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SENSORY TRANSDUCTION AS A PROPOSED MODEL FOR BIOLOGICAL DETECTION OF ELECTROMAGNETIC FIELDS

Harold Sonnier[1] and Andrew A. Marino[2,*]

[1]Department of Cellular Biology and Anatomy,
and [2]Department of Orthopaedic Surgery and Department of Cellular Biology and Anatomy, LSU Health Sciences Center, P.O. Box 33932,
Shreveport, Louisiana 71130-3932

ABSTRACT

Laboratory studies of the biological effects of low-frequency electromagnetic fields (EMFs) have demonstrated that the fields can produce or alter a wide range of phenomena. Explaining the diversity of the reported effects is a central problem. Our basic hypothesis is that the effects are generally indirect, and arise as a consequence of sensory transduction of the fields. In this view, EMF detection and its biological consequences occur in different types of cells. Experimental verification of the hypothesis will ultimately require data showing that the interaction of EMFs with tissue results in biological changes that are the same as or similar to changes that occur during sensory transduction. The goal was to identify the specific phenomena that would be expected to occur if the hypothesis were true. We therefore analyzed the presently accepted models of sensory transduction in the somatic and special senses. Many kinds of processes were identified in connection with transduction of different kinds of stimuli, but we found that a change in conductance of a membrane ion channel in a neuron or a neuroepithelial cell was the earliest process that occurred in all forms of sensory transduction. Evidence from an appropriate model excitable cell or tissue that EMFs affect membrane currents or membrane potential would therefore support the hypothesis that EMF transduction is a species of sensory transduction.

* Corresponding author. E-mail: amarino@lsumc.edu

INTRODUCTION

Electric and magnetic fields (EMFs) produced by the electrical power transmission and distribution systems (60 Hz in North America, 50 Hz in Europe) are present everywhere in the workplace and the general environment (1-3). Laboratory studies have associated the EMFs with an exceedingly broad range of biological effects. EMF exposure depressed corticosterone levels in some studies (4,5) and raised them in others (6,7). Hippocampal and hypothalamic dopamine levels also varied in animals exposed to EMFs, depending on field strength and other conditions. Effects were seen in rats and hamsters at 25-39 kV/m (8,9), and in macaque monkeys at levels as low as 0.1 gauss (10), although the results were not always reproducible (11). Norepinephrine and epinephrine levels were increased at 39 kV/m (8) and 100 kV/m (12,13), but were unaffected following exposure at other levels (14).

The pineal gland and its main hormone, melatonin, have been widely reported to be sensitive to EMF exposure (15). Pineal melatonin release is cyclical (16), and the phase of its release in rats was shifted by exposure for 15 min to a 1-gauss 60-Hz magnetic field (17). Primary pinealocyte cultures produced significantly less melatonin when exposed to 0.5 gauss, 60 Hz, for 12 hours (18). Teleocyst fish were affected by 0.4 gauss, 1 Hz (19), and human melatonin release was significantly depressed by 29 gauss, 40 Hz EMFs (20). Again, the results were not always replicable (21).

Electroencephalograms (EEGs) from monkeys were affected by 7 V/m, 7-10 Hz (22), and EEGs from cats were affected 200 G, 50 Hz (13). Significant effects were also observed in human EEGs (23-27). The effects occurred as soon as 2 s after initial EMF exposure of 0.8 gauss from 1.5-10 Hz (28,29), suggesting a direct interaction between the fields and a neural sensor.

Increased osteoblast and osteoclast activity in response to EMFs of 1.5-1.8 G were reported (30-32). EMFs significantly increased healing in fracture nonunions (30,33,34), and use of EMFs for this purpose is a standard medical treatment.

Cardiac rate and output were affected in dogs and cats at 100 G (35,36), but not in rats at 100 kV/m (37). More recent findings suggest the human heart is also susceptible to EMFs. Radio station workers fitted with mobile electrocardiogram monitors exhibited significant increases in heart rhythm abnormalities (38). Heart-rate variability, a result of neuronal and cardiovascular reflexes, was affected by 0.2 G (39), suggesting that EMFs may detrimentally affect cardiovascular health (40).

Immune function tested after cells were activated with standard immune stimulatory agents showed differences in function compared with non-irradiated cells (41). Concavalin-A-dependent calcium uptake was significantly altered in thymocytes exposed to 65 G (42). Changes in lymphocyte DNA synthesis, measured by [^{3}H]thymidine uptake, were also observed (43-45). Natural killer cell cytotoxicity was decreased in the presence

of 1-G 60-Hz EMFs in one study (46), and increased by pulsed magnetic fields (square-wave, 0.8 Hz, 120 mT maximum field strength) in another study (47). Additional effects of power-frequency EMFs include those on the growth rate of animals (48), development (49), behavior (50), and *in vitro* effects (51).

Explaining how the interaction of EMFs and tissue could produce the extraordinarily diverse effects that have been reported is a central problem. The purpose of this report is to propose and rationalize a hypothesis that could explain the observed diversity. We first describe the presently accepted view regarding how EMFs produce effects, and the major shortcoming of this view. A new approach is then proposed based on the idea that EMF detection is a form of sensory transduction. The mechanisms responsible for transduction in the somatic and special senses are reviewed in detail to ascertain the processes that are characteristic of sensory transduction, because experimental verification of our hypothesis will require evidence that the same processes also occur in connection with the detection of EMFs.

PARADIGMS FOR FIELD EFFECTS

The traditional approach to the question of how exposure to EMFs resulted in particular biological effects was to view the bioeffect as a consequence of a biophysical interaction between the EMF and the cell or tissue that manifested the effect. A physical interaction was pictured as having occurred, typically at the plasma membrane, leading to activation of one or more cellular second-messenger systems, and ultimately to a change in protein expression. In this approach, an explanation of EMF-induced bioeffects consists of an explanation of the detection mechanism and a delineation of the applicable second-messenger systems and their consequences on cell behavior. Several theories of detection were proposed, including theories that involved resonance, magnetite, and free radicals.

Resonance Theories

Ion cyclotron resonance (ICR) and ion parametric resonance (IPR) models were proposed in which ions resonated when exposed to certain combinations of fluctuating (AC) and static (DC) magnetic fields (52-55). In addition, stochastic resonance, an unrelated resonance theory, was proposed as a mechanism by which detection of any low-level stimuli could be enhanced by the presence of background noise (56-58).

Ionic resonance equations model interactions between fields and charged particles. The ion is characterized by its charge-to-mass ratio, and the relationship between frequency and intensity of the magnetic field necessary for resonance is determined from a heuristically derived equation. When an ion is placed in conditions

that satisfy its resonance equations it acquires energy from the field and can therefore interact with its environment. The change in energy level may be observed as alterations in conductance of ions through membrane channels, or alterations in enzymatic reactions and signal transduction cascades involving the resonant ion. The equations for the two theories are related, although some of the underlying assumptions differ.

Calcium movement through the cell membrane of human lymphocytes was affected by fields tuned for Ca^{2+} resonance (59,60). Diatom movement, which is based on membrane calcium transport, occurred consistent with the ICR model (61). The IPR model (54) was supported in reports involving behavioral changes in pain perception in land snails (62), and neurite outgrowth in PC-12 cells (63).

Stochastic resonance theory proposes a mechanism whereby stimuli with less energy than background noise might be detected and then transduced. This phenomenon has been shown to exist in various physical systems, but has only recently received support in biology (64). The role of stochastic resonance in EMF transduction is presently speculative (65).

Magnetite

Magnetite is a ferromagnetic compound that was initially detected in bacteria (66) and subsequently in human brain and other organs (67-70). The magnetite was localized in organelles called magnetosomes, possibly indicating a functional role for magnetite (71-73). Bacteria appear to use the interactions between magnetite and the earth's background magnetic field to navigate (74,75), and some animals containing magnetite have been shown to respond to low-level EMFs. For example, sea turtles, salmon, honey bees, and some birds incorporate biologic magnetite and display sensitivity to low-level EMFs (76-79). The mechanism by which magnetite interacts with the cellular processes is unproven, and the sensitivity of small concentrations of magnetite to low-level EMFs has been questioned (80).

Free Radicals and Enzymes

Free radicals are atoms or groups of atoms having an unpaired electron. Examples include the superoxide (O_2•), nitric oxide (NO•), hydroperoxyl (HOO•), and hydroxide (HO•) radicals. Free radicals have long been suspected to be culprits of cellular degradation (81), and the oxygen-derived free radicals are especially harsh. They strip electrons from the nearest molecule or atom, leaving it damaged and unstable. In organisms that use oxygen for cell respiration, enzymes have evolved that convert free radicals to more inert species. Free radicals are also second messengers in signal-transduction pathways (82). Nitric oxide, for example, is a proven mediator of vasodilation (83).

EMFs may increase the lifetime of free radicals (84), thus allowing longer incubation periods for the detrimental effects of free radicals to occur, or possibly altering the rates of reactions in which they participate. Little evidence has accrued to support the hypothesis that EMFs alter the lifetime of free radicals to the degree necessary for an increase in direct macromolecular damage to occur (85,86). The possibility of an effect of EMFs on free-radical-dependent signal-transduction cascades and enzymatic reactions (82) seems more likely. EMFs affected NO-dependent signaling cascades in hippocampal slices (87).

Several enzymes were reported affected by EMFs. Ornithine decarboxylase, which is thought to have a role in tumor production, exhibited increased activity due to EMF exposures in both in vivo and in vitro studies (88-90). Ethanolamine ammonia lyase is another reported magnetically sensitive enzyme (91-93). The enzyme uses vitamin B_{12} as a cofactor and the enzymatic reaction involves radical pairs. Protein kinase C (94-96) and the membrane enzyme Na,K-ATPase (97,98) were both found to be sensitive to EMFs.

Role of the Nervous System

However useful these or other biophysical theories may ultimately prove to be in particular cases, the view that EMF detection and its biological consequences both occur in the same type of cell probably cannot serve as the basis of a general explanation for EMF-induced bioeffects. The fundamental difficulty is that such an explanation would require the presence of an electrosensory mechanism in virtually all types of cells, which is the complete opposite of the strategy followed by multicellular organisms for detecting virtually every other external stimulus. The invariable pattern of sensory transduction consists of the detection of particular stimuli by highly specialized cells. It therefore seems implausible that an electrosensory mechanism occurs in all cell types.

Another possibility is that electrosensing occurs in only one or a limited number of types of cells. In this view, the observed EMF-induced bioeffects occur in non-EMF-detecting cells as an indirect consequence of the initial detection process. The nervous system is a natural choice, as it is the locus of the body's electrosensory mechanism. For example, changes in the cardiovascular system caused by electromagnetic fields (35-40) could be a result of transduction of the EMF in the nervous system because the heart is controlled by the central nervous system.

Neural mediation of EMF detection could, in principle, explain the bioeffects that are reported in many anatomically separate and functionally different organ systems because the nervous system plays a part in controlling them all. Recent developments in neuroimmunoendocrinology have established that the body's sensory and regulatory systems are highly interrelated (99,100). The effects of EMF transduction by the nervous system could therefore be observed in the heart, immune system, or the pituitary-adrenal

axis. Stress is a good example of stimuli mediated through the nervous system resulting in disparate effects in immune, endocrine, and neurological parameters.

The neural transduction hypothesis for EMFs is consistent with the evolutionary role of the nervous system, which is to extract environmental data of minute magnitude. In addition, the experimental evidence in EEG and hippocampal slice studies (87,101) is highly suggestive that EMFs directly affect the nervous system. A possible exception to the sensory transduction hypothesis is the effects seen in the treatment of nonunions (30,33,34) because clinical devices are designed to apply EMFs locally, and there is no evidence that nerves play a role in the osteogenic response.

SENSORY TRANSDUCTION MECHANISMS

If EMF detection generally occurs in the nervous system, as the evidence suggests, it may do so by an extension of the sensory transduction gestalt. But sensory transduction systems are necessarily diverse in order to accommodate the broad range of physical factors that can convey information to biological organisms. Therefore, it is unclear what it means, at the level of observation, to claim that the process of EMF detection is somehow similar to comparable processes for other physical factors. The present models of sensory transduction are analyzed in this section to ascertain the process or processes that would be expected to occur in connection with EMFs if EMF detection were a form of sensory transduction.

Hearing

Sound waves produce fluid motion in the inner ear, resulting in deflections of the basilar membrane which, in turn, activates neuroepithelial cells (hair cells). The apical and basal surfaces of hair cells are separated by tight junctions and bathed in endolymph and perilymph, respectively (102). The K^+ and Na^+ concentrations of perilymph are similar to those of extracellular fluid but opposite those of endolymph, resulting in a potential of 80-100 mV between the two fluids. As a consequence, a potential of about 140 mV normally exists between a hair cell's interior and the endolymph (103,104).

Numerous stereocilia, 6-7 μm long and about 0.2 μm in diameter, project from the apical surfaces of the hair cells. Stereocilia are packed with cross-linked actin filaments, and contain ion channels at their tips (105,106). The stiffness of the stereocilia facilitates pivoting at their narrow base in response to sound-wave-induced deflections of the basilar membrane to which they are attached, thereby causing the ion channels to open. The channels are permeant to monovalent and (to a lesser extent) divalent cations (107,108), and have unitary conductances of 21-50 pS (104). The non-selectivity of the channels together with the ionic concentrations of the endolymph suggests that K^+ carries most of the transmembrane current (109,110).

The membrane conductance changes result directly in receptor potentials (107,110,111). A tip displacement of only 50-120 nm is sufficient to produce a receptor potential that is 90% of the maximum (109). The short latency between stereocilia displacement and receptor potentials (less than 25 μsec) precludes a second-messenger-related channel as the initial transductory mechanism (102,107,108,110,112). Afferent synapses, probably based on glutamate (113,114), are located at the basal surface of hair cells (115,116).

Vision

Phototransduction takes place in the rod and cone cells of the retina. The cells are normally depolarized in the absence of light due to a cycling current called the dark current (117-119). Na^+ and Ca^{2+} carry most of the inward current through nonspecific cation channels (120,121) located in a region of the cell containing rhodopsin, an intracellular membrane protein that is responsible for photon absorption in all phyla having visual receptors (122,123). K^+ carries the outward phase of the cycling current through nongated leakage channels located in another region of the cell. Active transport mechanisms maintain ionic homeostasis during periods of darkness.

The rod and cone cells release glutamate continuously while in the dark (111,120,121). A change in light level is transmitted to the next retinal layer as a direct consequence of light-induced hyperpolarization, which results in diminished neurotransmitter secretion (the opposite of what occurs in all other sensory systems). The first step in hyperpolarization is the absorption of light by rhodopsin. A series of conformational changes (121,122) then occurs within femtoseconds (124), leading to formation of metarhodopsin II. Metarhodopsin II activates transducin (122,125), a G protein, and its α subunit activates phosphodiesterase, which hydrolyzes cyclic GMP. The decrease in cGMP results in closing of the nonspecific-cation channels, stopping the inward Na^+ current. Inhibition of the inward Na^+ current without a decrease in the outward K^+ current causes the cell to hyperpolarize, and results in a decrease in the basal secretion of glutamate (126,127). Subsequent conduction through the layers of retina is either electrotonic or chemical, but no action potentials are produced until the ganglion cell layer is stimulated (128).

Gustation

Taste is mediated in the taste buds, which are aggregates of 30-100 receptor cells interspersed throughout the tongue and pharynx and surrounded by specializations in the adjacent epithelial tissue (129,130). Taste is divided into five major categories (129,130). Substances that evoke bitter sensations are mediated by differing pathways including inositol triphosphate (IP_3) and Ca^{2+} (131,132), and intracellular cyclic adenosine mono-

phosphate (cAMP) and G proteins (133). A common point of convergence of these pathways is inhibition of conductance through apical K^+ channels (134).

Salty taste consists of taste for Na^+ and K^+. Na^+ selectivity is derived from amiloride-sensitive Na^+ channels on the apical surface of taste receptors (135), and from amiloride-insensitive Na^+ channels on the basal surface (130). K^+ transduction is also thought to occur through selective channels on both surfaces (129,130).

Two types of transduction mechanisms for sweet compounds have been established: one for saccharides, such as sucrose, glucose, and fructose; and another for non-sugar sweeteners, such as saccharin. Detection of saccharides has been linked to increased cAMP (136,137), probably mediated by G proteins (138). G proteins specific to taste receptors have been identified (139,140). Non-sugar sweeteners, in contrast, are detected by a pathway involving Ca^{2+} caused by changes in IP_3 (141). Both mechanisms result in membrane channel conductance changes and can occur in the same cell (142).

Stimuli that result in perception of sour taste are acids. The mechanisms of transduction are unknown (130), but multiple mechanisms are suspected (129,143). Umami is a specific taste for amino acids, such as glutamate (144). The mechanisms that mediate these responses are also unknown, but are hypothesized to involve specific receptors (145), G proteins, and cAMP (129,130).

Taste receptor cells possess voltage-gated ion channels that allow them to produce action potentials in response to the second-messenger induced changes in conductance of the membrane channels (129,146,147). Taste buds are afferently innervated by several cranial nerves (148), and ultrastructural evidence suggests that their contact points are chemical synapses, but no neurotransmitter has been definitively identified (130).

Olfaction

Olfactory transduction occurs in specialized neurons in the nasal epithelium. Cilia from the dendrites extend through the nasal mucosa into the external environment (16), and the axons pass through the cribiform plate at the base of the brain and synapse on the brain's olfactory bulb.

Receptors that mediate olfaction have not been identified. Given the huge selection of odorants and the many categories of smell that vertebrates can perceive, the number of odor receptors is probably large (149-151). One hypothesis is that odorant receptors have hypervariable regions, similar to antibodies, that allow detection of the thousands of perceptible odors.

Post-stimulus latencies up to 100 ms occur prior to the appearance of action potentials, suggesting that the ionic channels in the cilia are not directly opened by odorants (152). Many second messengers have been implicated in the mediation of odor detection, all of which ultimately result in activation of ion channels in the cell

membrane, which in turn results in a change in the inward current after stimulus (153-155).

Mechanical Transduction

Mechanical transduction is incorporated into many mammalian sensory systems including hearing, touch, proprioception, blood pressure detection by vascular endothelial and smooth muscle cells, and detection of bladder, intestinal, and heart filling (156,157).

Touch receptors are specialized endings of nerve cells, usually located beneath an epithelium; the cell bodies are alongside the spinal cord in the dorsal root ganglia. The cells are bipolar, meaning there are two processes per cell. One process is used as the sensor and the other enters the spinal cord, relaying the information to the brain. Touch receptors break with classical dogma by generating action potentials close to the tactile receptor ending, which is a dendritic structure, and not at the axon hillock (158). Although the receptors can have different sizes and shapes, the common activating stimulus is mechanical force (159,160).

Two types of proprioceptors in muscle, muscle spindles and Golgi tendon organs, are thought to convey information about dynamic and static position of the limbs to the central nervous system. Both receptor types have an afferent nerve ending in close juxtaposition with a modified muscle tissue (161,162).

Little is known about the process that actually couples mechanical force with changes in ionic conductance, but the short time interval between stimulus application and conductance changes suggests that the interaction is direct (163,164). It is believed that tension in the bilayer membrane is insufficient to induce conformational changes in the embedded ion channels. Consequently, components of the cytoskeleton are assumed to mediate the link between force and changes in conductance (164).

Membrane tension is proportional to the applied mechanical force (156), but conductance through the activated ion channel is not (165), suggesting that mechanosensitive ion channels are not simply elastic rings for which increased membrane tension opens the channel further, thereby increasing conductance. Some mechanosensitive channels transduce positive or negative forces selectively, but more commonly, either a positive or a negative force on the membrane elicits ionic conductances detectable by patch-clamping (157,166). Mechanosensitive channels are either selective for K^+ (167), or are a nonselective version with a reversal potential of 0 mV.

Pain

Nociceptors are commonly described in relation to both the type of stimuli sensitivity they manifest and whether they extend from myelinated or unmyelinated

nerves. The polymodal receptor, the most commonly studied unmyelinated nociceptor, responds to intense mechanical, thermal, and chemical stimuli (168). A common myelinated nociceptor is the A-fiber mechanoheat Type I, which is sensitive to mechanical and thermal stimuli. Receptors with specific sensitivities to thermal or chemical stimuli have been found (169,170). Some nociceptors are initially unresponsive to any stimuli, but after repeated noxious stimuli they become sensitive to mechanical and/or thermal stimulation (171,172).

Perception of pain can be induced by many different stimuli, suggesting the existence of many types of receptors, but the earliest events in its transduction have been difficult to establish. Mechanically mediated nociception transduction is thought to occur through the same mechanism as previously discussed for touch and hearing. Initial events in thermal transduction are not well characterized. Chemical transduction can occur through membrane proteins or intracellular receptors.

EMF DETECTION AS SENSORY TRANSDUCTION

The initial biophysical processes that mediate the body's interactions with external stimuli, such as light absorption by rhodopsin or mechanical deformation of stereocilia, for example, are unique to each stimulus. The reports described above indicate that the first clearly identifiable common mechanism in the sensory causal chain linking transduction and perception is a change in mean conductance of a membrane ion channel. Consequently, if EMF detection by the body is a sensory transduction phenomenon, it is reasonable to anticipate that EMF exposure will result in transduction by processes that modulate the membrane conductances of ion channels.

The general modes of the initial stages of sensory transduction as it is presently understood are depicted schematically in Figure 1 (173). Stimuli interact with plasma membrane structures or intracellular membrane-bound receptors in a neuron or a neuroepithelial cell, resulting in a change in mean channel conductance and, consequently, in production of a change in the local baseline membrane potential (receptor potential). The receptor potentials propagate electrotonically, and their time-averaged sum directly or indirectly triggers or modulates an afferent signal consisting of a pattern of spike potentials. Relatively few of the total number of neurons and neuroepithelial cells in the body can mediate sensory transduction, and those that do generally form small groups at specific locations in the body, for example in the eye, ear, nose, skin, and tongue. Origins of diffusely perceived sensations such as pain and temperature are more difficult to localize, but all available evidence indicates that their receptor cells mediate perception in a similar fashion.

Related sensory-transduction models of possible EMF-tissue interactions are depicted in Figure 2. The EMF could interact with an extracellular or membrane-bound

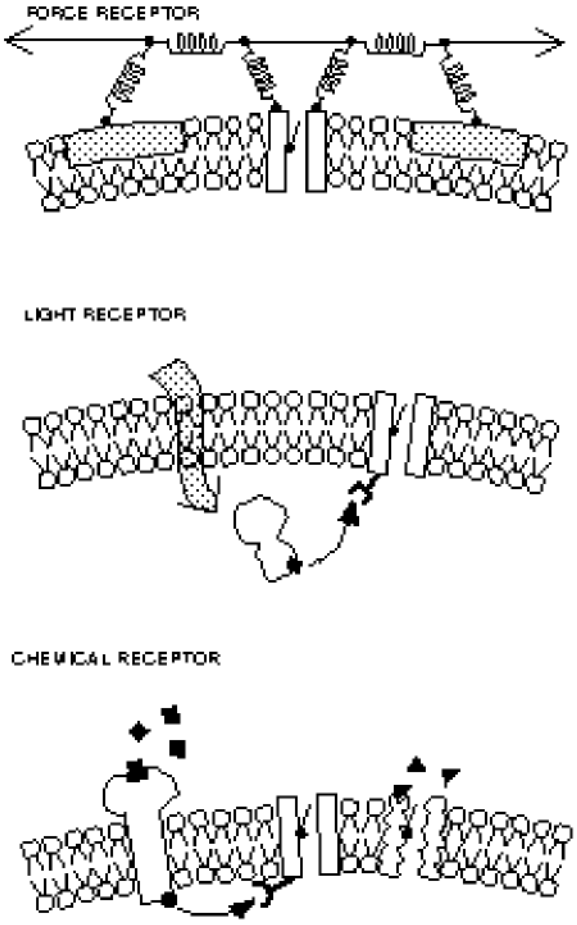

Figure 1. Signal transduction in three main classes of sensory receptors. Force transduction is directly coupled to channel conductance via a mechanically induced conformational change of the channel. In the detection of light, channel conductance is altered by intracellular messengers released after molecular events triggered by the interaction of light with rhodopsin. Chemical transduction may be indirect or direct. [Adapted from (173).]

protein, and thereby directly gate an ion channel, similar to the transduction process for mechanical force. Piezoelectricity is a form of electromechanical energy conversion in which a substance exposed to an EMF undergoes mechanical deformation (174). Many biological tissues are piezoelectric, most notably collagen (175), which is a prominent component of the extracellular matrix. It is possible that a piezoelectric protein in the extracellular matrix or on the membrane surface could gate stretch-sensitive ion channels. Further, because the cell membrane is transparent to many kinds of EMFs, particularly low-frequency magnetic fields, it is also possible that the putative piezoelectric protein could occur intracellularly, and gate ion channels via linkages mediated by the cell's cytoskeleton.

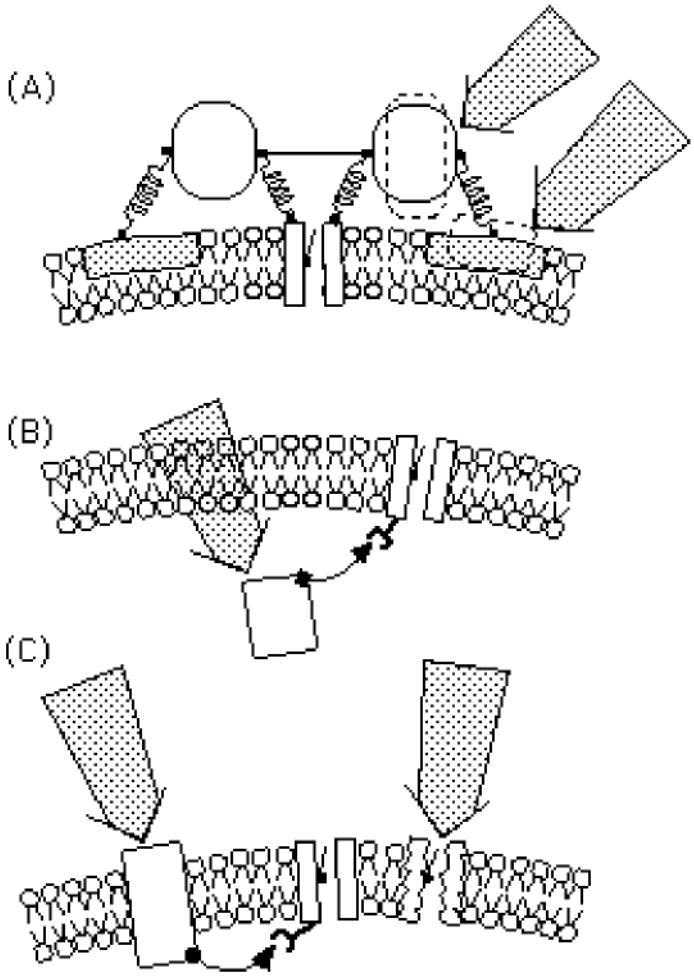

Figure 2. Sensory-transduction models of EMF-tissue interactions.

Alternatively, the ion channel could be gated internally by a chemical second-messenger, similar to the model for visual transduction (Figure 2B). The absorption characteristics of rhodopsin preclude the possibility that it could serve as the detector for EMFs other than those in the narrow frequency range corresponding to visible light. However, another substance capable of interacting more efficiently with EMFs could serve a similar function with regard to nonlight EMF frequencies.

Still other possibilities are depicted in Figure 2C. The locus of interaction with the EMF may itself be an ion channel, or a membrane-bound protein coupled via G proteins to an ion channel, similar to the mechanism by which the chemical senses are known to function.

Perception entails transduction, but the converse is not true. This is exemplified by the sensory components of the autonomic nervous system, such as those that mediate detection of bladder, intestine, and heart filling. The hypothesis that EMF detection is a sensory-transduction phenomenon does not, therefore, require that EMFs should be perceptible. Some EMFs are perceptible because they are sufficiently intense to generate heat which is detected by nociceptors, or to depolarize the axon membrane, thereby activating voltage-gated channels, resulting in production of spike potentials. Common environmental EMFs, however, are not sufficiently intense to activate nociceptors or voltage-gated channels in the axon (1-3). Thus, any consequences of their transduction will necessarily be subliminal, thereby making it difficult to identify where the interaction occurs and the cell type that subserves detection. The pattern used to localize sensory transduction sites was based on the ability to perceive the stimulus. That is, evidence was available to indicate where in the body to begin looking for the site of sensory transduction. Simply knowing or presuming that a stimulus is transduced by the nervous system in no way necessitates that any central or peripheral cell has the ability to directly respond to the stimulus.

A possible experimental test of the hypothesis that EMF transduction occurs by means of changes in channel conductance consists of observing the effect of EMFs on the membrane potential in a model excitable cell (Fig. 3). Subthreshold changes on the order of 100 μV would be sufficient to establish the plausibility of EMF sensory transduction, and the whole-cell configuration of the patch-clamp technique (176) is capable of providing the requisite sensitivity. Measurements on aggregates of cells connected by gap junctions (65,177) and the use of signal-averaging techniques might further increase sensitivity. If the experiment were performed in a standard model neuron such as the

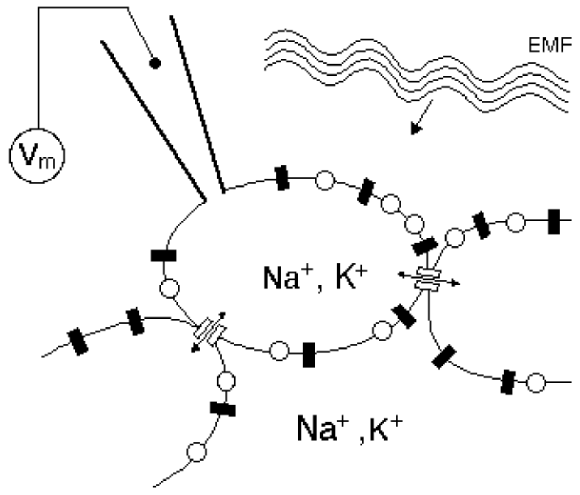

Figure 3. Proposed experiment for detection of EMF-induced changes in membrane potential in an aggregate of excitable cells connected by gap junctions.

SH-SY5Y cell line (178), the issue addressed would be whether EMF responsiveness was a general property of neurons. Alternatively, more specialized cell models may be required to demonstrate EMF sensitivity.

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