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"Biological Windows": A Tribute to W. Ross Adey

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Summary. We often do not realize how fast the time is running. It is now more than a year since the sad news for the death of William Ross Adey came. With kind agreement of Prof. Kostarakis my presentation at the 3rd International Workshop "Biological Effects of Electromagnetic Fields" was dedicated to the memory of this remarkable scientist, dear colleague and friend. I would like that this paper will be a tribute to the life and scientific achievements of Dr. Ross Adey. It is astonishing that among all his contributions in the field of Bioelectromagnetics, Dr. Adey introduced the term "window".

Keywords: biological windows, electromagnetic fields, myosin phosphorylation

Introduction

For me, every time I talk or think about "Biological windows" I see the face of Dr. Adey. I should rewind the tape to 1975/1976. More likely, it was the time when the accumulation of knowledge allows the idea to be in the air. In a short period of several months, three papers were published by research teams, which did not know each other. In a paper from the laboratory of Ross Adey (Bawin and Ross Adey, 1976) the term "biological windows" was introduced, the paper of Markov *et al.* (1976) discussed "resonance levels", while the paper of Ukolova *et al.* (1975) focused on "stages". While the publication of Ross Adey's team was on "frequency windows", the other two groups actually considered the "amplitude windows", even giving the observation different names. Despite the difference in terms, the sense of the three papers was the same—the authors found evidence for the existence of specific amplitude or frequency values at which the response of the biological system was more pronounced than in the surrounding amplitude or frequency intervals.

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For a while the term "window" was not accepted, even more—was rejected by scientists who today are in favor of this opportunity. However in the last two decades the concept of "biological windows" attracted the attention of scientists and now is discussed and investigated as a plausible tool for explanation of observed biological responses to applied electromagnetic fields (EMF). Reviewing a number of studies of these responses, one may find the word "window" in different combinations such as "biological window", "amplitude window", "frequency window", and less often "time window". In many cases the use of the word "window" alone or in combination is not logically supported. Some authors apply these terms when they cannot find a reasonable explanation of the results obtained during the study. A series of studies today reports the existence of "window" effects or resonance-type responses of biological systems to the amplitude and/or frequency metrics of the electromagnetic field. However, there is a lack of well-established and commonly accepted methods for biophysical dosimetry. A reasonable approach to the "window" problem must include a systematic analysis of a range of parameters such as magnetic flux density (amplitude) or frequency. It appears unreasonable to claim the existence of a "window" based upon of only three or four data

points, sometimes pick without any biological or physical logics.

In search of biological and physical reasons for the existence of biological windows one might invoke an analogy with normal windows that allow light to penetrate inside a house: the glass windows allow only a fraction of the electromagnetic spectrum to penetrate the house and some other ranges as ultraviolet or infrared do not penetrate through the regular windows.

A similar approach to physical factors such as electromagnetic fields (EMF) or magnetic fields (MF) should also take into account the fact that a given range of values must be analyzed before the "window" concept will be discussed. More and more studies have suggested that for non-ionizing radiation cannot be applied the principles of ionizing radiation when the increase of the dose enhances the effects. The principle "More means better" does not work for EMF initiated bioeffects.

During evolution, living organisms developed specific mechanisms for perception of natural electric and magnetic fields. These mechanisms require specific combinations of physical parameters of the applied field to be detected by biological systems. In other words, the "windows" are means by which discrete MF/EMF are detected by biological systems. Depending on the level of structural organization these mechanisms of detection and response may be seen at different levels, for example at membrane, cellular or tissue levels. Sometimes the "windows" function via signal transduction cascade, brain activity or the central nervous system.

The sensitivity of the biological systems to weak MF has been described elsewhere (Markov, 1979, 1984, 1991, 1989; Ross Adey, 1977, 1986, 1989), mainly in respect to the dependence of bioeffects on the amplitude or the frequency of applied fields. It may be interesting to know that all early publications made a link between "windows" and information transfer (Markov, 1979,1984; Ross Adey, 1977, 1986, 1989). Later experiments with Ca^{2+} efflux suggested that the increase in the calcium efflux also could be attributed to "windows". Other examples of modulation, frequency, and amplitude "windows" may be found in immunological responses, cellular function, teratological effects, and beneficial effects in the promotion of bone and soft tissue healing in animals and humans. (Markov, 1989, 1994, 2002; Markov and Todorov, 1984; Pilla and Markov, 1994; Nindl et al., 2002; Bassett, 1994).

Discussing the theoretical feasibility of a radical-pair mechanism Eichwald and Walleczek (2000) affirmed that this model is capable of accounting for bioelectromagnetic phenomena which depend on the field frequency in a non-linear, resonance-like fashion (frequency window), field amplitude (amplitude window), the combination of appropriate AC and DC magnetic fields, and the biodynamic state of the field-exposed system.

The cyclotron resonance model (Liboff, 1985) claimed that special combinations of applied AC and DC exists for particular ions, such as calcium, potassium, and magnesium. Later on other "resonance" models were proposed by Lednev (1991) and Blanchard and Blackman (1994). All these models are based upon consideration of the importance of ionic charge to mass ratio in establishing the appropriate "resonance" frequency of the AC signal.

Amplitude windows

In a series of experiments designed to study a large range of magnetic flux density (up to 100 mT) static magnetic fields applied to biosystems with different levels of organization (microorganisms, plants, and animals) a specific maximum of the observed bioeffects was found when the magnetic flux density was 45 mT (Markov, 1991, 1989). These early results were interpreted in terms of the electronic structure of the atom in respect of the existence of "permitted" and "forbidden" energy levels for the electron, and for that reason was initially called the "resonance hypothesis". Any transition between "permitted" state requires a define energy and because of that, the system will remain in a stable state. When the transition ends to "forbidden" energy level, the system can exchange the energy with the environment and therefore the observed effects are smaller and quickly disappear at these "non-permitted" states (Markov, 1984, 1994). In many respects this idea is similar to the "window" effects suggested by Balwin, *et al*., 1975 and Ross Adey (1975) at very weak time varying EMF, and further confirmed by others (Blackman *et al.*, 1985).

Probably the most systematic study of the 10–20 mT range of static magnetic fields was done by Zukov (1999) who wrote "In general, within the range of 10–15 mT the therapeutic effect of magnetic fields is expressed to the greatest degree which made it unnecessary to try to generate high levels of magnetic field induction".

It is remarkable that most of the pioneering studies of amplitude and frequency "windows" were performed by exploring the participation of calcium ions in the investigated processes and reactions. Our attempts to estimate magnetic field effects at the subcellular level discussed further in this paper also involves an assay that depends on calcium ions. In particular, cell free calcium-calmodulin dependent myosin phosphorylation appears to be a plausible tool for investigating the "window" hypothesis.

Cell free calcium dependent myosin phosphorylation

This paper discusses the experimental evidence obtained with several different types of magnetic fields in respect of amplitude window. The responses of this myosin phosphorylation sensor to alteration of frequency are a subject of separate publication. It is shown that the cell-free myosin phosphorylation could be a sensitive "biological dosimeter" for analyzes the responses of biological systems to changes in the magnetic flux density. The main advantage of this sensor is the small volume of 100 μl that allows nearly perfect mapping of the expected biological response within the target volume. Note, that the volume of this "dosimeter" is smaller than the volume of most physical sensors of magnetic flux density.

The assay involves five basic components: myosin light chain (MLC), myosin light chain kinase (MLCK), calmodulin (CaM), calcium ions and ATP. While ATP provides the energy for phosphorylation, the key player appears to be calmodulin because of its possibility to bind calcium ions and therefore to regulate the efficiency of phosphorylation.

We pointed out (Markov and Pilla, 1994) that calmodulin is essential for most of the cellular activities. It has been reconfirmed recently that the calmodulin is the most important Ca^{2+} receptor (Liboff *et al.*, 2003). Further, calmodulin mediates calcium regulation of number of enzymes such as adenyl cyclases, kinases, and phosphatases that are important components of signal transduction systems implicated in cell cycle progression and cytoskeletal rearrangement (Cohen and Klee, 1988). During the last decade the properties of several membrane pumps were associated with calmodulin, too. Gromadzinska *et al.* (2001) considered calmodulin as the most important physiological activator of the calcium pump, which stimulates V_{max} of the enzyme and increases its affinity to calcium.

Calmodulin, the ubiquitous intracellular Ca^{2+} sensor is now recognized as integral component of the intact channel complex in the sarcoplasmic reticulum (Wu and Hamilton, 1988). It was shown that in presence of micromolar concentrations of calcium ions calmodulin binding is associated with R_yR1 inhibition, whereas at nanomolar concentration of calcium calmodulin binding is associated with channel activation (Fruen *et al.*, 2000). Therefore, the proper selection of the calmodulin concentration is vital for many biochemical and physiological processes, both inside the cell and at the membrane surface.

The early modulation of calcium signaling by EMF is suggested as a plausible candidate for activation of a number of biochemical reactions. It should be noted that calcium ions appear to be essential in the first steps of transductive coupling of exogenous physical signals to biological tissues and in the ensuing steps of calcium-dependent signaling to intracellular enzyme systems (Bull *et al.*, 1993). Calmodulin is capable of detecting micromolar concentrations of Ca^{2+} and once bound to calcium, calmodulin undertake a more helical conformation to become the active species (Markov and Pila, 1994a, 1994b).

Myosin phosphorylation

During the past decade evidence has accumulated and about 15 papers have been published to show that cell-free myosin phosphorylation can be a plausible method for assessing the effect of magnetic fields. Myosin phosphorylation as a tool to study biological effects initiated by magnetic fields was pioneered in the laboratory of Lednev (Shuvalova *et al.*, 1991) and further developed in my laboratory (Markov and Pila, 1994a, 1994b, 1997; Markov, 1993). Research shows the phosphorylation of myosin light chain kinase (MLCK) strongly depends on the specific calcium binding protein calmodulin as well as on concentration of calcium ions.

The magnetic field sensitivity of myosin phosphorylation has been studied by us for a period of 10 years, with extensive efforts to establish optimal conditions for successful execution of the assay (Markov and Pilla, 1994, 1994, 1997; Markov, 1993). The same fundamental process has been examined focusing on a wide range of parameters: static fields (Markov and Pilla, 1994, 1997), field shielding with

high-permeability materials (Markov *et al.*, 1993), extremely low frequency magnetic fields (Markov and Pilla, 1994, 1997), as well as chemical properties (Markov, *et al.* 1993). Over the years in my laboratory serious efforts were applied to make the execution of the assay more effective:

- The gel electrophoresis method for assessing results was replaced by counting Cherenkov emissions. This change facilitates the prompt receipt of final readings, minimizes experimental subjective errors and makes the process of counting experimenter-independent.
- A slight modification of the reaction procedure allowed depleting the calcium concentration which made it possible to run the assay for up to 10 min and to establish a time dependence curve. The choice of 5 minutes exposure corresponds to the midpoint of the linear part of the time dependence curve and it allows the optimization of calcium dependence of the myosin phosphorylation.

Why does the cell free myosin light chain phosphorylation method appear to be a plausible tool for biological dosimetry of magnetic fields? The myosin phosphorylation assay has two properties that make it particularly well suited for studying the spatial characteristics of a various MF:

- The exposed volume is relatively small (100 μl), providing relatively focused field and gradient distributions;
- The physical target ensemble is in solution and thus very likely isotropically distributed in space, allowing for some simplifying assumptions to describe the field.

This allows dosimetry to be performed in a very small volume, which makes such samples very sensitive detectors of the biological response within the target volume. A further advantage is that the expense of routine runs of the assay are minimal, especially if one takes into account that a skilled experimenter is capable of executing 10–12 tests per day. This enhances the application of the method for fast screening of various magnetic field configurations. One disadvantage of the method is the need of a reliable source for the reaction components, presumably from the same manufacturers.

Experimental

The myosin phosphorylation experiments were performed by using myosin light chains and myosin light chain kinase isolated from turkey gizzard, kindly donated by M. Ikebe (University of Massachusetts, USA). Calmodulin (CaM) as well as the rest of chemicals was purchased from Sigma. The exact composition of the working solutions and the protocol for running the essay were described elsewhere (Markov and Pilla, 1994b; Markov, 2004; Engstrom *et al.*, 2002).

The low ratio MLC/MLCK ratio was chosen to obtain linear time behavior in the minute range (Markov and Pilla, 1997). This provided reproducible enzyme activities and minimized pipetting time errors. The experiments were conducted within a specially designed plexiglass chamber which was maintained at (37.0 ± 0.1)°C by constant perfusion of water pre-warmed by passage through a Fisher Scientific model 900 heat exchanger. The Cherenkov emission method was applied for counting the myosin phosphorylation in each sample/vial using a Beckman model LS 6500 liquid scintillation counter that counted ^{32}P incorporated into myosin light chains. For each exposure conditions in the magnetic field 5–11 independent runs of the experiment were conducted. The internal repetition rate was 6 readings for each independent run.

Two exposure systems were used in this study. The first system consisted of two $15 \times 10 \times 2.5$ cm ceramic NdFeB magnets configured with the opposite magnetic pole facing each other. The surface magnetic flux density at the geometric center of magnets was 75 mT. One of the magnets was placed in a static position and the other magnet with the help of a custom designed and manufactured fixture can be moved toward the first one in order to achieve various magnetic flux densities for the sample. Such an arrangement allows magnetic flux densities from 0.1 to 55 mT. Myosin phosphorylation was evaluated with an increment of 5 mT in the range of 5–55 mT. The cross-section of the magnetic field sensor was approximately the size of the cross-section of the sample of investigation. A 4048 model handheld F.W. Bell Gauss/Tesla meter was used to measure the magnetic field in the space between magnets and due to the similarities in size with the 100 μL reaction volume of the sample the high accuracy of measurements was achieved. On the other hand, in support of the isotropy assumption, it has been shown experimentally that the changes in the myosin phosphorylation in

ambient range magnetic fields are independent of the direction of applied field (Markov *et al.*, 1993).

The second exposure system TEMF has been described elsewhere (Williams and Markov, 2001). This system represents an ellipsoidal coil with 21″ large diameter and 14″ small diameter capable of generating a pulsating half-sinewave magnetic field with a frequency of 120 pulses per second. In the experiments reported here, the magnetic flux density measured in the exposure chamber was 5–25 mT changing in increments of 5 mT.

Results and discussion

Figure 1 represents the systematic analysis of myosin phosphorylation in response to applied static magnetic fields in the range of 5–55 mT. The first experimental point at 0 mT is the control value, i.e. the value of myosin phosphorylation when the sample was placed in the temperature chamber, but no magnetic field was applied. The myosin phosphorylation values are calculated as the average of at least 7 runs with 6 internal repetitions, which means that each data point is calculated from at least 42 independent counting. Such large collection of data provides extremely small values for the standard error of mean. It is seen that for all exposure conditions the values of myosin phosphorylation are significantly higher than the control. Two sharp maximums at 15 mT and 45 mT were clearly present.

Figure 2 shows the myosin phosphorylation data collected when the reaction mixture was exposed to TEMF in the range of 5–25 mT. Here again, the first

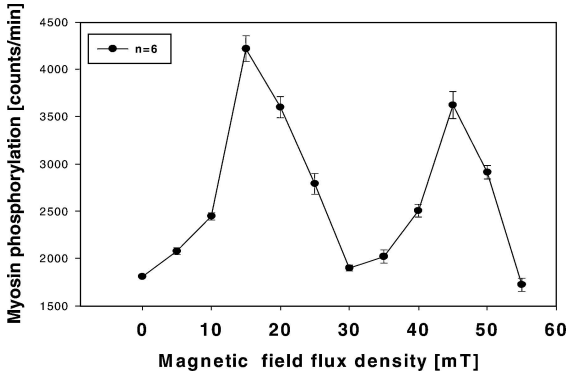

Figure 1. Myosin phosphorylation as function of applied static field.

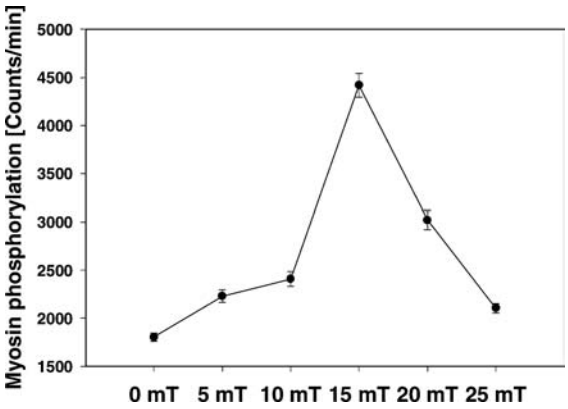

Figure 2. Myosin phosphorylation as function of applied pulsating magnetic field.

experimental point (at 0 mT) corresponds to the control. Actually, this is a sham control because the coil is supplied with rectified electric current allows to have sham control conditions when the coil is not connected to the current source. It is evident that under these experimental conditions the 15 mT sharp maximum is also present. Unfortunately, we were unable to create stronger magnetic fields in the TEMF device due to two reasons: (i) Higher fields require high current/voltage which was hard to generate in our laboratory and (ii) The higher the magnetic field, the greater the heat produced by the coil, thereby influencing the temperature conditions for the myosin phosphorylation. One must take into account that the biochemistry of the experiment is very sensitive to temperature conditions. Also, having an impedance of 12 ohms, the coil is supplied with about 11 A current (to create 25 mT magnetic field), which is about 1.5 kW of power.

If the response of the experimental mixture to both fields is compared (Figs. 1 and 2) one can see that for the whole range of magnetic flux density (up to 25 mT), a clearly demonstrated maximum of myosin phosphorylation is present for both static and pulsating magnetic fields at 15 mT magnetic flux density.

Studying the in vivo response of blood coagulation and anticoagulation system Markov and Todorov (1984) found out that from 10 different by amplitude magnetic fields, the maximal response was received at 15 mT AC (50 Hz) field for fibrinogen level and at 45 mT DC field for prothrombin time. What is the importance of these findings? First, it demonstrates the existence of two amplitude windows. Second, even the windows were well manifested, they related to two

different systems—coagulation and anticoagulation. Therefore, it may be of clinical importance: it is not enough to say "window", need to carefully investigate the response of a given system or organ before suggesting large scale therapeutic application

The 45 mT amplitude window has been also reported (Williams and Markov, 2001) when the production of proteins and nucleic acids in a culture of Candida *tropicalis* was exposed to magnetic fields in the range of 10–60 mT.

These very early observations, in parallel with the amplitude window suggested by Zukov (Bawin *et al*., 1975) are in line with observations presented in this paper that for static magnetic fields two amplitude windows could be considered—at 15 mT and 45 mT.

Having in mind that calmodulin is the principal receptor for calcium ions inside the cells, one may understand why the activation of calmodulin via calcium binding may alter the cellular physiology. The conformational changes which calmodulin undergoes under calcium binding in most cases result in activation of target proteins thus altering the metabolism and physiology of the cell. For example, the extracellular signals can activate a number of kinases in a defined sub region and many kinases even change their subcellular localization upon activation.

This reflects into spatial dynamics of signaling network and therefore is considered as key mechanism required for elaborate regulation of cellular behaviors (Markov and Pilla, 1994; Inagaki *et al.*, 2000). The results shown in this paper clearly demonstrate that this model system composed by materials, isolated from living tissues possesses a high sensitivity to applied magnetic fields.

Thus, the cell-free myosin phosphorylation assay could be a useful "biophysical dosimeter" that allows a quick screening and comparison of various signals. One should not forget that the response detected by the system is from a solution which models real muscle phosphorylation. What is also important, if a detail screening of the biological response was performed for a given therapeutic signal, it may be used for further improvement of the therapeutic use of the signal. On the other hand, the information may be obtained for any point of interest inside the target volume. I am close to the statement "The method may predict the efficiency of therapy that utilizes magnetic fields."

It is well accepted now that endogenous electromagnetic and magnetic fields are associated with many basic physiological processes ranging from ion binding and molecular conformation in the cell membrane to the macroscopic mechanical properties of tissues. Various receptors and transducers function by detecting, elaborating and transmitting electrical charges, currents and potentials as well as electromagnetic fields. The response of biological systems which are in a state different than their normal physiological one is stronger and this is another reason to suggest the use of magnetic/electromagnetic stimulation in many experimental and therapeutic conditions.

It is known now that EMF are more effective for systems out of equilibrium (due to disease or injury). It is also known that, for example, when fracture or wound appeared, an injury current originates. The best compensation for this current is electromagnetic compensation achieved by various low frequency (for fracture) and high frequency (for soft tissue injuries) devices. The art here is to identify the source of the problem (adequate diagnostics) and to select proper physical parameters of the field metrics (applied signal/treatment). This is exactly the area in which myosin phosphorylation assay and "window hypothesis" might be successfully applied. Virtually all identified steps in both "frequency and amplitude windows" are known to be calcium dependent (Adey, 1090) and this is another indication that the calcium dependent cell free myosin phosphorylation might be plausible tool in studying biological windows.

Such "windows of opportunities" are very successfully used in magnetic and electromagnetic field therapies. This is sometimes based upon systematic research but more often, selected magnetic/electromagnetic fields used for therapy are based upon the intuition of the inventor of the device and the medical staff. Why "selected"?—Because these values of the physical characteristics of the MF/EMF correspond to the "windows of opportunities". Living systems are ready to detect, absorb and utilize signals with specific characteristics and remain "silent" or unresponsive for the rest of the amplitude and/or frequency spectrum.

The early results, mentioned in the introduction and results obtained in this study, as well as their interpretation from the position of electronic structure of the atom in respect of existence of "permitted" and "forbidden" energy levels for the electron needs to be linked to the signal transduction mechanisms and to information exchange during the execution of important biological processes. The suggested existence of specific "permitted" levels which biosystems could attain under the action of a static magnetic fields having

defined amplitude more likely are related to the informational status of the system, manifested as defined conformational state of important proteins. When the amplitude/information is adequate to that necessary for the transition, the system may achieve a new "stationary" state at which it can remain for a certain period of time. Any other magnetic field (lower or stronger) would bring the system to transition to a state different from the "stationary" one, which appears to be unstable therefore the effects are lower and last for shorter period of time. To summarize, a number of studies have reported that biological systems developed specific amplitude windows for magnetic field. These "windows" should be considered as opportunity for a given biological system to react to exogenous magnetic field and assure the proper functioning of the system in general and selected part of it, in particular.

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