

## Biomarkers of induced electromagnetic field and cancer

J Behari\* & R Paulraj

School of Environmental Sciences, Jawaharlal Nehru University, New Delhi 110067, India

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The present article delineates the epidemiological and experimental studies of electromagnetic field which affects various tissues of human body. These affects lead to cell proliferation, which may lead to cancer formation. Certain biomarkers have been identified which are one way or the other responsible for tumor promotion or co-promotion. These are (i) melatonin, a hormone secreted by pineal gland, (ii)  $\text{Ca}^{2+}$ , which is essential in the regulation of the resting membrane potential and in the sequence of events in synaptic excitation and neurotransmitter, release are affected by electromagnetic field, (iii) ornithine decarboxylase (ODC), a rate-limiting enzyme in the biosynthesis of polyamines, considered as a useful biological marker; over expression of ODC can cause cell transformation and enhancement of tumor promotion. (iv) protein kinase is an enzyme, which transfers phosphate groups from ATP to hydroxyl groups in the amino acid chains of acceptor proteins, and (v)  $\text{Na}^+-\text{K}^+$  ATPase, which transports sodium and potassium ions across the membrane has a critical role in living cells. The various possible mechanisms depending upon non equilibrium thermodynamics, co-operativism, stochastic and resonance are discussed as possible models of signal transduction in cytosol, thereby controlling the transcription phenomena. Finally a mechanism comprising the extremely low frequency and radio frequency (RF)/ microwave (MW) modulated field is compared.

**Keywords:** Biomarkers, Cancer, Cell proliferation, Electromagnetic field

Cancer is a dreaded disease and remains a cause of continuing public and scientific concern. A new dimension to this has been added because of the speculation whether the low energy electromagnetic fields at a low level can cause changes in the biosynthesis. Interaction and mode of penetration of extremely low frequency fields with the biological system is shown in Fig. 1. A controversial point of investigations that still remains to be sorted out is the possibility of cancer promotion due to some of these leakage fields from high-tension lines. Electric as well as magnetic fields have been shown to stimulate transcription, and the effects of both fields have been compared with similar patterns of amplitude, frequency, and time dependence<sup>1</sup>. In the present review we are primarily concerned with the effect of extremely low frequency and modulated fields on the tumor promotion and to examine the physical basis of electromagnetic field (EMF)-bio-interaction.

### EMF-Bio-interaction in Relation to Cancer Promotion

Loberg *et. al.*<sup>2</sup> have carried out investigations in which, arrays containing cDNA for 588 cancer related

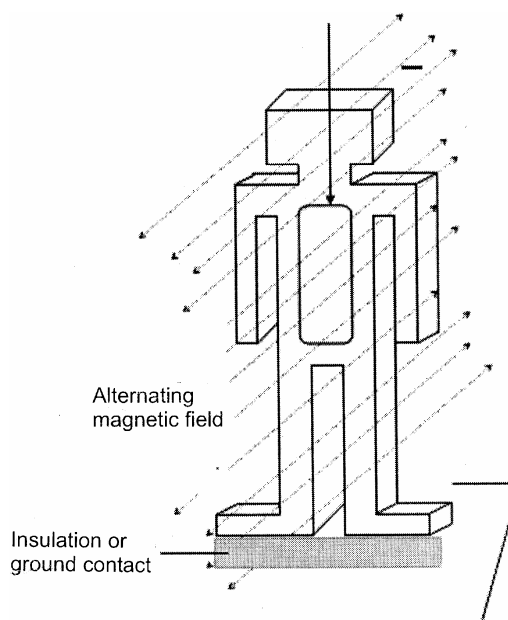


Fig. 1—Schematic of human body exposed to static and time dependent extremely low frequency electric and magnetic field.

\*Correspondent author  
Phone: 91-11- 26704323 (off)  
Fax. 91-11-26717586, 2617 1502  
E-mail. jbehari@hotmail.com

genes were used to approach the hypothesis that the biological activity of magnetic fields is mediated by alterations in gene expression. Several genes have been identified in magnetic field exposed cells whose expression was increased by at least two fold or decreased by 50% or more. However, no gene is found to be differentially expressed in each of three (0, 0.01 or 1.0 mT exposed for 24 hr) independent exposures for any cell type. Also no relationship between exposure intensity and differential gene expression has been reported. These studies failed to identify a plausible genetic target for the action of magnetic fields in human cells, and did not support for the hypothesis that magnetic field exposure alters the expression of genes that are involved in cancer development. One possibility that magnetic fields could influence cancer induction is the modulation of cellular responses to agents that damage DNA. Although the magnetic field itself is not genotoxic, it could alter regulatory mechanisms involved in cellular responses to DNA damage. Synergistic interactions between ionizing interactions and magnetic fields on the induction of genetic damage were found in human peripheral blood lymphocytes and Chinese hamster ovary cells, but not in another study of human lymphoblast cells. No synergism was found between magnetic fields and the chemical mutagens like hydrogen peroxide and mitomycin C<sup>3</sup>.

### Development of carcinogenesis

In view of the variability associated with the exposure field conditions the corresponding field induced data can be quite variable. Any connection with observed effects is thus difficult to correlate. Therefore, a connection between electromagnetic field exposure and tumor promotion is a matter of continuing debate. Because of its clinical significance the etiological and mechanistic origin of cancer demands a much greater attention. Development of cancer is a complex process, involving a sequence of events, which remains yet to be fully understood. However, it is understood that cell proliferation, apoptosis, invasion, and metastasis are complex phenomena controlled by complex series of pathways, which communicate with each other through a myriad of signalling cascades and contribute to tumor promotion.

### Important biomarker of tumor promotion

#### Melatonin

Welker *et al.*<sup>4</sup> found that the exposure of rats to an alteration of the earth's DC magnetic field (field

strength 0.5 gauss) significantly depressed the activity of the rate-limiting enzyme in melatonin production. These authors have observed that a horizontal rotation of the earth's magnetic field (MF) was able to change pineal indolamine metabolism. Several other authors have also reported induction of pineal metabolic and physiologic changes by weak DC MF<sup>5-8</sup>. These evidences suggest that MF exposure change the ability of the pineal gland to produce melatonin by mechanism that could be either direct or indirect. Rudolph *et al.*<sup>7</sup> have also reported that the intracellular second messenger, cyclic AMP, which mediates the nocturnal rise in pineal N-acetyltransferase (NAT) activity and melatonin content also depressed by the exposure of rats to static MF.

Some studies<sup>9,10</sup> on the effect of DC MF on pineal and serum melatonin levels indicated that these fields may cause a reduction in the ability of pineal gland to either produce and/or secrete melatonin (Fig. 2). These studies reveal that altered DC MF may reduce the melatonin forming ability to the pineal gland<sup>11</sup>.

Reiter *et al.*<sup>12</sup> have reported that pulsed DC magnetic field exposure increases free radical availability leading to decreased serum melatonin

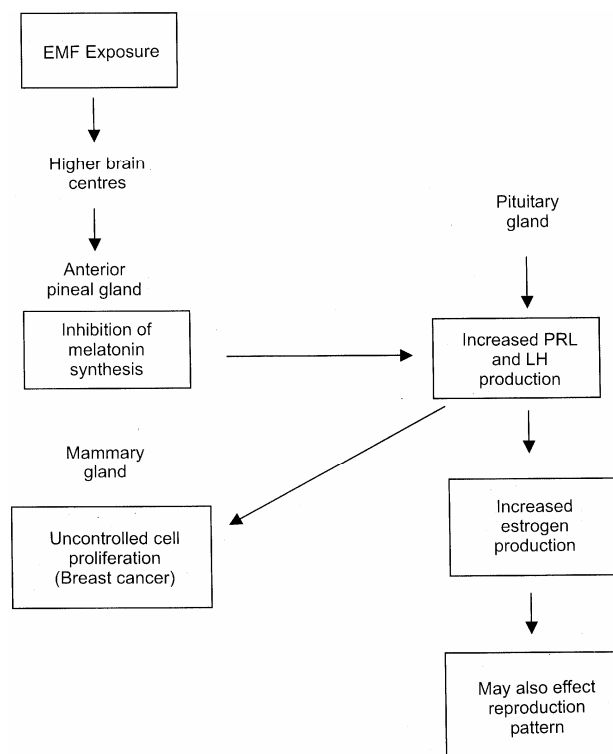


Fig. 2—Proposed model of EMF exposure promoting the growth of initiated tumor cells in breast tissue.

levels. Several workers<sup>13-16</sup> have also used high MF strengths (25mT) to prolong the half-life of free radicals. Roy *et. al*<sup>17</sup> have provided evidence that MF of 0.1 mT increases the half life of free radicals in biological systems. However, environmental magnetic fields to which most of the populations is subjected may not be able to affect half life of free radicals.

Lerchl *et. al*<sup>18,19</sup> have suggested that a mechanism by which pulsed DC MF inhibit the melatonin synthesis is the activity of the pineal gland. Alternating magnetic field suppresses the nocturnal production of the pineal hormone melatonin which in turn, could lead to an increased risk of breast cancer. Melatonin inhibits mammary tumorigenesis in animals *in vitro* and may have oncostatic effects on other types of cancer cells as well. However, not all epidemiological studies suggest that residential or occupational exposure to extremely low frequency magnetic fields (ELF MF) may suppress melatonin production also in humans. A widely accepted outcome of a set of investigations reveals that melatonin is related to the occurrence of breast cancer. Several studies have reported a suppression of the nocturnal melatonin concentration in rats after exposure to weak static or ELF MF.

A series of experiments were conducted to examine the changes in the melatonin concentration in rats exposed to 50 Hz magnetic fields. Various linearly, elliptically and circularly polarized magnetic fields of different field strengths ranging from 0.02-350  $\mu$ T (rms) were applied. The linearly polarized magnetic fields induce linearly polarized electric fields and currents, while the circularly polarized magnetic fields generally induce elliptically polarised electric fields and currents. The circularly polarized magnetic fields above 1.41  $\mu$ T significantly suppressed the melatonin concentration compared to the sham exposed group<sup>20</sup>, whereas no effect on melatonin concentration was found for the linearly and elliptically polarised magnetic fields of the same order of magnitude. However the mechanism responsible for difference in the results on magnetic field polarisation is not clear. Lerchl *et. al*<sup>19</sup> have pointed out that the eddy currents induced by the applied field could be responsible for this phenomenon. The pineal gland and the retina were discussed as possible site of interaction<sup>21</sup>. If the induced currents are responsible for the effects on the melatonin synthesis, then one would anticipate a significant difference between the characteristics of the currents induced in those organs by linearly and circularly polarized magnetic fields.

#### **Calcium efflux**

Calcium ion is a generally regulatory signal of cellular functions such as muscle contraction<sup>22</sup> microtubule assembly, stimulus secretion coupling in glandular cells and hormone mediated regulation of cyclic nucleotide levels<sup>23</sup>.  $Ca^{2+}$  are essential in the regulation of the resting membrane potential and in the sequence of events in synaptic excitation<sup>24-26</sup> and neurotransmitter release<sup>27,28</sup>. Anatomically  $Ca^{2+}$  -ions are differentially distributed in the brain tissue and have role in the transduction of weaker events.

#### **Ornithine decarboxylase (ODC)**

This is a rate-limiting enzyme in the biosynthesis of polyamines and is considered as a useful biological marker. The stimulating activity of ornithine decarboxylase can have important consequences, since it is essential for cell growth and DNA synthesis<sup>29,30</sup>. The enzyme is regulated by a wide variety of growth factors and hormonal activity at the cell surface. The activity of this enzyme is unique in a manner in which it can change rapidly and significantly in response to extracellular signals. Its activity is elevated in all rapidly growing cells such as transformed or cancer cell and is markedly stimulated by tumor promoting (phorbol ester) compounds. Both the tumor promoters phorbol esters and RF field act on cell membranes. It is now reasonably confirmed that many tumor promoters increase the ODC activity.

The resulting elevated production of putrescine is critical for the induction of tumors. Conversely, tumor formation can be prevented by the administration of a substance, which blocks the induction of ODC. Cell proliferation is a characteristic of the expression of malignancy in initiated cells. Agents such as DMFO which inhibit ODC formation, reduce the rate of cell proliferation and inhibit carcinogenesis in the two-stage model. The increase in ODC could be due to the enhanced proliferation of cells, induced by these fields. Its activity has been shown to be a possible indicator of EMF induced cellular responses<sup>31</sup>. Overexpression of ODC gene in cultured cells facilitates and in some cases can cause cell transformation and enhancement of tumor promotion<sup>32-36</sup>.

#### **Na-K-ATPase activity**

Transport of sodium and potassium ions across the membrane is a critical function of living cells. The viability of the cells depends on maintaining the concentrations of these ions within well-defined limits. This requirement is fulfilled by the  $Na^+ / K^+$  pump. The enzymatic machinery in the  $Na^+ - K^+$  pump

is the Na<sup>+</sup>/K<sup>+</sup> transporting ATPase which uses the energy from the hydrolysis of terminal phosphoryl group of intracellular ATP to transport across the cell membrane three Na<sup>+</sup> ions outward and two K<sup>+</sup> ions inwards against steep electrochemical gradients. Na<sup>+</sup>-K<sup>+</sup>-ATPase is the ion-pump enzyme in cell membrane. Change in enzyme activity due to electromagnetic field exposure is the most important factor affecting signal transduction.

The characteristic dependence of electric and magnetic field effects on enzyme activation can be explained by a signal transduction model in which enzyme activation increases with concentration of mobile charges within protein<sup>37</sup>. The Na - K-ATPase data show that, below an enzyme activation level of 0.05-0.1  $\mu$ moles P/min/mg protein, both fields increase enzyme function. It appears that magnetic fields always stimulate, but electric fields can inhibit as well as stimulate, depending on the level of activation.

#### **Possible mechanisms of magnetic field effects on carcinogenesis**

A time dependent magnetic field may be considered as an event of promoting carcinogenesis by inducing DNA damage. With subsequent field cycles the number of cells involved increases and the probability for a fresh damage and subsequently the possibility of new mutation increases. In this carcinogenic process ELF/MF could theoretically act at any of the three stages of the carcinogenesis cycle.

#### **Stage- I**

It is believed that strong MFs affect radical pair recombination, and thereby effecting the lifetime of free radicals. On the other hand the environmental ELF MF are of low intensity and there is a possibility of their generation of eddy currents in the biological bodies. By this process they may interfere with the physiological process and cellular protective responses against oxidative damage. The reported increase of DNA strand breaks in brain cells of rats exposed to ELF MF was blocked by melatonin. Because these substances are free radical scavengers, the findings suggest a possible association between ELF MF and free radicals. Amplitude modulated radiofrequency fields at brain wave frequencies also showed similar effects in developing rat brain tissue<sup>38</sup>. However, the mechanism to these phenomena remains to be fully understood.

#### **Stage -II**

**DNA Repair:** The critical event in the carcinogenesis is the alteration of DNA base sequence (mutation). A variety of DNA damage and correspondingly the appropriate DNA repair mechanism are highly variable. This provides many different types of molecular processes that could be influenced by ELF MF and may control DNA repair processes<sup>39</sup>. It has been reported that exposure of cultured mammalian cells to 50-60 Hz electric or magnetic fields does not affect the rate of repair of single or double strand breaks induced by UV radiation, ionizing radiation or various chemical agents. It is therefore suggestive that MF exposure modifies DNA repair in a way that enhances incorrect repair and thus leads to a significant increase in the alteration of base sequence at the repair site. This may lead to mutation.

#### **Apoptosis**

Apoptosis (programmed cell death) is of multi-cellular organism's main weapon of protection against genotoxic agents. Potential cancer cells can thus be removed by apoptosis. A corollary of above is that as inhibition of apoptosis is a candidate common mechanism for explaining tumor promotion. ELF MF has been reported to enhance apoptosis, suggesting that co-carcinogenic effect of MF may be different from that of the classical chemical promoters. The reported enhancement of apoptosis is of interest also because it may be an indirect indicator of MF interactions with the initial DNA damage or with DNA repair. If MF exposure leads to increased frequency of DNA damage or increases the number of repair failures, this would lead to an increase in apoptosis<sup>40</sup>.

#### **Stage -III**

**Cell proliferation:** Uncontrolled cell growth leads to carcinogenesis due to accelerated accumulation of mutations. Increased cell division is an indication of carcinogenesis effect of many agents that do not cause DNA damage and may yet be a contributing factor in genotoxic carcinogens. Katsir and Parola<sup>41</sup> support the findings that sinusoidally varying magnetic fields (SVMF) enhance cell proliferation and induces changes in membrane lipid-protein interactions as reflected by adenosine-deaminase (ADA) specific activity. Several *in vitro* studies have indicated that MF exposure alone or in combination with other agents affect cell proliferation and many important cellular regulation mechanisms, such as enzyme

activities, signal transduction and gene expression. MF exposures causing increased cell growth have been observed *in vivo*, although the effects are much weaker than those of known chemical tumor promoter. It may be pointed out that an application of tumor promoter on rat skin followed by a low level amplitude modulated field does not show enhancement of tumor growth<sup>42</sup>. This is attributed to the slow action of magnetic field stimulation. This is any way much smaller than the chemical agent.

Investigations examining dysregulation in cell proliferation and/or (apoptosis), two of the major factors contributing to the increase in cell number found in tumors have yielded controversial results. In fact, some investigators have seen variations in cell proliferation and apoptosis after exposure to ELF fields<sup>43,44</sup> while others have not observed such changes<sup>45,46</sup>.

#### **DNA high intramolecular conduction and strand break**

Measurements on DNA have shown that double helix is also capable of electronic conduction through the stacked base pairs<sup>47,48</sup>. The rate of electron flow within the stacked bases of DNA is over  $10^6$  sec, which is  $1.6 \times 10^{-13}$  coulomb/sec. Assuming DNA interior as 2 mm in diameter, correspond to an area of approximately  $3 \times 10^{-18} / \text{m}^2$  and a current density of about  $0.5 \times 10^5 \text{ A/m}^2$ . If normally the currents of this magnitude flow in the DNA, then significant interactions can occur with the relatively weak magnetic fields that stimulate transcription. It has been shown that DNA bends when charges on one side of a segment are neutralized<sup>49</sup> and such a conformational change would alter the conducting path within DNA. Another way to cause a change in the conduction path and confine the rapid electron flows to particular segments of DNA can be brought about by an enzyme that causes a base to flip out of the double helix<sup>50</sup>.

DNA damage is closely related to human health risk. Particularly, DNA damage in brain cells could affect neurological functions and also possibly lead to carcinogenesis and neurodegenerative diseases. Sarkar *et. al*<sup>51</sup> showed that RF fields affect DNA directly. Structural and genomic changes have been reported in the brain and testis of rats exposed to 2.45 GHz radiation<sup>51</sup>. More recently, Paulraj and Behari<sup>52</sup> reported DNA strand break by comet assay technique using single gel electrophoresis. They found a significant increase in the DNA migration (tail

length). Lai and Singh<sup>53</sup> reported that rats exposed to pulse or continuous wave of 2.45 GHz field for 2 hr, resulted in an increase of single and double strand breaks in the DNA of brain tissue.

#### **Mechanisms of signal amplification**

##### **Non linearities in the weak ELF MF biologic effects:**

The energy of ELF MF fields is 8-10 orders lower than kT. Hence, the mechanisms for signal amplification must exist in the cell membrane to influence biosystems. The possible solution to this is system's nonlinearity, in which a very small change in parameters can switch the system's qualitative or quantitative behavior. Any type of non linearity is found in chaotic systems, where such switching can be made by a small change in initial conditions. Such non-equilibrium and non-linear situations take place in cases where the association/dissociation of ions, charged groups, legend etc. is associated with changes in protein conformation. In unexposed conditions the equilibrium concentrations of the ions are maintained across the potential barrier following the non-linear Nernst equation. In this condition no net current flows across the membrane. If an alternating current is superimposed this gets disturbed<sup>54</sup>.

##### **Cooperativism**

In case of cell membranes cooperativism involves long range interactions between counter ions linked to surface molecules. This in fact is a coherent oscillation by which an ensemble of macromolecules acts together to change the ensemble from one stable state to another one. In this process the input signal to the system could be weak and the response need to be amplified by several order of magnitude. This energy amplification is responsible for several important events in biology<sup>55,56</sup>.

##### **Non-equilibrium thermodynamics**

Equilibrium thermodynamics and statistical mechanics of living matter are inadequate to deal with the problem of the primary ELF-EMF interactions with living cells, because a membrane which has a field of  $10^7 \text{ V/cm}$  can be depolarised by as small field as in the range  $10^{-7} - 10^{-1} \text{ V/cm}$ . A main consequence of non-equilibrium process is that the windowing phenomena can be explained on the basis of such processes. It is postulated that specialized molecular organization senses weak EMF signals<sup>57</sup>.

##### **Macromolecular phase transitions at ELF**

The outer layer of phospholipids multiply charged heads (polyanions) as a two dimensional crystal

mosaic of giant dipoles (p-sites) interpenetrated by glycoproteins (glycocalyx) with cationic binding sites (c-sites). When an ELF electric field is applied to the system, in one of its allowed modes of oscillation, a Bose-Einstein condensation is produced, where all the energy is channelled to such a mode. Examined in this way the system behaves like a macroscopic quantum oscillator, exhibiting a long range order phase transitions. Such a formulation can be applied for seeking conformational changes in macromolecules, whereby a relaxation spectra is found with sufficient amplitude to induce such a change with the occurrence of cooperativity. A modulated HF or a ELF fields interactions with living or biomolecular matter to cell membranes, non-linear mechanism play a key role in the process of transmembrane coupling of the signal to the cytoplasm.

#### Stochastic resonance

Any biologic system is subjected to both external and internal noise. However, the mechanism by which a nonlinear dynamic system responds to the influence of noise is not fully understood. At the very outset, the presence of noise in dynamic systems is usually considered an unwanted interference. However, in many non-linear systems, the presence of noise can be used for amplification of weak signals. The phenomenon of stochastic resonance (SR) is characterized by such an enhancement of signal to noise ratio. It is further characterized by the initial increase in the noise strength, the signal to noise ratio increases reaching a maximum and then decays for the larger values. In this scheme a sub threshold signal is not amplified. The signal to noise amplification is obtained when the spectral frequency,  $\omega$ , is equal to the modulation frequency ( $\Omega$ ). The signal-to-noise ratio deduced from the power spectrum has an enhancement profile, given by the relationship<sup>58,59</sup>

$$S/N = (C/D^2) \exp | -\Delta U / D | ,$$

where C is a constant, D measures the noise strength (proportional to the mean square), and  $\Delta U$  measures the height of the barrier between the two symmetrical wells.

This phenomenon is pertinent to ionic channels of the plasma membrane. The intensity of noise, an inherent characteristic of the system, is internal, and is temperature dependent. A comprehensive picture

involving all the above amplification factors is shown in Fig. 3.

#### Comparison between bio-effects due to ELF and ELF-modulated RF/MW fields

RF/MW fields modulated at ELF frequencies are found to produce ELF like effects. No single model yet explains the observed bio-effects across the spectrum from ELF to millimeter waves. Many effects are independent of RF frequency but relate closely to modulation frequency (ELF) of the RF field. There is wide speculation that the detection of certain modulation components of RF/ microwave fields may be related to intrinsic property of tissue organization. The available data indicate similarities between certain cell ionic and biochemical responses to ELF fields, and to RF/microwave fields amplitude modulated at these same ELF frequencies. This suggests that demodulation of RF/microwave fields may be a critical parameter in controlling the biological processes.

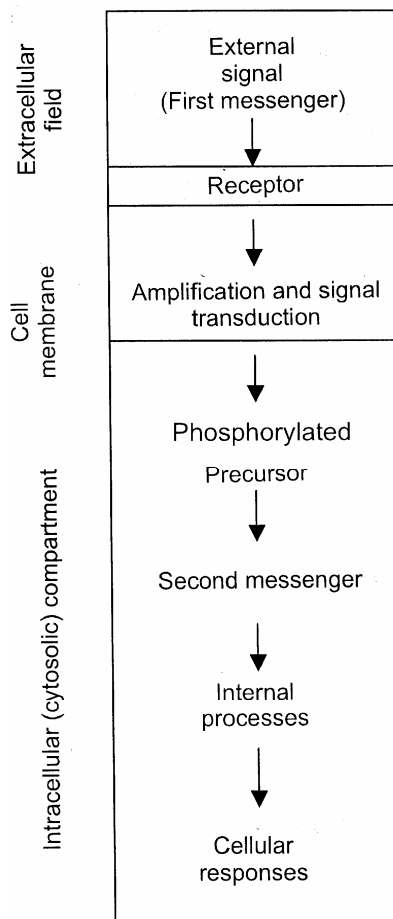
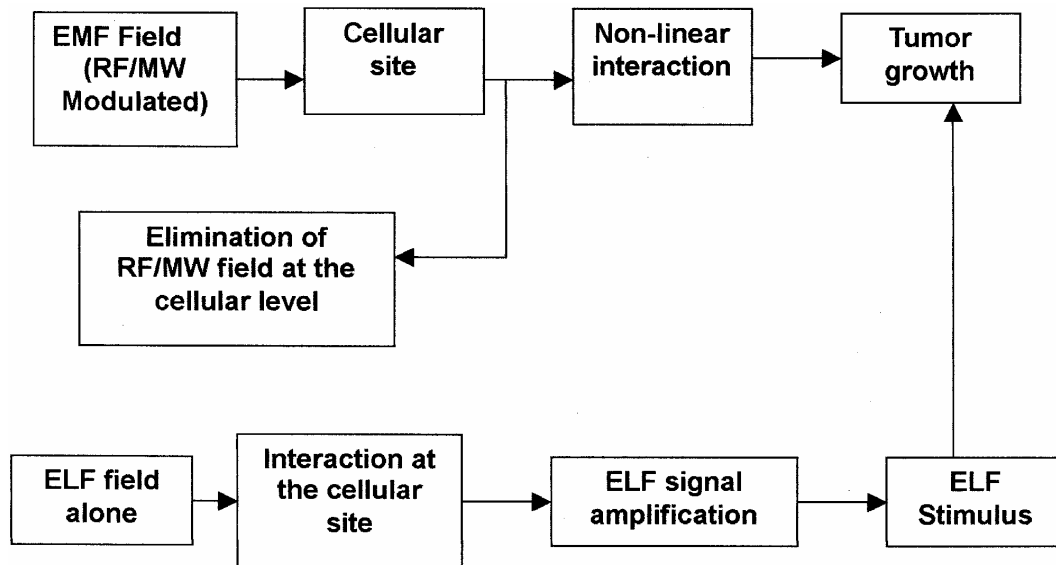


Fig. 3—Diagrammatic representation of signal transduction pathways by membrane receptors.



Flow diagram – EMF biometeraction

A model of EMF-Biointeraction has been summarized in the flow diagram.

### Conclusion

EMF influence cellular activities through ion channel, enzymatic alteration and structural changes in macromolecules. Low frequency electric fields do not penetrate cells very effectively because of the low dielectric constant of the cellular membrane. Electric field affects charge distribution at interfaces but penetrates into the interior by polarizing the interface and forming an electric double layer with mobile charges in a protein or DNA. Biomarkers such as melatonin (ii)  $\text{Ca}^{2+}$  (iii) Ornithine decarboxylase (ODC), (iv) protein kinase, (v)  $\text{Na}^+\text{-K}^+$  ATPase have been found as the conceivable indicator of cell growth and development.

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