extracellular fluid of the retina is in the range 10–60 mV m^{-1} at 20 Hz. There is, however, considerable uncertainty attached to these values. In addition, the extrapolation of values in the extracellular fluid to those appropriate for whole tissue, as used in most dosimetric models, is complex, depending critically on the extracellular volume and other factors. With regard to the frequency response, Reilly (2002) suggests that the rise in threshold above 20 Hz is the result of relatively long membrane time-constants of around 25 ms. However, at present, the exact mechanism

underlying phosphene induction is unknown. It is not clear whether the narrow frequency response is due to intrinsic physiological properties of the retinal neurons, as suggested by Reilly (2002) above and by Attwell (2003) considering active amplification process in the retinal neuron synaptic terminals, or is the result of central processing of the visual signal (Saunders and Jefferys 2002; Saunders 2003). This issue can only be resolved through further investigation.

OTHER TISSUES

Other electrically excitable tissues with the potential to show network behavior include glial cells located within the CNS (e.g., Parpura et al. 1994), and the autonomic and enteric nervous systems (see Sukkar et al. 2000), which comprise interconnected non-myelinated nerve cells and are distributed throughout the body and gut, respectively. These systems are involved in regulating the visceral or "housekeeping" functions of the body; for example, the autonomic nervous system is involved in the maintenance of blood pressure. Muscle cells also show electrical excitability; cardiac muscle tissue has electrically interconnected cells. However, Cooper et al. (2003), in a review of cardiac ion channel activity, conclude that weak internal electric fields much below the excitation threshold are unlikely to have any significant effect on cardiac physiology. Nevertheless, EMF effects on the heart could theoretically result from indirect effects mediated via the autonomic nervous system and CNS (Sienkiewicz 2003). Effects on the endocrine system could potentially also be mediated this way, although the evidence from volunteer experiments indicates that acute ELF magnetic field exposure up to 20 μT does not influence the circadian variation in circulating levels of the hormone melatonin (Warman et al. 2003), nor other plasma hormone levels (ICNIRP 2003).

With regard to the possible effects of exposure to electromagnetic fields on reproduction development, there is now considerable evidence that endogenous DC electric fields of around 10–100 V m^{-1}, generated by the asymmetric distribution of ion channels on embryonic epithelia, play an important role in normal developmental processes (Nuccitelli 1992, 2003). Such fields have been found in association with epithelia of the neural folds and neural tube as well as the embryonic skin and gut; disruption of these endogenous electric fields in amphibia and chick embryos results in aberrant development of the nervous system, somites and tail structure. In addition, such fields have been shown to affect neurite outgrowth and nerve cell growth in vitro (Saunders and McCaig 2005). However, the extent to which these effects could be induced by exposure to ELF fields is uncertain. The results of EMF studies on mammalian development in which animals have been exposed to power frequency magnetic fields of up to 20 mT have shown no effects on gross external, visceral or skeletal malformation (Juutilainen 2003). The induced electric fields in these studies will have been very much smaller than the DC electric fields cited above. The only finding that showed some consistency is the increase in minor skeletal variations reported in several rodent studies.

DISCUSSION AND CONCLUSION

It can be concluded that electrically excitable tissue, notably nerve and muscle tissue, can be stimulated by sufficiently intense electric fields induced in body tissue by rapidly changing ELF magnetic fields. However, such fields are likely to be encountered only in highly specialized medical or laboratory environments.

The integrative properties of the synapses and neural networks of the CNS render it, and therefore cognitive function, sensitive to the effects of physiologically weaker electric fields, below the threshold for direct nerve excitation. However, the only direct evidence of this in volunteers exposed to ELF magnetic fields is the induction of phosphenes, a perception of faint flickering light in the periphery of the visual field. The minimum threshold flux density is around 5 mT at 20 Hz, but rises at higher and lower frequencies.

There are good reasons for thinking that the retinal circuitry is an appropriate albeit conservative model for induced electric field effects on CNS neuronal circuitry in general, but consistent evidence for such effects on cognitive function is lacking. This may be because the ELF exposures used in such studies ($<$2 mT), and the resulting induced electric fields in CNS tissue, have been too low to elicit such effects.

Phosphene electric field thresholds in retinal tissue have been estimated to lie between about 50–100 mV m^{-1} at 20 Hz. General arguments have been proposed for a flat frequency response for CNS effects at this threshold range between 10 Hz and 1 kHz, based on considerations of ion channel kinetics, notably the slow inactivation of sodium channels (10 Hz) and an upper limit on ion channel kinetics of around 1 ms (1 kHz). However, recent in vitro data tend to support the view that such effects will only occur at frequencies below 100 Hz.

With regard to other tissues, the sensitivity of their voltage-gated ion channels is likely to be lower than those of nerve and muscle cells specialized for rapid electrical signaling. These tissues also lack the integrative properties of synapses and neuronal networks that render the CNS potentially more vulnerable.

In conclusion, there are good reasons why ELF guidelines on exposure to magnetic fields should be based on restrictions that avoid effects on cognitive function, but sound evidence for thresholds and frequency responses require further scientific investigation.

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