MINIREVIEW

A Puzzle of the Effect of Magnetic Field on Biological Cells

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Abstract: The mechanism for interactions of magnetic field, particularly in extremely low frequency with biological cells is still puzzle to the scientific researchers. Our investigations have guided to the speculation of roles of the magnetic field for the cell-cell communication in physiological responses. To explain the complexity, the experimental evidences and observations and their associated theories have been included in this review. The result of a disruption of the homeostatic regulation of the cells responding to a specific strength and frequency of magnetic field can be as the signal that triggers signal transduction to modulate the cell-cell communication. This review leads into the stochastic systems in cell, for instance, ion channels on cell membrane, providing a basis for signal amplification to disrupt the cell homeostatic regulation. [Life Science Journal. 2005;2(1):16-21] (ISSN: 1097-8135).

Keywords: biological effect; cell; magnetic field

1 Introduction

Biological cells have been shown to respond low frequencies electromagnetic fields as well as in chemical and biochemical reactions (Dobson, 1996). Puzzle of the energy of the fields is too low to the noise in cellular level to produce observable effects (Adair, 1991; 1992; 1994). Therefore, the physical mechanism of primary interaction between the magnetic fields and the biological target sites, such as electrical charge in motion, molecules structure with magnetic moments and the application of Faraday law, generating local electrical current by a varying magnetic field has mainly concluded only amplification mechanisms can solve the puzzle. As we know, the interaction should be very weak at field strength less than 10 Gauss and the frequency below 100 Hz. If considering the stochastic resonance model, the amplification of weak electromagnetic interaction signals can be modulated by external fields (Jung, 1993). By considering ferromagnetic transduction model, the minimum applied magnetic fields would produce a torque on a biogenic magnetite particle coupling via the cytoskeleton to the ion gates. The deformation of the cell membrane and the closing of the ion gates would occur quickly enough to compensate for the forced opening of the gate as long as the frequency of the forcing field was below 100 Hz, regardless of the strength of the applied field. Dawson et al. (Dawson, 1996) used scalar potential finite difference code for low frequency electromagnetic computations and to model induction in anatomically realistic human in terms of average and maximum electric field intensities. The calculation revealed the induced dosimetry amount for various major organs upon exposing to extremely low-frequency electromagnetic fields. The whole body induced maximum current density is about 21 micro amp per meter square from a 50 Hz to a 60 Hz source frequency and from a 1 amp per meter to a 0.1 Gauss source strength. Comparatively, the cell culture dosimetry for low frequency magnetic fields study by Hart (Hart, 1996) has shown the induced current density averagely about 0.9 micro amp per meter square from a 60 Hz source of frequency and a 1 Gauss source of field strength. Accordingly, the induced effect between the human body and the cells *in culture* clarified the interaction mechanisms involved could be different. The mechanisms whereby ELF electromagnetic field stimulates changes in biological functions of cells *in culture* may not guarantee that would cause the same biological effect *in vivo*. Many researchers therefore switched their interest to the biological effect of very high frequency band of wireless communication protocol just because of the support funding being hard to continuous for ELF biological effect study.

2 The ELF Biological Effect

The concern of the exposure to extremely low frequency (ELF) electromagnetic fields may present a health hazard to workers and the public. The controversial and contradictory finding in the scientific research, especially from epidemiological studies is puzzle (EPRI, 1994). Research of ELF elec-

tromagnetic fields interaction caused biological effect in biological system includes experimental investigations on both *in vivo* and *in vitro*. In present, the researchers have been interested in both to the electric fields and magnetic fields as well as identifying a possible mechanism for ELF acting as a cancer initiator, promoter or co-promoter. On the other hand, epidemiological studies have shown very weak connection between ELF exposure and leukemia, brain cancers, breast cancer and lung cancer. Almost all related research studies were in flaws, for instance, numbers of cases were too low to look at cancer subtypes, lack of specific exposure, lack of reliability of data, lack of statistical power and lack of control for repeaters. There is no reliable supporting data for an association between ELF exposure and cancer risk in the public. There is no conclusive evidence so far from the epidemiological evidence that electric or magnetic fields cause a risk of cancer. The researcher only holds a possibility of the risk of cancer of ELF electromagnetic fields occupational exposures. Oppositely, experimental investigations with cellular systems have shown that electromagnetic fields can interact with biological systems. Several researchers have confirmed cellular effects involving the movement of calcium ions through cellular membranes under ELF interaction (Fewtrell, 1994). The significance of this effect as it relates to possible adverse health outcomes is still not understood. Direct effects on significant cellular molecules, such as DNA, have not been observed. No direct mutagenic or carcinogenic effects on animals have been observed. Current research has shifted to focusing on the role of ELF (particularly magnetic fields) as a tumor promoter or co-promoter. However, it is still no effects were observed on mice exposed without the chemical promoter yet. The overall view obtained from the research literature indicates that while some biological effects of exposure to ELF electric and magnetic fields occur, there are no resulting adverse health effects from these exposures. In the United States, a large number of research papers and overview reports have been produced along with numerous conferences over the past 15 years. Unfortunately, the findings remain controversial and contradictory. There is insufficient data to determine if a cause and effect relationship exists. The National Council on Radiation Protection and Measurements (NCRP) in Bethesda, Maryland, set up a committee chaired by Dr. W. Ross Adey to review the possible health effects of ELF. The National Academy of Sciences committee, chaired by Dr. Charles Stevens, Salk Institute, California released a report in 1996 concluding no clear, convincing evidence exists to show that residential exposures to electric and magnetic fields (EMFs) are a threat to human health. The United Kingdom's National Radiological Protection Board (NRPB) established an Advisory Group on Non-Ionizing Radiation in 1990 to review the scientific evidence and determine the extent to which this evidence suggests possible health risks. The International Non-Ionizing Radiation Committee (INIRC) of the International Radiation Protection Association (IRPA) in cooperation with the Environmental Health Division of the World Health Organization (WHO) developed recommendations for 50/60 Hz electric and magnetic field exposure limits. At the 8th Congress of the IRPA in May 1992, the IRPA established a new independent scientific organization, the International Commission on Non-Ionizing Radiation Protection (ICNIRP) as a continuation of the former IRPA/INIRC. In April 1998, ICNIRP published guidelines for limiting electromagnetic field exposures for frequencies up to 300 GHz, including 50/60 Hz.

3 Energy Transduction in Cell

The mitochondria in cell contain the series of catalysts known as the respiratory chain collect transport reducing equivalents to react with oxygen for forming water. The reducing equivalents,-H or electrons, are made from oxidation of carbohydrate, fatty acids and amino acids. The cell system couples respiration to generate the high energy intermediate ATP, termed oxidative phosphorylation involved NADH, Succinate, Ubiquinol, Ferrocytochrome and ATP synthase five protein lipid enzyme complexes. Three different mechanisms including chemical coupling hypothesis, the conformational coupling hypothesis and the chemiosmotic hypothesis have been proposed to explain the energy transfer between electron transport and ATP synthesis (Menendez, 1996). Accordingly, electron transport along the respiratory chain can be the source of electromagnetic field to exert forces on the proton. Through these forces, electromagnetic coupling hypothesis is proposed to describing the protons are moved from the mitochondrial matrix to the exterior. In the mean time, the protons moved by the field toward the inner membrane pass through its protein components plays the role of proton channel. Just as if in a motor, ELF triggers the electrical energy, transfer of electrons along the respiratory chain, to produce proton translocation, which is mechanical energy, be used in cell system.

4 Stochastic Resonance

Several resonance theories, for instance, ion cryotron resonance (Liboff, 1991), parametric resonance were proposed to describe the biological effect caused by ELF fields. For the problem of synchronization of the relaxation time and the noise, it is hard to find the evidence of resonance in cell system. Nevertheless, because of ionic channels of cell membranes are elemental molecular switches for channel states, open or close, in spite of the small size of the channel, high resolution ion current detection allows us to watch electrical activity of a single ionic channel isolated within a micrometer patch of a cell membrane. The state-transition behavior between the open and close states of an ion channel characterizes many biological processes. The experimental results suggested that the potential oscillation could be driven by the oscillation in the intracellular concentrations of cyclic AMP and calcium in two-state model system (channel closing and opening). The signal-to-noise ratio increases when the state-transition rate of membrane channel influenced by the frequency response of the intracellular sensing system. An applied ELF (electric or magnetic field) field is an important factor to perturb the rate of state-transition of membrane channel in opening or closing. Jung (1993) has developed stochastic resonance driven process for multichannel systems and shown the optimal choice of parameters can lead to signal amplification. From the stochastic resonance theory, time average of the total current through a set of N channels can be calculated. To access the magnitude of amplification of the responding signal caused by external ELF field in cell, the membrane with N voltage gated channels and biochemical oscillator (calcium oscillation) must be considered. Because of this modulation, the external ELF field signal is transformed into a periodic component in the ion current across the membrane. As we have focused in the study on the primary mechanisms that a biological cell can use to amplify weak external influences, a system of identical ion channels embedded in a membrane and synchronously modulated can significantly amplify the original signal. The amplification of the signal to noise ratio is proportional to the square root of the number of channels modulated and inversely proportional to the square root of the sum of the average channel relaxation times.

5 Role of Gap Junctions

In cell, six connexin 43 subunits oligomerze in the Golgi apparatus into a connexon, called hemi channel and be transported to plasma membrane of the cell. Before pairing process, hemi channels are closed to avoid leakage of cellular contents and entry of extra-cellular materials. During the pairing of connexons and aggregation into plaques at the plasma membrane, connexin 43 is phosphorylated at least twice and connexons are attracted to those located on the adjacent cells. Two connexons join in an end-to-end manner to form a complete channel. The channels aggregate into large gap junction plaques open to connect two cells for cell-to-cell communication and is called gap junctional intracellular communication (GJIC), which can be modulated by environmental factors, such as drugs, X-ray, electromagnetic fields etc. Since the function of the GJIC, cultured cells coupled *in vitro* except the stem cells and cancer cells (Trosko, 1991; 2001). Furthermore, in basic signal transduction, we want to know what the gap junction growth regulatory signal within cells is. The cAMP is a very important gap junction signal molecule. This signal molecule can pass between cells through gap junction channels and affects cell growth. The levels of the cAMP can oscillate within the cell and generates oscillation in growth control. The amplitude of the oscillations would be dampened by GJIC. However, cAMP is not the only signal molecule that may affect GJIC. Increasing drug penetration and dispersal in tumors would increase GJIC. Gap junction channels in cell membrane can create a stochastic two-state system, opening or closing of the channels, to amplify weak signal caused by ELF fields.

6 Physics Correlation between GJIC and ELF Magnetic Field

The diffusive current equation for connexin 43 channels can be written as

$$< I > = \sum_{k=1}^{m} kP(k) \tag{1}$$

where probability $P(k)$ indicates total m channels is taken into account for opening k channels from all cell-to-cell communications on the surface of the cell mono layer. Therefore,

$$P(k) = \frac{m!}{k!(m \div k)!} (P^{o})^{k} (P^{c})^{m-k} \tag{2}$$

$$\frac{dP^{o}}{dt} = r^{c}P^{c} - r^{o}P^{o} \tag{3}$$

$$\frac{dP^{c}}{dt} = r^{o}P^{o} - r^{c}P^{c} \tag{4}$$

where r^{c} is the rate of changing from c-state to o-state and r^{o} is the rate of changing from o-state to c-state of the connexin 43 channels activating totally on the cells mono layer surface. Generally, r^{o}

does not have to be same with r^c since the life times of the o-state and c-state may vary. To clarify the physical meaning, we further assume the current through an open channel as i. The diffusive current caused by GJIC channels can be rewritten as

$$<I>= miP_s^o \quad (5)$$

where P_s^o is the modulated probability for o-state by external ELF field signal. According to theory of Jung (1993), the power spectral component originated from the signal is given by

$$S_k=\frac{(mi)^2}{2}\sum_{q=1}^{\infty}|C_q|\delta(\omega-q\omega_k) \quad (6)$$

C_q is the Fourier expansion coefficients of P_s^o.

In comparison with equations (3) and (6), the signal-to-noise ratio (SNR) of the characteristic frequency of the cell system can be depicted (Galvanovskis, 1997).

$$\mathrm{SNR}=\left|\frac{\text{signal amplitude}}{\text{background amplitude}}\right|^2 =A^2\left|\sqrt{m\frac{\pi}{\Delta\omega}\frac{r^o r^c}{(r^o+r^c)}}\right|^2 \quad (7)$$

where m is the number of channels, A is the amplitude and $\Delta\omega$ is the bandwidth of the external ELF field signal.

7 Specific Inhibit and Promote of GJIC

Many researchers have developed new techniques to inhibit or promote the expression of a target gene in culture cells and animals. ELF magnetic field treatment is one of the main factors that scientists are interested. We proposed a new way to separate the background and signal and revealed the evidence of existing stochastic resonance system buried in biological cells by GJIC essay under ELF magnetic fields. Specific inhibit of GJIC within mouse osteoblast cells in culture under the exposure of ELF magnetic field (Teng, 2002) depicted several possibilities, blockage of connexin gene expression, connexin gene knockout and transfection of defective connexin genes. Additionally, specific enhancement of GJIC within mouse osteoblast cells under the exposure of different doses of ELF magnetic field (Hart, 1996) can be transfected of functional connexin genes.

8 SNR Spectrum

By using of the probe of Gauss-meter, cells-induced magnetic fluctuation can be shown as

$$\{B_i^c\}=\{B_1^c, B_2^c, \cdots, B_{2000}^c\} \quad (8)$$

Equation (8) contains the cellular response signal of the reaction to the external ELF magnetic field (Teng, 2003). The sampling time was 0.0005 second. The probe was located at the distance 10^{-4} m perpendicularly to the center of single layer of the cell surface in culture dish. The Gauss-meter was manufactured by F. W. Bell Company (series of 9550) in Florida of USA. Oscilloscope was manufactured by Agilent Company (54621A) and can be used to convert $\{B_i^c\}$ to voltage sequence $\{V_i^c\}$ as

$$\{V_i^c\}=\{V_1^c, V_2^c, \cdots, V_{2000}^c\} \quad (9)$$

Matlab and Fortran programming were used for power density spectrum analysis of these voltage sequences. $\{B_i^m\}$ for the first control was taken 2000 times per second at the distance 10^{-4} m perpendicularly to the culture dish with only medium in it. Geo-field control $\{B_i^n\}$ was taken with the same sample rate at the distance 10^{-4} m perpendicular to the empty culture dish recording local geomagnetic field fluctuation. The corresponding $\{V_i^m\}$ and $\{V_i^n\}$ can be obtained by the same way as $\{V_i^c\}$ previously. Furthermore, trial signals,

$$\Omega_i(n)=A_i\times\sin(\omega_i n), 1\mathrm{Hz}\leqslant\omega_i\leqslant 60\mathrm{Hz},$$

where signal amplitude $A_i = F\times V_{\max}$, F is the adjustable fraction factor and $V_{\max}$ is such, $V_{\max}=\max(\{V_i^c\})$, as to the maximum value of the sequence $\{V_i^c\}$. By taking into consideration of signal amplitudes at F values, for instance, $F=0.7, 0.4$, and 0.03 respectively, the corresponding amplitudes would be

$$A_{0.7}=0.7\times V_{\max},$$
$$A_{0.4}=0.4\times V_{\max},$$
$$A_{0.03}=0.03\times V_{\max}$$

for a given trial signal at ELF ω_i (1 Hz$\leqslant\omega_i\leqslant$60 Hz). We computed autocorrelation function of $\{V_i^c\pm\Omega_i(n)\}$ and its Fourier transforms to obtain their corresponding signal-to-ratio ratio. The SNR spectrum, then, for $\{V_i^c\pm\Omega_i(n)\}$ at frequency could be simply a second order equation as

$$a\times(S_{\omega_i}(F))^2+b\times S_{\omega_i}(F)+c=0 \quad (10)$$

Accordingly, substituting the SNR at different F (different amplitudes at frequency) into the equation, we can solve unknowns a, b and c. If c-value is much bigger than zero, then, the SNR of the intrinsic signal peaked at ω_i is detected (Teng, 2005). The value of c is about 0.07.

In the paper by (Galvanovskis, 1997), the SNR could be written as

$$S\omega_i(F)=(F\times V_{\max})^2\times m\times Q\times\frac{2\pi}{\omega_i(\tau_o+\tau_c)}$$

when the life time of c-state and o-state equal to 10^{-6} second. Under optimal condition, the quality factor $Q=\frac{\omega_s}{\Delta\omega}$ approximately equals to 100 at 60

Hz with bandwidth $\Delta\omega = 0.6$ Hz and $F = 0.6$. The numbers of GJIC channels are taken 1000 per cell (Galvanovskisz, 1997). The SNR value is fit to the value calculated from SNR spectrum suggested by Teng (Teng, 2005).

9 Discussion

We examined the role of the ELF magnetic field in the biological cells system. It is hard to imagine how the forces of evolution could have led to biological mechanisms that respond to ELF magnetic field in cells, because low frequency fields have not been present during virtually all of evolution. So far, there is still no direct evidence that ELF magnetic field can affect the physiological endpoints within cells in culture. However, enough evidences have shown the biological effect that the cell responded to the interaction of externally applied ELF magnetic field (Kaiser, 1996). Since GJIC affiliates with many physiological endpoints, changing of the characteristics of GJIC causes the biological effect within cells in culture. A confluent cell culture in a vertical magnetic field could receive several different exposures. If the cells are not tightly jointed to each other and to the walls, then the system is homogeneous. Different cell types could experience very different induced current and electric field distributions under the same magnetic field exposure in similar dishes. Gap junctions joint the cells and are open to allow current paths connect the cell interiors. They produce the current paths throughout the interiors of the cells in the cell culture. Most of the time, two dimensional model is oversimplify the current density distribution that is actually experienced by cells in a culture dish. Value for the induced current density, in effect, is the top surface perpendicular to the applied magnetic field. When the magnetic field is applied along the surface of the cells, perpendicular to the normal direction of the surface, the homogeneous system would be inapplicable around the central planes, but it could be used away from the central region.

10 Conclusion

If a cell culture is exposed to a vertical magnetic field for a relatively long period, the exposure received by the cells may change during the course of the experiment. Trusko et al. (Trosko, 2001; Upham, 1998) originated the perfusion of the dye produced by the function of the GJIC in cell culture to study the cell physiology. Teng et al. first proposed the signal-to-noise SNR spectrum calculation of the near magnetic field in 2002. They have revealed the possibility of signal transduction pathways perturbed by ELF magnetic fields at different characteristic frequencies and the stochastic resonance frequencies within the cells. The result of a modulation of the GJIC within the cells responding to a specific strength and frequency of magnetic field can be as the signal that triggers signal transduction in cell.

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