

INTERACTION OF LOW FREQUENCY ELECTRIC FIELDS WITH THE NERVOUS SYSTEM: THE RETINA AS A MODEL SYSTEM

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Abstract—The retina provides an example of effects, the visually perceived ‘phosphenes’, being generated in nervous tissue by external electric or magnetic fields of low frequency and intensity. What is known about the cellular mechanisms by which the phosphenes are generated is reviewed, whether they provide useful information for setting limits on the magnitude of induced electric fields to which nervous tissue can be safely exposed is assessed, and some difficulties in translating these values of internal fields into safe values of external electric or magnetic fields are considered.

INDUCTION OF ELECTRIC FIELDS IN THE HUMAN CENTRAL NERVOUS SYSTEM

Time varying electromagnetic fields induce a time varying field within exposed humans. This section outlines the main factors determining the electric field produced in the central nervous system (CNS), and will be used later in this review to illuminate the mechanisms by which electric and magnetic fields may stimulate the retina, and to assess how to convert safe limits for fields in the CNS into safe limits for fields in the external air (see References 1 and 2 for a more detailed treatment).

Induction by external electrical fields

At the boundary between the air and the body, current flow across the interface must be continuous. In general, the current density in the air, J_{air} , has conductive and displacement (capacitive) parts:

$$J_{\text{air}} = (g_{\text{air}} + i2\pi f\epsilon_{\text{air}})E_{\text{air}}, \quad (1)$$

where g_{air} is the conductivity of air, $i = \sqrt{-1}$, f is the frequency of the field E_{air} , and ϵ_{air} is the permittivity of air. The relative amplitude of the conductive and displacement currents is given by $g_{\text{air}}/2\pi f\epsilon_{\text{air}} = (10^{-14} \text{ S m}^{-1})/(2\pi f \cdot 9 \times 10^{-12} \text{ F m}^{-1})$. For 50 Hz fields, this fraction is only 3.5×10^{-6} , so Equation 1 can be approximated to

$$J_{\text{air}} = i2\pi f\epsilon_{\text{air}}E_{\text{air}}. \quad (2)$$

In the body, the current flow could have conductive and displacement parts:

$$J_{\text{body}} = (g_{\text{body}} + i2\pi f\epsilon_{\text{body}})E_{\text{body}}. \quad (3)$$

As sketched in Figure 1, in the brain, current flow can occur through two pathways, i.e. in the space between the cells and across the cell membranes and through the cells. The extracellular space occupies about 20% of the

volume of the brain in most areas (although it can be smaller: 13% in hippocampus⁽³⁾ and as little as 2% in some retinal layers⁽⁴⁾). The extracellular space can be considered to be composed of 140 mM NaCl, for which⁽⁵⁾ $g = 2.15 \text{ S m}^{-1}$ (at 35°C). A value of $\epsilon \sim 2.5 \times 10^8 \times 9 \times 10^{-12}$ can be extrapolated from data⁽⁶⁾ for 140 mM NaCl at 50 Hz, which gives $2\pi f\epsilon/g = 0.33$; taking this number at face value would suggest that displacement currents are significant and contribute 5%

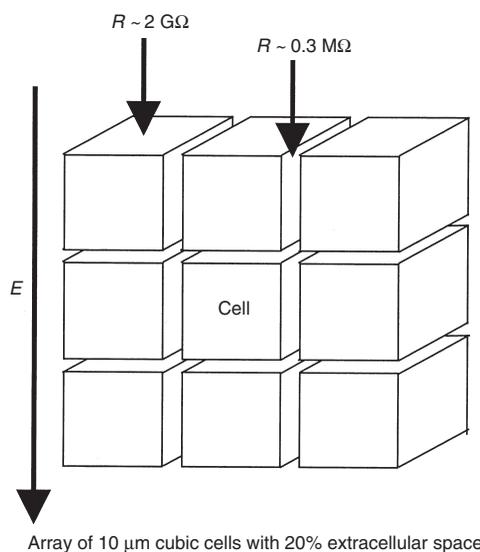


Figure 1. Paths for current flow induced by external electromagnetic fields. A simplified diagram of the brain’s cellular structure to aid understanding of extra- and intra-cellular current flow. Each cell is represented as a 10 μm cube. The overall extracellular volume fraction is 20% (typical for much of the brain). Current flow in the direction of the field (E) can be through the cells, whose membranes give a resistance of about 2 GΩ for the conduction through the mean area per cell, or through the extracellular space, which offers a resistance of only 0.3 MΩ per cell.

(from the modulus of Equation 3) to the amplitude of the electric field; however, this value of ϵ is probably artefactually high due to electrode polarisation (similarly the conductivity measurements⁽⁶⁾ for NaCl are 10-fold too high compared with other data⁽⁵⁾) and displacement currents can be neglected in the extracellular spaces of the body⁽¹⁾. To assess the possibility of conductive or capacitative current flow across the membranes of cells in the brain, it will be assumed that each 100 μm^2 face of the hypothetical 10 μm cubic cells in Figure 1 has a membrane resistance of $\sim 2 \text{ G}\Omega$ (since cerebellar granule cells of diameter 5 μm and area 65 μm^2 have a resistance of around 3 $\text{G}\Omega$ near their resting potential⁽⁷⁾). This is much greater than the resistance of the extracellular pathway between the cells (obtained as (resistivity of $1/(2.15 \text{ }\Omega\text{m}) \times (10 \text{ }\mu\text{m long})/(1.5 \text{ }\mu\text{m wide (for a 20% extracellular volume fraction around cubic cells) } \times 10 \text{ }\mu\text{m deep}) = 3.1 \times 10^5 \text{ }\Omega$. Thus, essentially all the conductive current flow is through the extracellular space. For current flowing along the long axis of spatially elongated cells, as focussed on below, the extracellular volume fraction is the same as the fractional area available for current flow, so the restriction of current flow to the extracellular space is predicted to decrease the effective conductivity for the bulk tissue by a factor of around 5–10 for a 10–20% extracellular volume fraction, to about 0.2–0.4 S m^{-1} , which is similar to what has been measured experimentally for grey matter⁽⁶⁾. (For non-elongated cells, or current flowing perpendicular to the long axis of elongated cells, the decrease of conductivity from the free solution value is greater: e.g. by a factor of 6.23 rather than 5 for a 20% extracellular space for the cubic cell model shown in Figure 1.) At higher frequencies, current is also expected to cross cell membranes via their capacitance. A 100 μm^2 face of the cells in Figure 1 will have a capacitance of around $C = 1 \text{ pF}$ (assuming $1 \text{ }\mu\text{F cm}^{-2}$), giving an impedance at frequency f of $1/(2\pi fC)$. At 50 Hz, this is $3.2 \times 10^9 \text{ }\Omega$, which is much greater than the $3.1 \times 10^5 \text{ }\Omega$ resistance of the extracellular pathway. Only at frequencies above 700 kHz does displacement current across the cell membrane become significant compared to current flow through the extracellular space. For low frequency electric fields, therefore, Equation 3 becomes

$$J_{\text{body}} = g_{\text{body}} E_{\text{body}}, \quad (4)$$

where g_{body} reflects current flow solely through the extracellular space. Equating the magnitudes of current flow at the air–human interface from Equations 2 and 4, we find that

$$E_{\text{body}}/E_{\text{air}} \sim 2\pi f \epsilon_{\text{air}}/g_{\text{body}}, \quad (5)$$

which is $0.7\text{--}1.4 \times 10^{-8}$ for $f = 50 \text{ Hz}$ and $g_{\text{body}} = 0.2\text{--}0.4 \text{ S m}^{-1}$. Thus, for an external field of 10 kV m^{-1} , as can be experienced under power lines, the induced extracellular field in the brain will be about 10^{-4} V m^{-1} , or 0.1 mV m^{-1} .

The simplified anatomy in Figure 1 provides insight into how this field will appear as voltages in the brain. For a vertical line drawn through the extracellular current passing pathway, there will be a linear change of voltage with distance along the field direction, and the magnitude of this change will be proportional to the frequency of the field but inversely proportional to the tissue conductivity (from Equation 5). For a vertical line drawn through the cells, most of the impedance is in the cell membranes, and it is across the membranes that most of the voltage change will appear. The current flow induced by the field is given by Equations 4 and 5 as:

$$J_{\text{body}} = g_{\text{body}} E_{\text{body}} = 2\pi f \epsilon_{\text{air}} E_{\text{air}}, \quad (6)$$

which is independent of the tissue conductivity. Although it has been pointed out above that capacitative current flow across cell membranes can be ignored when calculating the extracellular field or total current flow induced by an extracellular field, this is not the case when considering the transmembrane voltage induced by electric fields: the membrane capacitance allows significant current flow, compared to that allowed by the membrane resistance, when the frequency becomes similar to the reciprocal of the membrane time constant, i.e. at around 100 Hz. The possibility that this can account for the characteristic frequency dependence with which external electric and magnetic fields can stimulate the retina will be considered below.

In summary, this section has reviewed work showing that when an external time varying electric field is present:

- (1) induced electric fields are inversely proportional to the tissue conductivity;
- (2) induced current flow occurs almost entirely in the extracellular space, so the effective tissue conductivity (and induced field) depends critically on the extracellular volume fraction;
- (3) for a 10–20% extracellular volume fraction, induced electric fields are $\sim 10^{-8}$ of the magnitude of the external electric field applied;
- (4) induced voltage drops and current flows are proportional to the field frequency;
- (5) induced current flows are independent of the tissue conductivity;
- (6) voltage changes appear across cell membranes and so can alter cell function; current flow across membranes is partly capacitative at power line frequencies, and so induced transmembrane voltages depend on the field frequency.

Induction by external magnetic fields

As a consequence of Maxwell's equations, electric fields produce magnetic fields, and time varying magnetic fields induce electric fields within the body. For a circle of radius r within the body, Faraday's law gives the magnitude of the induced electric field as⁽²⁾

$$E_{\text{body}} = \pi r f B, \quad (7)$$

where f and B are the frequency and magnitude of the applied electric field, respectively. As for induction with an electric field, the field produced in the body is proportional to frequency. The resulting current flow is given by

$$J_{\text{body}} = g_{\text{body}} \pi r f B. \quad (8)$$

Unlike for induction with an electric field, this is proportional to the effective tissue conductivity and so will be critically dependent on the extracellular volume fraction. From Equation 7, the magnitude of 50 Hz magnetic field needed to induce, in a brain of radius 7.5 cm, an electric field equal to the 0.1 mV m^{-1} evoked by a 10 kV m^{-1} external electric field, is $8.5 \text{ } \mu\text{T}$.

Conversion of internal electric fields to voltage changes across cell membranes

It seems likely that, to produce an effect on nervous tissue, induced electric fields need to change the potential of neurons and thus alter the gating of ion channels. (This is not the only mechanism possible, however — many other possibilities are assessed in Reference 2.) Solving the cable equation for the transmembrane potential, V_m ,

$$\lambda_m^2 d^2 V_m / dx^2 = V_m + \tau_m C_m dV_m / dt,$$

(where the d.c. space constant λ_m is given by $\lambda_m^2 = r_m / (r_o + r_i)$; r_m , r_o , r_i and C_m are the membrane resistance, external resistance, internal resistance and capacitance per unit length, respectively; and $\tau_m = r_m C_m$ is the membrane time constant) for a cylindrical cell elongated in the x direction, with sealed ends at $x = 0$ and $x = L$, predicts that opposite transmembrane voltage changes are produced at each end of the cell. For a sinusoidally varying applied field at frequency f ,

$$E_a = E e^{i2\pi f t},$$

the steady state time varying voltage change (i.e. ignoring transient effects when the field is first switched on) at the end of the cell is given by

$$\Delta V_m = E_a \lambda (1 + (r_o / r_i)) (e^{L/\lambda} - 1) / \{1 + e^{L/\lambda} + 2(r_o / r_i)(\lambda / L)(e^{L/\lambda} - 1)\}, \quad (9)$$

where the effective a.c. space constant is given by

$$\lambda = \lambda_m / (1 + i2\pi f \tau_m)^{0.5} \quad (10)$$

(from Reference 8, Equation 18, with G_c set to zero for sealed ends of the cable; $i = \sqrt{-1}$). This predicts a maximum voltage change if the field frequency is low ($2\pi f \tau_m \ll 1$) and the cell length is much greater than the space constant ($L \gg \lambda_m$), with magnitude

$$\Delta V_{m,\text{max}} = E \lambda_m (1 + (r_o / r_i)). \quad (11)$$

For $r_o / r_i = 4$ (for an extracellular volume fraction of 20%), an extracellular field of 0.07 mV m^{-1} (as would

be produced by a field outside the body of 10 kV m^{-1} , see above), and a d.c. space constant of $1600 \text{ } \mu\text{m}$ (as can occur for the horizontal cell network of the retina), this predicts a voltage change of only $0.6 \text{ } \mu\text{V}$.

In general, the condition $2\pi f \tau_m \ll 1$ does not hold for mains power frequencies or above. Capacitative current flow has two effects influencing the resulting voltage change induced in cells: it allows current to enter the cell more readily, but it lowers the effective space constant. To investigate the effect of capacitative current flow, Figure 2 plots the magnitude (modulus) of the complex voltage change in Equation 9 as a function of frequency for various assumed values of L/λ_m (see the figure legend for the plotted equation). The induced voltage is predicted to fall-off with increasing frequency, but this fall-off occurs at higher frequencies for smaller values of L/λ_m . At all frequencies, the induced voltage is lower than the maximum d.c. value for $L \gg \lambda_m$, given by Equation 11.

Why use the retina as a model for field effects on the CNS?

Electric fields could, in principle, affect the processing of information as graded electrical potentials in the dendrites of neurons in the brain, or the initiation and transmission of action potentials generated by voltage gated calcium and sodium channels, or might somehow affect biochemical signalling in the brain. All of these possible target mechanisms exist in the retina: neurons in the outer retina process information as graded voltage changes like the dendrites of central neurons, while amacrine and ganglion cells in the inner retina generate calcium and sodium action potentials, and all the intracellular and extracellular biochemical signalling pathways known in the brain are also found in the retina. Furthermore, given that long cells are most likely to have larger voltages induced in them (see above), it is interesting that the retina contains elongated bipolar cells oriented perpendicular to the plane of the retina, and contains elongated processes of horizontal and amacrine cells (often coupled by gap junctions which will increase their effective length) oriented in the plane of the retina. The length of these processes is comparable to that of the dendrites of cortical or hippocampal pyramidal cells.

Given all these similarities, there are two compelling reasons for using the retina as a model system to assess the effect of electric fields on the CNS. First, the retina is designed to amplify small signals, being able to detect the arrival of single photons in the presence of ongoing biochemical and electrical noise. Secondly, and most importantly, an alteration of retinal function by an applied field is (as discussed below) easily detected perceptually, while a subtle field induced modulation of the operation of (say) association cortex might not be detected psychologically.

Retinal phosphenes and the fields needed to produce them

Exposing the retina to electric or magnetic fields has long been known to generate the appearance of flickering lights in the periphery of the visual field⁽⁹⁻¹³⁾. These so-called phosphenes are maximal with fields of frequency around 20–30 Hz, are not evoked by applying the same field outside the skull near the visual cortex, correlate in location with the position on the retina of the most intense part of the field, and are abolished by pressure on the eyeball⁽⁹⁾, demonstrating that they are produced in the retina. The occurrence of phosphenes in the periphery, rather than the centre of the visual field, may reflect the orientation of the cells detecting the fields (see below), a higher proportion of rod photoreceptors in the periphery, or a greater degree of summation of signals in the periphery by convergence of synapses from photoreceptors to bipolar cells and from bipolar to ganglion cells (see below). In the rest of this section, an estimate will be given of the membrane potential changes which may generate phosphenes, from

the measured magnitudes of magnetic or applied electric field needed to produce the phosphenes.

For magnetic stimulation, the threshold field for evoking human phosphenes at ~25 Hz is ~10 mT⁽¹²⁾. This is similar to the field needed to induce ganglion cell spiking in isolated frog retina (20 mT⁽¹⁴⁾). From Equation 7, the electric field that 10 mT could induce is ~60 mV m⁻¹ if the magnetic field extended over all of a 7.5 cm radius brain, or ~10 mV m⁻¹ if the field was only present over a 2.5 cm diameter eyeball (probably a more accurate description of these experiments with localised fields). For a 20% extracellular volume fraction and a 15 ms membrane time constant, Equation 9 predicts that, at 25 Hz, the voltage induced at the end of a neuron of length L and space constant λ will be $0.25-2.17 E_{\text{extracellular}}\lambda_m$ (for $L/\lambda_m = 0.5-10$). For 100 μm long retinal bipolar cells, $\lambda_m \sim 215 \mu\text{m}$, so L/λ_m may be around 0.5 (in rat⁽¹⁵⁾; mammalian rods are thin and only slightly shorter, and may have similar values), while for the dark adapted electrically coupled horizontal cell network, λ_m can be as large as ~1600 μm and

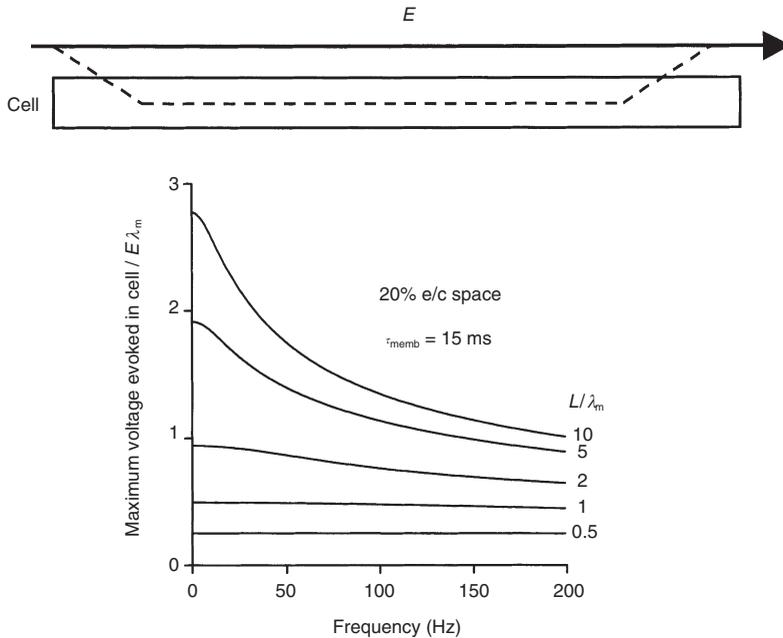


Figure 2. Conversion of extracellular field to intracellular potential change. Top: schematic elongated cell aligned along electric field E . Most of the current flows through the extracellular space (heavy line), but a small fraction enters the cell via its conductance and capacitance, and flows along the cell. Bottom: calculated maximum transmembrane voltage change produced at the ends of a cell of length L , membrane time constant $\tau_{\text{memb}}=15$ ms and d.c. electrical space constant λ_m as a function of field frequency. Plots are from the modulus of Equation 9, given by:

$$|\Delta V_m| = \frac{LE(r_i + r_o) [e^{2a} - 2e^a \cos(b) + 1]^{1/2}}{\{ [r_i^2(a^2 + b^2)] [e^{2a} + 2e^a \cos(b) + 1] + 4r_o^2[e^{2a} - 2e^a \cos(b) + 1] + 4r_o r_i [a(e^{2a} - 1) + 2be^a \sin(b)] \}^{1/2}}$$

where $a^2 = \frac{1}{2} \left(\frac{L}{\lambda_m} \right)^2 \{ \sqrt{1 + (2\pi f \tau_m)^2} + 1 \}$ and $b^2 = \frac{1}{2} \left(\frac{L}{\lambda_m} \right)^2 \{ \sqrt{1 + (2\pi f \tau_m)^2} - 1 \}$.

L/λ_m for the whole cell network could effectively be 10 (in cat⁽¹⁶⁾). For an extracellular field of 10–60 mV m⁻¹, as estimated above, these numbers predict transmembrane voltage changes of only 0.5–3 μ V in bipolar cells (and probably similar in rods) and 35–210 μ V in horizontal cells. For comparison, the voltage change produced by a single photon in rods is \sim 1000 μ V (in monkey⁽¹⁷⁾), and in bipolar cells is \sim 250 μ V (in dogfish⁽¹⁸⁾). Thus, on first analysis, it seems that the predicted induced voltages are small compared with even the signals induced by single photons (which are themselves not much greater than the ongoing electrical noise in retinal cells). The predicted size of the induced voltages could be increased slightly if the extracellular volume fraction was smaller than the 20% assumed above (the voltages depend on r_o/r_i (Equation 9): increasing this parameter from 4 to 9, to switch from a 20% to a 10% extracellular volume fraction, increases the voltage response to a 25 Hz field 1.4-fold for $L/\lambda_m = 10$). In the next section, amplifying mechanisms which might explain how the small induced voltage could alter retinal function sufficiently to produce a visual percept will be considered.

For phosphenes induced by electric fields, the current density needed to produce a phosphene at 25 Hz has been estimated⁽¹¹⁾ as 1 μ A cm⁻² or 10 mA m⁻². For a 20% extracellular space ($g = 0.4$ S m⁻¹), this would imply an extracellular electric field of 25 mV m⁻¹ (from Equation 6), similar to the field estimated above for a magnetic field stimulation, which is predicted to produce a voltage change in bipolar and horizontal cells of 1.5 and 85 μ V, respectively. These values would be increased if the extracellular space fraction was less than 20%.

Possible mechanisms for phosphenes

To explain the high sensitivity of the retina for the production of phosphenes induced by electromagnetic fields, it is appealing to imagine that a small signal produced by the fields could be greatly amplified within the retina. The high gain of the phototransduction biochemistry would be the first stage at which such amplification could occur, but phosphenes appear to be induced after the stage of the retina at which dark adaptation occurs⁽¹⁰⁾ and so, presumably, are not a direct effect on the phototransduction apparatus.

Downstream of phototransduction, on the direct pathway through the retina from photoreceptors to bipolar cells to ganglion cells (Figure 3), a visual percept could be induced by a small voltage induced by an electromagnetic field modulating the output of the synapses of the photoreceptors or of the bipolar cells. Both of these synapses are specialised to transmit small signals reliably by virtue of their ribbon structure⁽¹⁹⁾, which provides a large number of vesicles to be released and so improves the postsynaptic signal-to-noise ratio (light, or electric fields, modulate the ongoing release rate of

a large number of vesicles, decreasing quantal noise compared to a situation where only a few vesicles are being released). There are also a number of specialised features of these synapses, which ensure the transmission of small signals or improve the signal-to-noise ratio, as follows. In the retinae of amphibia, the transmission of signals from the rod synapse has a very high gain for small signals, but saturates with signals larger than a few mV^(20,21). By contrast, for rodent rod ON bipolar transmission, the saturation of postsynaptic glutamate receptors makes the gain of synaptic transmission low for the smallest signals, but large for signals just above the size of those produced by a single photon in order to improve the signal-to-noise ratio⁽²²⁾. A probably related phenomenon has been observed in dogfish ON bipolar cells: very dim background light which isomerises only 1 rhodopsin per 10 rods produces a potentiation of the bipolar cell response to superimposed flashes⁽²³⁾. An additional amplification device exists in the synaptic terminals of bipolar cells, at least in goldfish⁽²⁴⁾: depolarisation of the ON bipolars which mediate dim signal transmission through the retina leads to the activation of voltage gated calcium channels in the synaptic terminals, which evoke a regenerative calcium action potential. This kind of mechanism could, in principle, explain the optimal frequency of 25 Hz which is observed for electromagnetic fields producing phosphenes. This optimal frequency is not explained by simple cable theory predictions of the voltage produced by time varying fields (Figure 2), but could be explained as a consequence of the kinetics of voltage gated channels which are amplifying the voltage produced by the applied field. In fact, the calcium spikes studied in Reference 24 (at 20–23°C in skate) had a refractory period

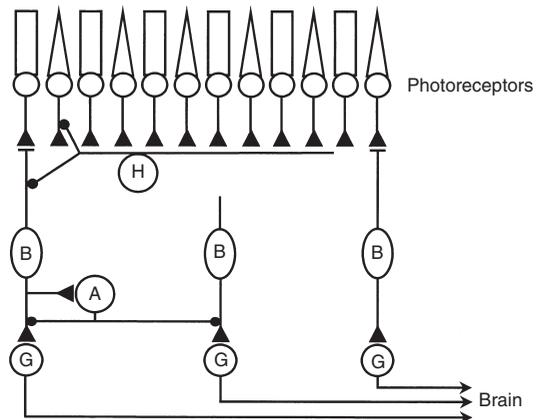


Figure 3. Schematic diagram of the retinal wiring. Light is absorbed by the rod and cone photoreceptors and converted to an electrical signal. This is then transmitted through the radial pathway of the retina through bipolar cells (B) to ganglion cells (G), which send action potentials to the brain. Lateral information flow occurs through horizontal cells (H) in the outer retina and amacrine cells (A) in the inner retina.

of 1 s, but a (large) acceleration of their kinetics at 37°C in humans might explain the 25 Hz selectivity of the electromagnetic field response.

In the lateral pathways within the retina (Figure 3), release of the inhibitory transmitter GABA from horizontal cell synapses onto photoreceptors or bipolar cells might also explain the effects of external fields. As pointed out above, the extensive electrical coupling of horizontal cells increases the voltage which is induced in them by external fields. However, the release of transmitter at these synapses is thought to be mediated by reversal of GABA transporters, rather than by conventional exocytosis⁽²⁵⁾. This process has an intrinsically weaker voltage dependence than that produced by the voltage dependence of the calcium channels which control exocytosis. The rate of release of GABA or glutamate by reversed uptake increases e-fold with each ~20 mV depolarisation^(25,26), while the release of glutamate at the rod output synapse increases e-fold every ~2 mV^(20,27,28).

Finally, at the output of the retina, radially oriented fields could increase the firing of retinal ganglion cells. This process could be promoted if in humans, as in frog, the extracellular volume fraction is very low in this cell layer⁽⁴⁾ (2%).

Determination of whether applied fields act on radially oriented cells (photoreceptors, bipolar cells, ganglion cells) or on laterally oriented cells (horizontal or amacrine cells, ganglion cell axons) could, in theory, be determined by the location in the visual field of the phosphenes, if the exact orientation of the applied fields were known. Fields in the front-to-back direction through the eye should excite radially oriented cells in the centre of the retina, but excite laterally oriented cells in the periphery of the eye (Figure 4). Unfortunately, in most experiments, it is not totally clear what the exact orientation of the fields within the retina is, preventing use of the fact that phosphenes appear predominantly in the periphery of the visual field to establish which cell types they are produced by. Brindley⁽²⁹⁾ suggested that radially oriented cells produced phosphenes, on the basis of the phosphene pattern produced by differently positioned pairs of electrodes, but it is hard to be certain of the direction of current flow without detailed modelling.

As outlined above, the voltage change which is likely to be produced in individual cells by electromagnetic fields may be too small to generate a detectable signal in the absence of special amplifying mechanisms. However, as all experiments on the effects of such fields inevitably apply the field over a large area, it is possible that convergence of signals in the retina could lead to a detectable signal being produced above the ongoing noise in the system. A small, synchronised, induced signal in many (say) photoreceptors could produce a detectable change in the voltage of bipolar cells that receive inputs from the many photoreceptors.

Safe limits for field exposure based on retinal phosphenes

In setting safe limits for the electric or magnetic fields that humans are exposed to, it is often hypothesised that the fields act by polarising neuronal membranes. In this case, it would ideally be most useful to define the safe limits in terms of the external electric or magnetic field value that produces a certain voltage change in neurons (rather than, as is often done, in terms of the current density in the tissue), since neuronal voltage gated channels are controlled by membrane potential. Whenever specifying such limits, it is crucial to specify the frequency of the field since the induced extracellular electric field is proportional to the frequency (Equations 5 and 7). A major problem in specifying the fields which can produce phosphenes is experimental variability: different experimenters obtain threshold values of applied current for evoking phosphenes which can differ by a factor of 1000 (reviewed in Reference 30). However, in addition to experimental variability, when setting exposure limits on fields two uncertain conversion factors have to be evaluated: the relationship between the external field in the air and the extracellular electric field in the tissue, and the relationship between the extracellular field in the tissue and the voltage change produced in neurons.

The relationship between the field in air and the extracellular field is hard to assess accurately, particularly for the application of electric fields: the extracellular field

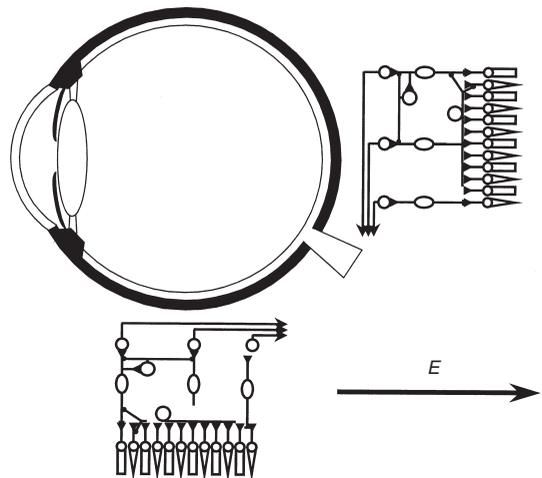


Figure 4. An electric field in a given direction will polarise different neural elements in the central and peripheral retina. Schematic diagram of the eye, together with copies of the retinal wiring from Figure 3 (not to scale), showing the orientation of cells in the central and peripheral retina. The field E will polarize radially oriented cells (photoreceptors, bipolar cells) best in the central retina but will polarise tangentially oriented cells (horizontal cells, amacrine cells, possibly ganglion cell axons) in the peripheral retina.

depends critically on the tissue conductivity and hence on the extracellular volume fraction, which can vary dramatically from one layer of tissue to the next on a very short spatial scale (2–11% in frog retina⁽⁴⁾). Different researchers make very different assumptions for the retinal conductivity when reporting their data in terms of electric fields in the tissue, e.g. 0.1 S m^{-1} ⁽³⁰⁾, 0.56 S m^{-1} (for the sclera plus retina⁽³¹⁾), and 1.5 S m^{-1} ⁽³²⁾ (more appropriate to the vitreous humour than the retina). This 15-fold range of assumed conductivities will produce an apparent 15-fold range of 'threshold extracellular fields', calculated from the same measured threshold current density. Furthermore, simplifying assumptions used to make modelling of current flow tractable, such as postulating smooth layers of tissue having the same conductivity, may be invalidated by inhomogeneities produced by high conductivity blood vessels penetrating the neural tissue⁽³¹⁾.

The relationship between the extracellular field and the voltage change produced in neurons will also depend critically on neuronal geometry, so it may be inappropriate to employ the same threshold extracellular field at all CNS locations to calculate exposure limits. The threshold field producing a significant change of function is likely to differ for tissues of different anatomical and synaptic organisation (e.g. neocortex, retina and cerebellum).

A reasonable estimate of the external fields needed to produce retinal phosphenes is 10 mT or 10 mA m^{-2} , which may correspond to an induced extracellular field in the retina of $10\text{--}60 \text{ mV m}^{-1}$, and to an induced neuronal transmembrane voltage change of $0.6\text{--}200 \text{ }\mu\text{V}$. There is no reason to believe that similar fields would not alter information processing in other regions of the brain. However, in other regions of the brain, exposure to such fields may not produce a conscious perception that nervous system function is being affected. If, as a precautionary principle, one did not want to alter CNS

function at all by applying external electromagnetic fields, then the safe limit for exposure must be set at below the field levels which produce retinal phosphenes, i.e. below $10\text{--}60 \text{ mV m}^{-1}$ in the body. The IEEE⁽³³⁾ has recommended, for the general public, a maximum extracellular field at 20 Hz in the CNS of 6 mV m^{-1} , near or 10-fold below the threshold field needed to produce phosphenes, and a roughly equivalent maximum magnetic field of 0.9 mT. However, they also specify a maximum electric field in air of 5000 V m^{-1} , which, at 25 Hz (and assuming $g_{\text{body}} = 0.2 \text{ S m}^{-1}$), would produce an extracellular electric field of only $35 \text{ }\mu\text{V m}^{-1}$ (from Equation 5), at least 300-fold lower than the threshold field producing phosphenes, so their restriction on the air field is much more restrictive than their restriction on the internal field.

The usefulness of setting limits based on phosphene production can be assessed by comparing how the threshold extracellular field, thought to produce phosphenes, compares with that needed for modulation of other cellular activities. Very high fields (150 V m^{-1}) can control intracellular processes, such as the plane of cell division⁽³⁴⁾. Fields of $\sim 10 \text{ V m}^{-1}$ in the body are sufficient to evoke action potentials in nerve or cardiac muscle fibres⁽³³⁾. Compared with these processes, the fields needed to evoke phosphenes (10 mV m^{-1}) are 1000-fold smaller, pointing to the significance of both averaging (by synaptic convergence) and amplifying mechanisms for the production of phosphenes. The electric detectors of sharks are much more sensitive still⁽³⁵⁾, detecting fields of $\sim 1 \text{ }\mu\text{V m}^{-1}$, demonstrating the potential for effects of electric fields well below the levels that produce phosphenes.

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