ELECTROMAGNETIC BIOLOGY AND MEDICINE

http://informahealthcare.com/ebm
ISSN: 1536-8378 (print), 1536-8386 (electronic)

Electromagn Biol Med, 2015; 34(2): 151–155
© 2015 Informa Healthcare USA, Inc. DOI: 10.3109/15368378.2015.1036076

informa healthcare

ORIGINAL ARTICLE

Diseases caused by defects of energy level and loss of coherence in living cells

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Abstract

Human and animal diseases are brought about by pathological alterations of production, composition, and conformation of macromolecules and structures in cells. Additional contributing factors include changes in physiological states caused by disturbances of energy supply, energy transduction, energy dissipation in moving or oscillating parts, and parasitic energy consumption. Disturbances of energy states may endanger existence of the system. The cell-mediated immunity (CMI) response of T lymphocytes correlating with their adherence properties was examined using antigen prepared from the serum of inbred laboratory mice strain C3H H^{2k} infected with lactate dehydrogenase elevating (LDH) virus. LDH virus is a parasite on the cellular energy system. Significant CMI response was elicited in T lymphocytes prepared from the blood of patients with cancer of different phenotypes, acute myocardial infarctions, schizophrenia, and recurrent spontaneous abortions in early pregnancy from unknown reasons. The CMI response is assumed to monitor transferred information about decreased levels of energy states and decoherence in the cells caused by mitochondrial malfunction, parasitic consumption, production of lactate, and possibly other disturbances. The LDH virus infection or similar pathological processes caused by different agents might be connected with the diseases and monitored by the examined CMI response. A large amount of mitoses with chromosome defects in aborted fetuses suggest increased mutability of genomes caused by defective energy states.

Keywords

Cell-mediated immunity response, LDH virus antigen, cancer, acute myocardial infarction, schizophrenia, spontaneous abortion from unknown reasons, pathological energy states

History

Received 3 February 2015
Accepted 27 March 2015
Published online 9 June 2015

Introduction

Living cells are built from micro- and nano-scale components at the boundary between the quantum and macroscopic worlds. Structures of proteins, deoxyribonucleic, and ribonucleic acids (DNA and RNA, respectively) are formed by folded fibers whose parts set up permanent electric dipoles and/or multipoles, hence their assemblies may result in a ferroelectric state. Proteins are folded structures of polypeptide chains organized in α helices and β sheets with coils of polypeptide chain providing links between them. The internal interactions within the polypeptide chain inside the protein depend on attractive dispersion forces, repulsion forces of non-bonded electron shells, electrostatic interactions, hydrogen bonding, hydrophilic and hydrophobic interactions with water molecules surrounding the protein, and salt bridges. Proteins may exist in different conformational substrates which are described by highly complex energy landscapes (Frauenfelder, 2005). Small globs of different types can cause conformational changes in proteins and changes in the amount of stored energy. Fröhlich (1980) formulated a hypothesis stating that nonlinear vibrations in the electric polar parts of macromolecules and biological structures result in the generation of endogenous electrodynamic/electromagnetic fields (EDM/EMG). These electromagnetic fields can be

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resonantly excited by energy sources and may also cause interactions between oscillating fields of different structures that can explain various long-range effects and specificity/selectivity of biological recognition. Resonant frequencies of microtubules are measured in the range below 1 GHz (Pokorný et al., 2011; Sahu et al., 2013; Vedruccio and Meessen, 2004) and also at about 20 THz ($\sim$700 cm^{-1}). If the energy supply to an electric polar system is sufficiently high, then the polar oscillations are coherent. Coherent oscillations are capable of providing biological functions such as force effects resulting in interactions, transport of molecules and particles, organization, synchronization, and information transfer and storage (Pokorný, 2012; Pokorný et al., 2013). The generated EDM/EMG is an essential component of the state far from thermodynamic equilibrium. The human brain is the material substrate for cognitive processes such as thinking, consciousness, instinct of self-preservation, and control function of the body. The activity of the brain depends on the electrodynamic quantum processes. Coherent oscillations of electric polar nonlinear macromolecules and structures excited by metabolic energy supply and generation of coherent EDM/EMG are assumed to be a necessary condition of life and consciousness emerging from it (Pokorný et al., 2013).

Microtubules are the structures generating EDM/EMG in eukaryotic cells. In the interphase, microtubules emanate from the centrosome in the cell center and some of them are connected to the structures at the plasma membrane. In the M phase, microtubules form a mitotic spindle managing separation of chromosomes. Several mechanisms are utilized for the energy supply to microtubules. The energy is supplied by the hydrolysis of guanosine triphosphate (GTP) to guanosine diphosphate (GDP) in β tubulin subunits following microtubule polymerization (Pokorný, 2004). The motion of motor proteins along microtubules is fuelled by ATP and microtubules function like a heat bath for energy losses (Pelling et al., 2004). These biochemical energy transduction processes are also very likely additionally driven by non-utilized energy liberated from mitochondria. Chemical reactions release photons and in this way may also supply energy to oscillations in the UV and visible wavelength regions. In the M phase, energy is supplied through a process called treadmilling – a continuous polymerization of microtubules in the center and depolymerization at the poles of the mitotic spindle.

A layer of ordered water (called clear or exclusion zone) is created around microtubules whose surfaces are electrostatically negatively charged (Amos, 1979). A strong electric field is also formed around mitochondria which are aligned around microtubules in the interphase. The intensity of the electric field is about 3.5 MV/m at the outer mitochondrial membrane and about 600 kV/m at a distance of about 2 μm from it (Tyner et al., 2007). Ordered water in the region of high intensity of the electric field forms a gel-like structure losing its viscous damping property (Ling, 2003; Pollack et al., 2006; Zheng et al., 2006). Water ordering lowered around dysfunctional mitochondria causes increased damping of the microtubule oscillations (Pokorný, 2012). Effects of energy disturbances on the initiation and proliferation of cancer origin have been extensively analyzed by Seyfried and Shelton (2010).

Some pathological states of living cells may be caused by disordered macromolecules and structures, over production, and/or reduction of expression of some functional molecules (enzymes, kinases, phosphatases, etc.). Other pathological states may be dependent on the disturbed metabolic energy processing, supply, decreased intensity of the static electric field around mitochondria in the cell, increased damping, and decreased power of microtubule oscillations and cellular EDM/EMG (Pokorný et al., 2013). Deficient energy states might cause perturbations of cellular morphology (and/or chemical reactions) but their mutual connections have not yet been studied. Direct measurement of energy states in cells was performed, for instance, by Lamprecht (1980). Energy-dependent pathological states were assumed to be inscribed in the immune system. One of the infection agents, which are parasitic on the energy system of the cell, is the lactate dehydrogenase elevating (LDH) virus. Essential information on the LDH virus is based on the experimental studies on mice (Brinton, 1994; Plagemann, 1996). Cell-mediated immunity (CMI) response to infection with the LDH virus was studied by Jandová et al. (1979, 2001, 2004, 2005, 2009a). Long-term experimental research disclosed that antigen prepared from the blood of mice infected with the LDH virus elicits CMI response of T lymphocytes of patients with cancer (Ca), acute myocardial infarction (AMI), schizophrenia (Sch), and women displaying recurrent spontaneous abortions in early pregnancy with no gynecologically examined reason and women who had given birth to stillborn babies or babies with inherited organ malformations on dissection (Abort).

Experiments with CMI response to LDH virus antigen was prepared and performed in the period from the early 1970s up to the end of the year 2000. The results are published in different journals and also in national (Czech) language which makes access to these studies difficult to non-Czech researchers. The main part was published by Jandová et al. (2001, 2009a,b). This text is an overview of the subject concerning disturbances of energy-dependent processes causing pathological states.

Materials and methods

Preparation of cells

T lymphocytes were separated from venous blood of healthy humans and Ca, AMI, Sch, and Abort patients. The cancer types included cancer of the cervix, endometrium, ovary, breast, lung, and melanoblastoma, and otorhinolaryngological cancers. Histopathological verification of the cancer diagnosis was provided. The abort group contains women displaying recurrent spontaneous abortions without any gynecologically apparent reason within the first 3 months of gravidity. The women had given birth to stillborn babies or babies with inherited organ malformations on dissection. The healthy group (HG) contains women in the first 3 months of physiological gravidity. The method of preparation of cells is comprehensively described by Jandová et al. (2001, 2009a). T lymphocytes of AMI, Sch, and Abort patients were prepared equally (Jandová et al., 2009b; Mejsnarová et al., 1981).

Preparation of the LDH virus antigen

The LDH virus antigen (A) is an immunologically functional fraction prepared from the serum of inbred laboratory mice

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strain C3H H^{2k} infected with the LDH virus. High-pressure gel chromatography was used to separate the active antigen fractions at 340 nm and the columns were filled by Separon Gema Glc® gel (Jandová et al., 1978). Description of the preparation methods of the antigen is given by Jandová et al. (2001) and some preparation details together with the gel chromatograms of the LDH virus antigen fractions have been published in article (Jandová et al., 2009a). The active part of the antigen was proved to be RNA (Jandová et al., 1995).

Measurement and evaluation

Experiments were performed double blind; the origin of blood and diagnoses were imparted after LAI assay evaluation. Diagnoses of gynecological and breast cancer patients were determined at the Department of Gynaecology and Obstetrics of the First Faculty of Medicine, Charles University in Prague. The otorhinolaryngological cancer patients were examined and treated at the Department of Otorhinolaryngology of the Third Faculty of Medicine, Charles University in Prague. Diagnoses of AMI and Sch were determined at the 3rd Department of Medicine and at the Department of Psychiatry of the First Faculty of Medicine, respectively, where the patients were treated. In individual experiments the groups of patients and of healthy controls were matched. To elicit the immune response of the T lymphocytes prepared according to the method described by Jandová et al. (2001), the antigen was mixed at a ratio of four parts of the T cell float to one part of the antigen. Antigen was mixed with the suspension just before 60 min sedimentation process started. T lymphocytes in the suspension sedimented in the test tubes from green Sial glass. The same exposure conditions were used for T cells from healthy humans and from Ca, AMI, Sch, and Abort patients. The temperature during experiments was kept in the range 22–28 °C.

The results are expressed as a relative number $M = 100\,m/m_0$ (in %) of non-adherent cell, where m_0 and m are the numbers of cells in suspension before and after sedimentation–adhesion process. The evaluation of statistical significance of differences between the number of non-adherent cells without and with antigen was carried out. The nonparametric Mann–Whitney test was used.

Association of the CMI response to the LDH virus antigen with pathology of the cellular energy production was an original contribution published in the article ''Diseases'' of the Cellular Energy System by Jandová et al. (1979). Therefore, the experimental investigations were undertaken on the basis of the hypothesis that CMI response to the LDH virus antigen reflects the presence of defects of energy levels and loss of coherence in the cell depending on disturbed oxidative mitochondrial function – a common ''denominator'' of a group of diseases.

Data in Table 1 and Figure 1 were measured in the period 1976–2000 (the total number of cases is above 8000).

Experimental results

Figure 1 and Table 1 display CMI responses expressed in a relative number of non-adherent T lymphocytes (M) without and with antigen of the four types of diseases: Ca, AMI (Jandová et al., 1979, 2009b), Sch (Jandová et al., 2009b), and Abort (Jandová et al., 1979; Mejsnarová et al., 1981). The preliminary studies on Sch patients were published by Dvořáková et al. (1985) and Zvolský et al. (1985). With no antigen, the CMI response in all four cases corresponds to healthy humans. Antigen shifts the CMI response above the M_H boundary into the disease region. Statistical significance of the differences between the M values of groups without and with antigen is 0.01 (Jandová et al., 2009b). (The similarity of adherence properties of T lymphocytes from Ca, AMI, Sch, and Abort patients supports the hypothesis regarding the

Table 1. The number of cases (N) of non-adherent T lymphocytes (M) prepared from blood of healthy humans (H) and patients with cancer (Ca), acute myocardial infarction (AMI; Jandová et al., 1979, 2009b), schizophrenia (Sch; Jandová et al., 2009b), and healthy women in the first three months of gravidity (HG), and patients displaying recurrent spontaneous abortions in early pregnancy from unknown reasons (Abort; Jandová et al., 1979; Mejsnarová et al., 1981), without antigen and with LDH virus antigen (A).

	N			
Healthy humans and cancer patients	Total number of cases	(%)		
		$M < M_H$	$M_H \le M \le M_C$	$M_C < M$
H	1721	100	0	0
H + A	1960	96.68	2.65	0.67
Ca	1100	99.55	0.45	0
Ca + A	2298	0.6	2.05	97.35
AMI	50	100	0	0
AMI + A	50	0	0	100
Sch	583	100	0	0
Sch + A	467	2.31	6.30	91.39
HG + A	45	97.7	0	2.3
Abort	45	100	0	0
Abort + A	45	2.3	0	97.7

M_C and M_H denote boundaries of the noise region between the M values of healthy humans and patients with the examined diseases (healthy and disease region), respectively.

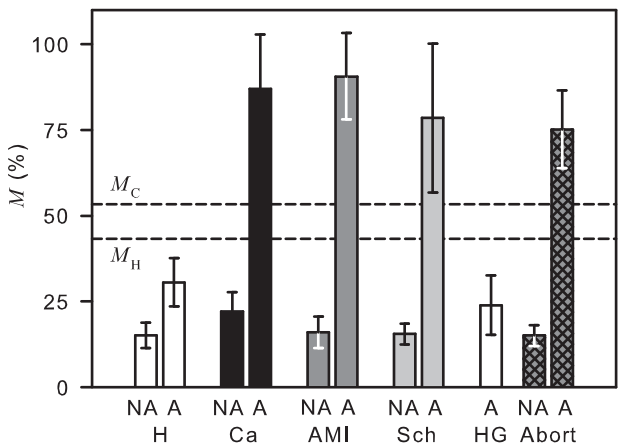


Figure 1. The mean values and the standard deviations of the relative number (M) of non-adherent T lymphocytes prepared from blood of healthy humans (H) and patients with cancer (Ca), acute myocardial infarction (AMI), schizophrenia (Sch), and healthy women in the first three months of gravidity (HG), and patients displaying recurrent spontaneous abortions in early pregnancy from unknown reasons (Abort), without antigen and with LDH virus antigen (A). The main part of the experimental data (H, Ca, AMI, and Sch) is published in Neural Network World (Jandová et al., 2009b) and used with a kind permission of the editor.

defects of energy level and loss of coherence in the cell but does not prove it.)

In the Abort group, analysis of chromosome configurations in the mitotic pictures disclosed more mitoses and the mitoses exhibited more cases of associated acrocentric chromosomes (Mejsnarová et al., 1981). These results confirm a connection between the CMI response to the LDH virus antigen and an increased mutability of the genome.

Statistical significance of the differences between *M* values of healthy humans and of patients with Ca, AMI, and Sch is published in the article of Jandová et al. (2009b). Statistical significance of the $HG + A \times Abort + A$, and $Abort \times Abort + A$ is at the level of 0.0001 evaluated by the Mann–Whitney and Wilcoxon test, respectively.

Discussion

LDH virus is a member of a new family of positive strand RNA viruses classified as genus Arterivirus. The virion possesses an envelope and a spherical nucleocapsid which are 50–60 nm in diameter (Li et al., 1998). A large amount of LDH enzymes (now classified as NAD 1.1.1.27 Oxidoreductase) in plasma manifest the infection with a LDH virus. The elevation of LDH levels is five- to 10-fold in comparison with non-infected cells but with no apparent harm to the host. LDH catalyses the conversion of NADH to NAD^+ and vice versa (Rowson and Mahy, 1975). Pyruvate, the final product of glycolysis and one of the input compounds for mitochondrial energy processing, is converted to lactate. Changes of the immune activity in the acute phase of infection with LDH virus are given in the article (Leclercq et al., 1978).

About 90 years ago, Warburg observed a substantial reduction of oxidative metabolism in cancers (Warburg, 1956; Warburg et al., 1924) and linked it to causes of cancer. The pyruvate transfer to mitochondria is inhibited in cancer cells (the Warburg effect), or in fibroblasts associated with cancer cells (the reverse Warburg effect) described by Pavlides et al. (2009). Interest in mitochondrial defects in cancers was re-established about 10 years ago as the mitochondrial dysfunction was assumed to be a critical distinguishing aspect of cancers (Carew and Huang, 2002; Cuezwa et al., 2002; Chatterjee et al., 2006). Bonnet et al. (2007) restored mitochondrial normal function and healthy state of cancer cells. Compared with normal cells, in cancer cells (the Warburg effect) or fibroblasts (the reverse Warburg effect), the zones of strong static electric field formed around the dysfunctional mitochondria are diminished, the gel-like structure of the ordered water disturbed, and the Fröhlich electrically polar oscillations in microtubules damped. The CMI response to antigen seems to be inscribed into the T lymphocyte ''memory'' in and/or between the links of oncogene mutation and mitochondrial dysfunction along the cancer transformation pathway. The CMI response might monitor defects of energy level and coherence in the cells and may represent transferred information about mitochondrial dysfunction (Jandová et al., 2009b) and/or parasitic energy consumption. We believe that mitochondrial dysfunction is a gateway to malignancy.

Myocardial mitochondrial dysfunction may be involved in the pathogenesis of cardiac contractile dysfunction (Burger and Abel, 2008). Multiple defects in mitochondria are central and essential to heart failure progression (Marin–Garcia and Goldenthal, 2008). Mitochondria have been implicated in various cardiac pathologies, including ischemia–reperfusion injury, cardiomyopathy, and congestive heart failure (Gustafsson and Gotlieb, 2008).

In the Sch patients, the information has to be transferred across the blood–brain barrier to the immune system. Susceptibility gene for schizophrenia modulates mitochondrial function promoting fragmentation in neurons (Kvajo et al., 2008). Evidence suggests dysfunction in mitochondria (Shao et al., 2008). Due to low energy supply or damping of microtubule electrical oscillations, the generated EDM/EMG might be excited below a required coherence level for a complete function of the brain as an integral whole.

The generally accepted view limited the role of the LDH virus solely to mice pathogens. It should be admitted that the LDH virus infection might be associated with the diseases examined in this study or that similar pathological processes caused by different agents (mainly viruses) are monitored by the examined CMI response. Disturbances of metabolic energy processing, the static electric field around mitochondria, electrically polar oscillations, and EDM/EMG cannot be neglected in assessment of pathological states in biology.

Conclusion

The LDH virus antigen elicits non-adherence response of T lymphocytes taken from cancer patients, patients with acute myocardial infarction, schizophrenia, and women with recurrent spontaneous abortions in early pregnancy from unknown reasons and women who had given birth to stillborn babies or babies with inherited organ malformations on dissection. The RNA of the LDH virus is a parasite of the cellular energy system and LDH enzymes may disturb pyruvate transfer to mitochondria. The cell-mediated immunity response of the studied diseases seems to monitor transferred information on insufficient energy and/or coherence level in the cells, in particular involving coherent electric polar vibrations. We conclude that the mechanisms of the diseases studied in this report are intimately involved in pathological changes of fundamental processes underlying the living state.

Acknowledgment

The authors pay tribute to the late Professor Emilio Del Giudice for his pioneering contributions to the application of quantum electrodynamics to biology, for his scientific support of the Prague symposia on biophysical aspects of cancer since 1987, and for his great humanistic attitude to science and life. We also keep alive the memory and names of our colleagues Josef Koštíř, Karel Heyberger, Tomáš Hraba, Jiří Čoupek, Blanka Mejsnarová, and Oto Wichterle who made the greatest contribution to the development of materials and facilities necessary for antigen purification.

Declaration of interest

The authors report that they have no conflicts of interest.

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