Bioelectromagnetics 37:1–13 (2016)

Review

Why Magnetic and Electromagnetic Effects in Biology Are Irreproducible and Contradictory?

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The main source of magnetic and electromagnetic effects in biological systems is now generally accepted and demonstrated in this paper to be radical pair mechanism which implies pairwise generation of radicals in biochemical reactions. This mechanism was convincingly established for enzymatic adenosine triphosphate (ATP) and desoxynucleic acid (DNA) synthesis by using catalyzing metal ions with magnetic nuclei (^{25}Mg, ^{43}Ca, ^{67}Zn) and supported by magnetic field effects on these reactions. The mechanism, is shown to function in medicine as a medical remedy or technology (trans-cranial magnetic stimulation, nuclear magnetic control of the ATP synthesis in heart muscle, the killing of cancer cells by suppression of DNA synthesis). However, the majority of magnetic effects in biology remain to be irreproducible, contradictory, and enigmatic. Three sources of such a state are shown in this paper to be: the presence of paramagnetic metal ions as a component of enzymatic site or as an impurity in an uncontrollable amount; the property of the radical pair mechanism to function at a rather high concentration of catalyzing metal ions, when at least two ions enter into the catalytic site; and the kinetic restrictions, which imply compatibility of chemical and spin dynamics in radical pair. It is important to keep in mind these factors to properly understand and predict magnetic effects in magneto-biology and biology itself and deliberately use them in medicine. Bioelectromagnetics. 37:1–13, 2016. © 2015 Wiley Periodicals, Inc.

Key words: magnetic effects; magneto-biology; ATP synthesis; DNA synthesis; magnetic isotopes; radical pair mechanism

INTRODUCTION

There are many factors controlling biochemical reactions, however the most intriguing is the magnetic field. The ability to respond to magnetic fields is ubiquitous and universal among the five kingdoms of organisms. Magneto-biology, as well as electromagnetic biology, is a field of knowledge, which considers the influence of magnetic fields, both permanent and alternating, on the biological systems at all levels: molecular, cellular, and whole organism. No doubt that magnetic field does affect the human health; this is a key factor stimulating both scientific and social interest in magneto-biology. There are also other factors: the influence of the electromagnetic fields (EMF) of cell phones and high-voltage power transmission lines; magneto-reception, orientation, and navigation of migrating animals; the relationship between the human health and the solar magnetic activity, etc. Magneto-biology has gone beyond the frame of a science and has become a social problem. Magnetic and electromagnetic effects are a means to elucidate in vivo biochemistry, to enhance adenosine triphosphate (ATP) synthesis in cells, to control enzymatic desoxynucleic acid (DNA) synthesis in cell proliferation, and to stimulate cortex activity. Moreover, magneto-biology is a key to better understanding biology itself and it is vitally important in medicine.

Grant sponsor: Russian National Scientific Fund; grant number: 14-23-00018.

Conflicts of interest: None.

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Received for review 22 May 2015; Accepted 1 December 2015

DOI: 10.1002/bem.21947
Published online in Wiley Online Library (wileyonlinelibrary.com).

However, in magneto-biology there are many irreproducible and contradictory observations, which remain enigmatic. The purpose of the paper is to analyze the reliable sources of magnetic effects, to elucidate the reasons of their inconsistency, to show how and at what conditions magnetic effects exhibit themselves and how they may be controlled, switched on or off.

Magnetic Control in Chemistry and Biochemistry

Chemistry is not the whole life but the life is controlled by chemistry. Chemistry is generally supposed to be reigned by Coulomb energy. However, asides of energy there is another, much more strict and powerful controlling factor, angular momentum. As a scientific kingdom chemistry is ruled by king and queen, by angular momentum and energy. In contrast to energy forbiddance, which is not very strict, because there exists a tunneling, that is, penetration through the energy barrier (at least for the hydrogen atoms), the prohibition on the angular momentum is absolutely strict. Conservation of angular momentum (electron spin) is a fundamental and universal principle: all chemical reactions are spin selective; they are allowed only for those spin states of reactants whose total spin is identical to that of products but they are forbidden if they need to change spin.

Magnetic interactions are universal means to overcome spin prohibition of processes in chemistry and biochemistry, they are means to control, to accelerate chemical and biochemical reactions by magnetic fields, both external—permanent or oscillating, and internal magnetic fields of magnetic nuclei. Magnetic energy is by many orders of magnitude less than the Coulomb energy; it may be certainly ignored in the total chemical energy balance; but contributing next to nothing in chemical energy, being negligibly small, magnetic interactions are the only ones able to change electron spin of reactants and switch over the reaction between spin-allowed and spin-prohibited channels, controlling the reaction pathways and chemical reactivity. The scheme below (Fig. 1) illustrates the essence of magnetic control. A simple example is a two-spin system, a radical pair [R˙˙R] which exists in the two spin states: singlet (total electron spin is zero) or triplet (spin is unity). Being chemically identical these states are absolutely different in chemical reactivity: only singlet pair is able to recombine into the molecule R-R. Three magnetic interactions, which produce triplet-singlet spin conversion, transform triplet pair, in which recombination is spin forbidden, into the reactive singlet pair.

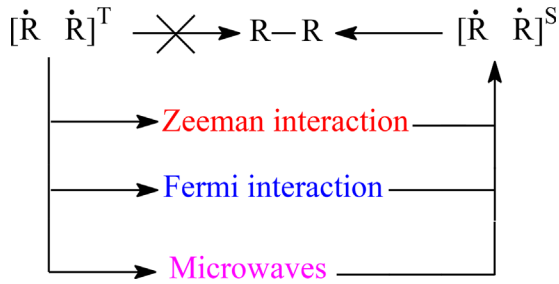

Fig. 1. Magnetic interactions, which produce triplet-singlet spin conversion, responsible for the magnetic and electromagnetic effects in chemistry and biochemistry [Buchachenko, 2015].

These three interactions catalyze chemical and biochemical reactions and induce magnetic and electromagnetic effects. As will be shown later they manifest themselves in isolated mitochondria and in the whole living organisms stimulating ATP synthesis and eliminating ATP deficiency at cardiac diseases. They affect enzymatic DNA synthesis and killing the cancer cells, they control trans-cranial magnetic stimulation against cognitive deceases. They exhibit themselves even in polymerase chain reaction, the most popular reaction in genetics, and may be used to control it. Magnetic effects are the means to monitor ecologically important processes in soils, natural waters, and nutrients by detection of magnetic isotope effects. Magnetic catalysis is a controllable phenomenon; it may be switched on or off by using magnetic isotopes or paramagnetic ions respectively; it seems to be the most reasonable and significant factor in magneto-biology for explaining numerous and frequently enigmatic biomedical effects of electromagnetic fields, for the search of new magnetic effects in biology and medicine. This paper shows how magnetic catalysis functions and what important phenomena in biochemistry are induced by its functioning.

Physical Mechanisms in Magneto-Biology

There are two types of physical mechanisms that can operate in magneto-biology and give rise to magnetic and electromagnetic effects—macroscopic and molecular. The former can be manifested in processes involving particles (micro-crystals, mitochondria) or structures (membranes). If these particles have large anisotropy of magnetic susceptibility, then the energy of their magnetic interaction with magnetic field can be comparable with the thermal energy kT and in this case these particles or structures can be oriented or deformed by magnetic forces (similarly to liquid crystals). As a result, the properties and the chemical reactivity of deformed particles (e.g., membranes) may change. However, magnetic effects of

this type can be significant only in strong and durable magnetic fields, that is, under exotic conditions. Therefore, the contribution of macroscopic mechanisms to magneto-biology, including magnetic resonance imaging, can be certainly ignored.

Another physical model implies that the alternating EMF interacts only with moving charges giving rise to the known Lorentz forces $F = (e/c)$ [v B], or $F = (e/c)\ vB\ Sin\ \alpha$, where v and B are the charge velocity and magnetic field intensity vectors and α is the angle between them. However, dielectric media lack moving charges like those existing in metals, in plasma, or in semiconductors. Therefore, the Lorentz magnetic forces seem to be of minor importance in biological media, and the model does not provide a magneto-reception mechanism. These arguments are not in favor of macroscopic mechanisms and urge to appeal to molecular mechanisms.

Radical Pair Mechanism as a Key to Magneto-Biology

There are many indications that the magneto-biology is mostly based on chemistry. It is often naively thought that the appearance of paramagnetic particles in biochemical processes is a sufficient condition for the magneto-biological effects to appear. But magnetic field can only align electron spin; microwave irradiation can even change spin orientation. However, chemistry (and, naturally, biochemistry) does not depend on the spin orientation of a single radical. Being the receiver for microwaves, a single spin can ensure neither magnetic, nor electromagnetic biochemical effects.

Now it is certainly established that the molecular radical pair paradigm is the most physically reliable basis to understand and deliberately use biochemical magnetic effects in medicine [Buchachenko, 2009; Messiha et al., 2014]. Many biochemical processes (such as photosynthesis or energy pumping of mitochondria) are accompanied by generation or participation of paramagnetic species (radicals or radical ions) but only those generating radicals or ion-radicals in pairs, are magnetic field-dependent and magneto-sensitive because each partner of the pair has unpaired, not cancelled, electron spin (angular momentum), and magnetic moment.

Radical pair mechanism (RPM) implies that two radicals are produced simultaneously (e.g., by electron transfer); unpaired electron spins of the radicals may be arranged parallel (it is triplet spin state) or anti-parallel (singlet spin state). It was mentioned above (see previous Section) that spin states of the pair, singlet and triplet, being identical in structure, are different in chemical reactivity: in triplet state the reactions are forbidden. The population of the states is controlled by magnetic fields, both external ones and internal fields of magnetic nuclei. Magnetic interactions induce singlet-triplet spin conversion and switch over the reaction between spin-allowed (singlet) and spin-prohibited (triplet) channels, controlling the reaction pathways, and chemical reactivity. Namely, radical pair is a spin nano-reactor that functions as a magnetic field receiver for both constant and oscillating fields; it is a general chemical key to magneto- and ELF-biology. Moreover, radical pair mechanism is reliably established in chemistry; it certainly functions also in biochemical reactions because life on the molecular level is controlled by chemistry [Steiner and Ulrich, 1989; Buchachenko, 2009; Hore, 2012].

The question may appear why radical pair mechanism appeals to only spin behavior and ignores orbital angular momentum, which may also control reaction. Indeed, orbital angular momentum operates in gaseous reactions but in condense media (i.e., in biology) orbital momentum is quenched, averaged by molecular motion. In contrast to orbital momentum, which is strongly tied with molecular orientation, spin is weakly bound with molecular orientation and weakly depends on the molecular motion and surrounding. For this reason spin states are controlled almost exclusively by magnetic forces. It is indeed a physical foundation of the radical pair mechanism and its efficiency in magneto-biology.

Magneto-Biology: Why it Is an Intriguing Subject?

There is a very large body of contradictory and non-reproducible magneto-biological observations but no explanations and reliable understanding. It is a discouraging circumstance for magneto-biology. As noted by Grosberg [2003], the whole magneto-biology demonstrates a "sad picture of contradictory and non-reproducible experiments," its observations appear very often to be mysterious, ambiguous, non-reproducible, and contradictory. No understanding means that there is no way to deliberately control magnetic field-sensitive processes in biology and medicine. And this is not due to the lack of diligence or knowledge of the observers; it is a state of science. Below only some examples of such contradictions are present.

A 2–6 G (50 Hz) alternating field changes the rate of *lac* transcription in *E.coli*: a 3 G magnetic field suppresses the transcription but a 5.5 G field again stimulates it [Aarholt et al., 1982]. Magnetic field of 14100 G increases the transcription rate of 21 genes but decreases this rate for 44 other genes

in *Shevanella oneidensis* [Gao et al., 2005]. For *E. coli* alone, out of the 18 studies undertaken just to detect magnetic field effects, one-third of the works report effects of one sign, one-third report effects of the opposite sign, and in the rest of studies no effect was detected at all [Pazur et al., 2007]. Nearly the same is true for the studies of enzymes, bacteria, and fungi. It relates to both permanent and oscillating fields.

Epidemiological studies have revealed that EMF is related with some cancers like leukemia and melanoma [Zaporozhan and Ponomarenko, 2010]. On the other hand, cell level studies have shown that EMF have no direct mutagenic effects on DNA but have a modifying effect on the metabolism and normal operation [Yalçın and Erdem, 2012]. In some studies of the in vivo effects of electrical and magnetic fields it was reported that the DNA is not affected negatively [Williams et al., 2006]. However, EMF at the level of 1–4 G on the DNA replication was shown to inhibit the DNA synthesis in Jurkat cells [Nindl et al., 1997].

Jones et al. [2006, 2007] failed to reproduce sizeable magnetic field effects for two enzyme reactions in vitro: the conversion of ethanolamine to acetaldehyde by the bacterial enzyme ethanolamine ammonia lyase [Harkins and Grissom, 1994] and the reduction of hydrogen peroxide by horseradish peroxidase [Taraban et al., 1997]. In both cases, the changes in catalytic rates reported in the original articles were large; nevertheless, they were not reproduced. The third case was an unsuccessful attempt by Harris et al. [2009] to replicate the observation that the growth of *Arabidopsis thaliana* seedlings was significantly affected by magnetic fields of 5 G [Jones et al., 2006].

Magnetic field sensitivity of a number of flavoenzymes, as well as of model system, involving stepwise reduction of a flavin analogue by a nicotinamide analogue—a reaction is known to proceed via a radical pair—was investigated [Messiha et al., 2014]. Magnetic field sensitivity was not observed; it was concluded that thermally driven, flavoenzyme catalyzed reactions are unlikely to be influenced by exposure to external magnetic fields. In the oxidation of linoleic acid, catalyzed by soybean lipoxygenase, neither magnetic field effect [Hwang and Grissom, 1994], nor ^{17}O magnetic isotope effect [Glickman et al., 1997] were detected, although this reaction is certainly known to proceed through the radical pairs; the latter demonstrates significant ^{17}O magnetic isotope effect in non-enzymatic reactions [Buchachenko, 2009].

The numerous examples of the inconsistencies and contradictions in the magneto-biological effects are presented in excellent and exhaustive reviews (see, for instance [Grissom, 1995; Galland et al., 2005; Pazur et al., 2007; Rodgers, 2009; Ghodbane et al., 2013; Vijayalaxmi and Scarfi, 2014]) and in the recent monograph [Buchachenko, 2015]. Such an ambiguous state discredits magneto-biology as a science and provokes distrust to its findings. The majority of those who are involved in studies of magneto-biological effects are perfectly aware that the blind and vain search, the route from hypothesis to proof, that is, to understanding, is faced with a barrier: the lack of molecular mechanisms to form the foundation for the chemistry of biologically significant magnetic field-dependent processes. However, there are three fields in magneto-biology where magnetic effects are firmly established; moreover, they are functioning in medicine as the medical remedies or technologies and may be understood in terms of molecular mechanisms. All of them are directly related to enzymatic phosphorylation.

Phosphorylation as a Key Reaction in Biochemistry

An overwhelming majority of the biochemical reactions are those of phosphorylation, that is, the transfer of phosphate group PO_4^{3-}, individually or with attached molecular fragment (nucleotide, for instance). Phosphorylation plays a crucial role in the functioning of living organisms. Cell proliferation, gene expression, energy supply, the growth, and reproduction of living organisms, the functioning of immune, mental and cell communication systems, physical mechanics and muscular contraction, metabolism—all these processes occur by phosphorylation of ADP, DNA, proteins, and many other molecules in cells. Phosphorylation was traditionally thought to be a molecular, a nucleophilic reaction; no paramagnetic species, no radicals were suspected to be formed in the reaction. Recently this claim was corrected: by using isotopic technologies radical pair mechanism of the phosphorylation in the three processes of paramount importance, three cornerstones of the life chemistry—enzymatic ATP synthesis, DNA replication, and enzymatic phosphorylation of proteins—was discovered [Buchachenko, 2009; Buchachenko et al., 2012; Buchachenko and Kouznetsov, 2014]. The functioning of the radical and, hence, magnetic field dependent mechanism in the phosphorylation constitutes a physically clear molecular concept as a key to understanding numerous enigmatic

phenomena in magneto-biology and magneto-medicine. Below it will be shown how this mechanism functions.

Trans-Cranial Magnetic Stimulation

A new technology of brain and cortex neuron stimulation by oscillating magnetic fields is being rapidly introduced into medicine, in particular, into neurophysiology; the magnetic fields are supplied to patients' head by means of magnetic coils fed by alternating current [Bailey et al., 2001; Yamaguchi-Sekino et al., 2011]. The alternating magnetic field, generated by the coils, penetrates through the cranial bones (this gave rise to the name "trans-cranial") and acts on the neurons. This technology brings about two significant questions: (i) whether or not biological subjects (in particular, neurons) are able to perceive the magnetic field and (ii) whether or not the magnetic reception is significant for the functioning of these subjects. Direct medical experience answers yes to both questions: it is possible to treat cognitive disorders and neurological diseases (stroke consequences, epilepsy, Parkinson's disease, pain syndromes, paralysis, and schizophrenia). Moreover, there is reliable evidence that trans-cranial magnetic stimulation (TMS) performs molecular transformations in the cortex, which are remembered and retained for long (weeks and months) after the TMS operation has been switched off. This long-term effect is a great advantage of TMS as a medical technology. However, it raises the question: what are the molecular mechanisms of the effect?

Most of TMS works pursue purely medical, therapeutic goals. The studies performed at the molecular, biochemical level can be classified into two groups. One group deals with analysis of the effect of gene polymorphism on the sensitivity to TMS; in other words, they try to find out what genes act as TMS receivers and what gene is TMS-insensitive [Zanardi et al., 2007; Cheeran et al., 2008; Fedi et al., 2008]. The second group of works deals directly with the TMS-induced changes in genome; they address the changes in the enzyme activity and gene expression stimulated by TMS. In the TMS recurrent pulse mode (1–10 Hz), enhanced expression of genes, translating the *c-Fos* and *zif268* proteins in the rat cortex, was demonstrated [Selcen et al., 2008]. At low-frequency (0.1 Hz) but high-amplitude ($5000–10^5$ G) TMS, significant effects in the proliferation and differentiation of the neural stem cells in the cortex of neonatal rats were detected [Meng et al., 2009], the most pronounced effect being attained in the 40000 G field.

Numerous works of this type certainly demonstrate that the TMS magnetic signals stimulate gene expression and production of some enzyme proteins—and this accounts for the long-term therapeutic effect of TMS. It was revealed [Feng et al., 2008] that repetitive transcranial magnetic stimulation (rTMS) induces significant increase of ATP content and MAP-2 expression in the left brain, following ischemic insult, and different rTMS parameters had different effects on the ATP level and the MAP-2 expression in the left striatum. It is concluded that rTMS may become a potential adjunctive therapy for ischemic cerebrovascular disease. The rTMS was shown to induce neuronal long-term potentiation or depression [Wang et al., 2011]. Neuro-protective effect of high-frequency rTMS in a rat model of transient cerebral ischemia was investigated using positron emission tomography [Gao et al., 2010]; rTMS therapy was shown to increase glucose metabolism and inhibit apoptosis in the ischemic hemisphere. TMS was shown to modulate astroglial gene expression, inducing the first stage of a reactive response [Meng et al., 1997]. Numerous works of such type (for review see [Huerta and Volpe, 2009]) prompt with confidence that magnetic TMS signals stimulate gene expression and production of various enzymes; namely these magnetically induced effects are responsible for the long-termed medical function of TMS.

One may consider two mechanisms for the origin of TMS: first, the intracranial electric fields and currents induced by oscillating electric component; second, the magnetic field, both permanent and oscillating. The former are supposed to generate Lorentz forces; however, this mechanism as shown above (see Section "Physical mechanisms in magneto-biology") is hardly dominating as a source of transcranial magnetic stimulation. The latter seems to be the most important; it unambiguously exhibits itself via magnetic control of enzymatic DNA synthesis and polymerase chain reaction (see below). DNA synthesis is a direct means to modify genes in the TMS technology and produce medical effects.

Magnetic Control of the ATP Synthesis

Magnetic field effects on the enzymatic ATP synthesis (Fig. 2) were detected for the creatine kinase in vitro [Buchachenko and Kouznetsov, 2008a]. Different dependence of the rates for kinases with $^{24}Mg^{2+}$ and with $^{25}Mg^{2+}$, that is, with ions having nonmagnetic and magnetic nuclei ^{24}Mg and ^{25}Mg respectively, are due to the different contributions of magnetic interactions: in the former case only Zeeman interaction induces singlet-triplet conversion, although

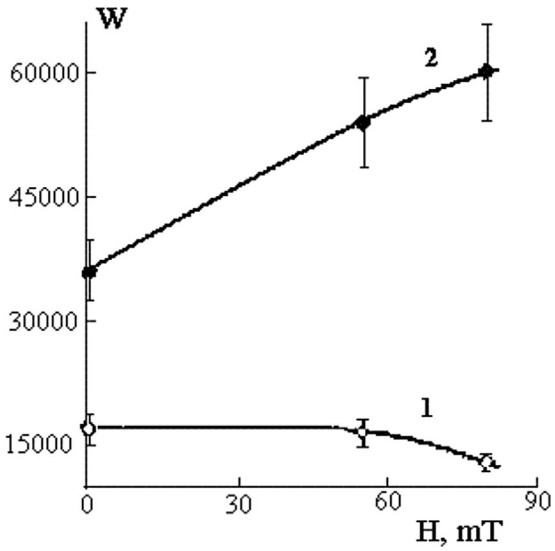

Fig. 2. The rate **w** of ATP synthesis by creatine kinase loaded with non-magnetic isotope ions $^{24}Mg^{2+}$ (1) and with magnetic isotope ions $^{25}Mg^{2+}$ (2) as a function of the magnetic field. [Buchachenko et al., 2008a].

in the latter case both interactions, Zeeman and Fermi, function.

Magnetic field effect is induced by difference of Zeeman energies $\Delta g\beta H$ of the radical pair partners, where Δg is a difference of the g-factors of partners. For the pair with ^{24}Mg, both $\Delta g\beta H$ and Fermi interaction with ^{31}P nuclei are small and magnetic field effect is also small, so that the curve 1 is almost flat. For the pair with ^{25}Mg, Fermi interaction with ^{25}Mg is significant; interference with Zeeman coupling removes degeneration of the electron-nuclear levels and results to the curve 2 (for details see [Buchachenko and Kouznetsov, 2008a]).

Magnetic fields of the magnetic nuclei produce even more powerful effects. In experiments with creatine kinases (CK), which were loaded with isotope ions $^{24}Mg^{2+}$, $^{25}Mg^{2+}$, and $^{26}Mg^{2+}$ it was shown that enzymatic activity of kinases with nonmagnetic nuclei ^{24}Mg and ^{26}Mg were identical, although kinase with magnetic nuclei ^{25}Mg was almost twice more efficient (it is seen on Fig. 2 in zero magnetic field). It is an evidence that magnetic isotope effect does occur in ATP synthesis, although classical, mass-dependent effect may be ignored [Buchachenko et al., 2005a,b; 2008a,b,c; 2009; 2010a,b]. Similar effect was detected in CK loaded with isotopic ions $^{40}Ca^{2+}$ (nonmagnetic nucleus ^{40}Ca) and $^{43}Ca^{2+}$ (magnetic nucleus ^{43}Ca) [Buchachenko et al., 2011]. Enzymatic activity of mitochondrial CK with $^{67}Zn^{2+}$ ions (magnetic nucleus ^{67}Zn) is also markedly increased with respect to that of CK with nonmagnetic isotope $^{64}Zn^{2+}$ ions (Fig. 3) [Buchachenko et al., 2010c].

The new function of magnetic isotopes to strongly catalyze ATP synthesis was revealed in many ATP-producing kinases, in isolated mitochondria and in vivo living organisms (rats, rabbits, goats) [Buchachenko et al., 2005a, 2007, 2012; Pedersen et al., 2010]. The latter effect is used to stimulate ATP synthesis in heart muscle in order to prevent hypoxia and other pathologies related to the deficiency of ATP.

The ability of nuclear magnetic fields to stimulate ATP synthesis in the heart muscle of living organisms is demonstrated in Figure 4; it shows that $^{25}Mg^{2+}$ ions produce ATP in heart by 3–4 times more efficiently than $^{24}Mg^{2+}$ ions [Buchachenko and Kouznetsov, 2014]. The effect of $^{67}Zn^{+2}$ ions has also been tested on leukemic cells; the toxicity in cells of acute B-lymphoblastic leukemia was almost four times lower in comparison with zinc ions of natural isotope composition (dominates nonmagnetic ^{64}Zn) [Orlova et al., 2012]. This result manifests pharmacological potential of magnetic isotopes as an efficient remedy for the treatment of heart diseases (for details see review Buchachenko et al. [2012] and references therein).

Magnetic effects are the solid evidence in favor of the radical pair mechanism, which implies electron transfer and generation of the radical pairs in singlet

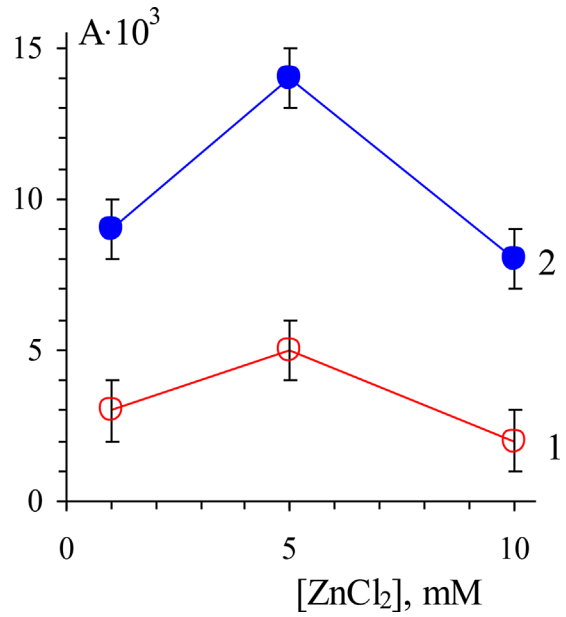

Fig. 3. The rates of ATP synthesis by CK in mitochondria as a function of zinc isotopes: $^{64}ZnCl_2$ (1) and $^{67}ZnCl_2$ (2). A is the radioactivity of ATP (in scintillations/min/mg of protein) [Buchachenko et al., 2010c].

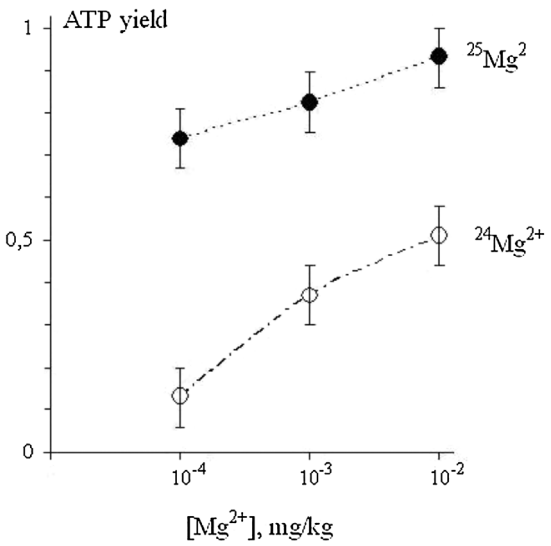

Fig. 4. The recovery degree (RD) of the ATP production in rats as a function of amount of the heart muscle targeted magnesium ions. RD stands for the extent of restoration of a hypoxia-suppressed myocardium tissue ATP content, that is, zero RD means a total ATP deplete, although RD = 1.0 shows a complete restoration of normal pre-hypoxia myocardium ATP level [Buchachenko and Kouznetsov, 2014].

spin state; magnetic field stimulates singlet-triplet spin conversion and switches on a new, triplet channel of phosphorylation. It provides an additional yield of ATP, which increases the total production of ATP by 2–3 times.

It is necessary to be aware that the radical mechanism, being firmly established, is just inevitable, because on the pathway of compression of reactants in any molecular machine (enzyme) low energy electron transfer occurs, which precedes high energy nucleophilic reaction. Radical pair mechanism, being controlled by magnetic interactions, is switched on, when at least two metal ions enter in catalytic site: the first one is tightly bound with phosphate group, the second one is free, not attached to phosphate group; it acts as an electron acceptor, it is a main actor of the ion-radical mechanism. Magnetic isotope/magnetic field effects on the enzymatic ATP synthesis certainly demonstrate reliability of the radical spin selective mechanism of this reaction.

Magnetic Control of Enzymatic DNA Synthesis

DNA synthesis is known to occur by polymerases, magnesium-dependent molecular machines, which attach nucleotide phosphate monomer molecule to the growing DNA chain. Chemical mechanism of the attachment was traditionally thought to be nucleophilic, which does not imply participation of any spin-carrying, paramagnetic intermediates. The elementary reaction of the DNA synthesis is almost identical to that of the ATP synthesis. The identity of the key steps in these two processes, the addition of phosphate group to ADP and attachment of nucleotide to the DNA strand via phosphorylation, stimulated to search for the magnetic effects in the latter.

For this purpose, the enzymatic activity of the polymerase β was measured in the presence of pure isotope ions $^{24}Mg^{2+}$, $^{25}Mg^{2+}$, $^{26}Mg^{2+}$, $^{64}Zn^{2+}$, and $^{67}Zn^{2+}$. The activity was found to depend on the nuclear magnetic moment: the ions $^{25}Mg^{2+}$ and $^{67}Zn^{2+}$ with magnetic nuclei ^{25}Mg and ^{67}Zn strongly suppress enzymatic activity of polymerase (Fig. 5) [Buchachenko et al., 2013a,b].

Polymerase chain reaction, well known as a fundamental technology in chemical genetics, also exhibits strong effect of the nuclear magnetic field [Buchachenko et al., 2013b] similar to that found for the polymerase β (Fig. 6).

Nuclear magnetic field effects on the enzymatic DNA synthesis demonstrate irrefutable reliability of the radical spin selective mechanism of this reaction. This conclusion is supported by observation of magnetic field effect on the DNA synthesis (Fig. 7).

The observation simultaneously of both magnetic isotope and magnetic field effects on the enzymatic DNA synthesis unambiguously indicates that its mechanism includes paramagnetic intermediates, that is, asides from the nucleophilic mechanisms carefully analyzed by Schlick et al. [Alberts et al., 2007; Bojin and Schlick, 2007] there exists another, radical mechanism, similar to that which was discovered for enzymatic ATP synthesis. Nucleophilic mechanism of the nucleotide attachment to the growing DNA macromolecule implies direct addition of $3'O^-$ ion of the ribose ring to the P_α atom of the incoming nucleotide phosphate and simultaneous release of pyrophosphate anion [Steitz and Steitz, 1993; Steitz, 1999]. Radical mechanism, coexisting with nucleophilic one, suggests electron transfer from $3'O^-$ ion to the $Mg(H_2O)_n^{2+}$ ion as a key, primary reaction (for details concerning this mechanism see [Buchachenko et al., 2013a,b]). Radical mechanism of the DNA synthesis is reliably validated; moreover, discovery of magnetic effects on the DNA synthesis simultaneously proves commonly accepted nucleophilic mechanism. Indeed, at the low concentrations of metal ions there are no magnetic effects; they appear only at the concentration ≥ 0.5 mM.

Since magnetic nuclei ^{25}Mg and ^{67}Zn strongly suppress enzymatic activity of polymerases (Figs. 5 and 6) magnetic ions $^{25}Mg^{2+}$ and $^{67}Zn^{2+}$ were tested as a means to kill cancer cells [Buchachenko, 2015].

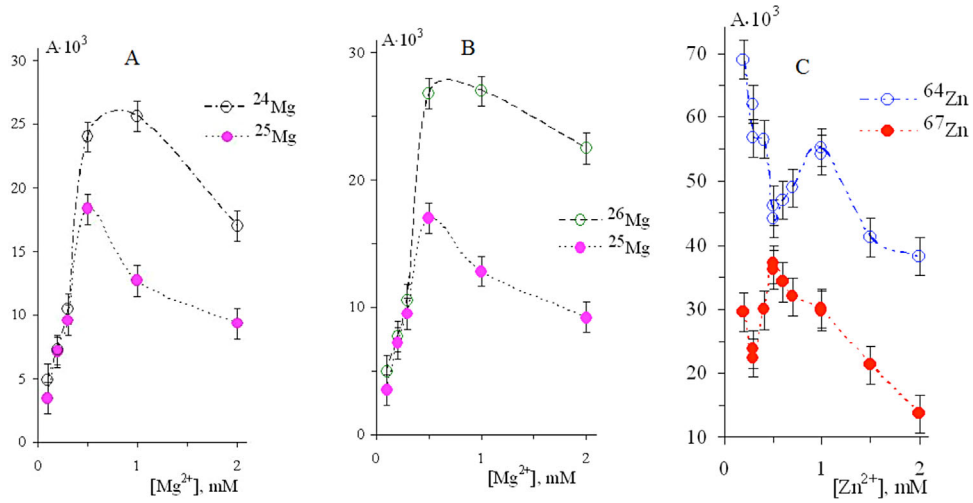

Fig. 5. The rate of the DNA synthesis by polymerase β as a function of the magnesium and zinc ion concentration in pairs $^{24}Mg^{2+}/^{25}Mg^{2+}$ (**A**), $^{26}Mg^{2+}/^{25}Mg^{2+}$ (**B**), and $^{64}Zn^{2+}/^{67}Zn^{2+}$ (**C**). [Buchachenko et al., 2013a].

The ions were delivered into the cells by specially designed nano-container PMC16 [Amirshahi et al., 2008; Sarkar et al., 2008; Rezayat et al., 2009]. Experimental magnitudes of LD_{50} (they characterize 50% of the cell survivability) for these molecules, loaded with magnesium or zinc ions, were measured to be strongly different for the cancer and healthy cells (Fig. 8).

These results reliably demonstrate different survival of both sorts of cells; they show that cancer cells are much more vulnerable with respect to nuclear magnetic ions than the healthy cells. The effect has two causes: first, mainly by nuclear magnetic field, which suppress enzymatic activity of polymerases; second, by dominating selectivity of cancer cells having probably more receptors to the PMC16 than healthy cells. Evidently, this medical aspect of magnetic effects is extremely promising.

Three Sources of Irreproducibility of Magnetic Effects

Magnetic effects are reliable, the most versatile tools and unambiguous indicators of the reaction mechanisms; their observations are irrefutable arguments in favor of radical (mostly, electron transfer) reactions. However, inverted statement is invalid: if magnetic effects are not exhibited it does not mean that radical mechanism is not operating. There are three factors that prevent detection of the magnetic effects even if radical mechanism is certainly known to function, that is, the absence of observed magnetic effects is not diagnostic of the absence of radical pairs.

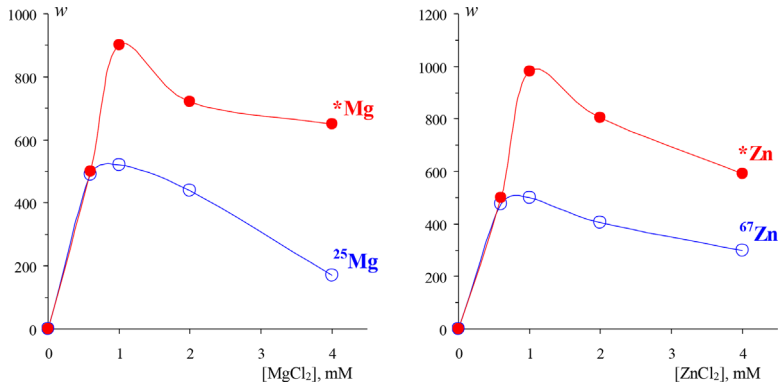

Fig. 6. The yield of DNA (*w*) in the PCR-induced DNA synthesis with magnetic (^{25}Mg and ^{67}Zn) and natural ($^{*}Mg$ and $^{*}Zn$), mostly nonmagnetic ions, as a function of the ion concentration [Buchachenko et al., 2013b].

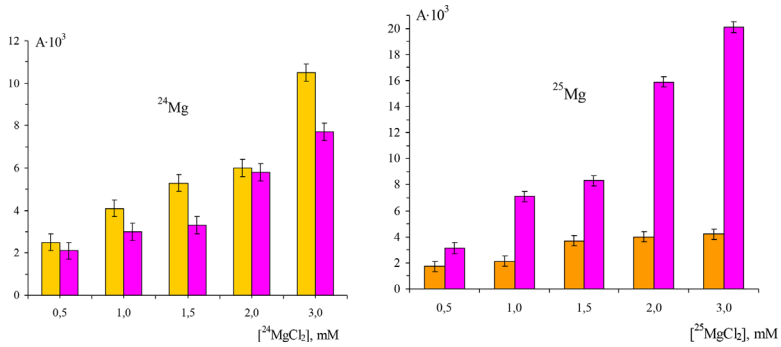

Fig. 7. Magnetic field effect on the rate of DNA synthesis by pol β loaded with $^{24}Mg^{2+}$ and $^{25}Mg^{2+}$ ions. Tritium radioactivity A is measured as the number of counts/min/mg DNA. Yellow (left) columns refer to the experiments in the Earth magnetic field; magenta (right) columns refer to the experiments carried out in the magnetic field 1600 G [Buchachenko et al., 2013b].

The presence of paramagnetic metal ions. Magnetic effects as an indicator of the radical mechanism may be switched off by iron ions; Figure 9 confirms this statement: the presence of $FeCl_2$ even in concentration 10^{-2} mM is enough to eliminate nuclear spin/magnetic field effects. Moreover, the quenching of these effects by paramagnetic ions may be used to quantitatively separate contributions of nucleophilic and radical mechanisms in enzymatic processes [Buchachenko and Kouznetsov, 2014].

Such type of quenching effect was present in elegant and perfect experiments carried out by Crotty et al. [2012a]. They failed to reproduce magnetic effects on the ATP production by creatine kinase. However, the samples of $MgCl_2$ used by these authors happened to be contaminated with Fe ions in amounts (both indicated in original paper [Crotty et al., 2012a] and corrected later [Crotty et al., 2012b], which are enough to destroy nuclear spin selectivity and delete both magnetic isotope and magnetic field effects.

Quenching effect was directly confirmed by measuring ATP yield produced by two sorts of mitochondria, loaded with $^{25}MgCl_2$ and $^{24}MgCl_2$ respectively [Svistunov et al., 2013]. Mitochondria were isolated from several rat tissues and the ATP yields were correlated with independently determined iron contents in these mitochondria. Isotope effect IE, that is the ratio of the ATP yields produced by mitochondria with $^{25}MgCl_2$ and $^{24}MgCl_2$ respectively, is different for the different tissues (Fig. 10). The mitochondria with high contents of Fe (spleen, liver) reveal no isotope effect (IE≈1.0), however mitochondria isolated from skeletal muscle, heart, kidneys and brain exhibit both low content of Fe and large isotope effect (IE≈1.8) in the ATP production. It immediately follows that the stimulation of the ATP synthesis by $^{25}Mg^{2+}$ ions has a sense only in the tissues with low content of Fe in mitochondria. In particular, an outstanding promotion of the in vivo ATP synthesis in heart muscle (Fig. 4) occurs due to the low iron content in the heart mitochondria.

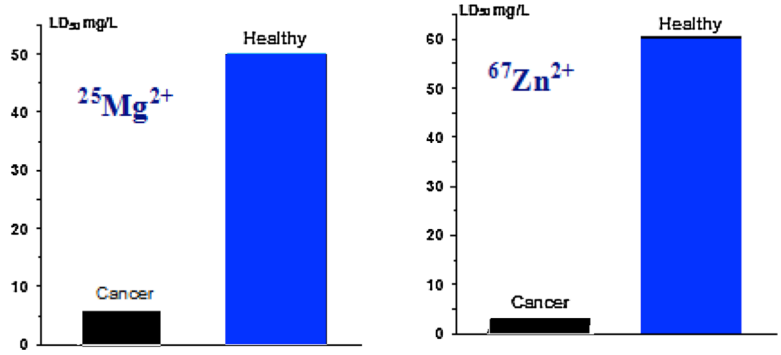

Fig. 8. The LD_{50} of the PMC16 loaded with $^{25}Mg^{2+}$ and $^{67}Zn^{2+}$ ions for the cancer (HL-60) and healthy cells [Buchachenko, 2015].

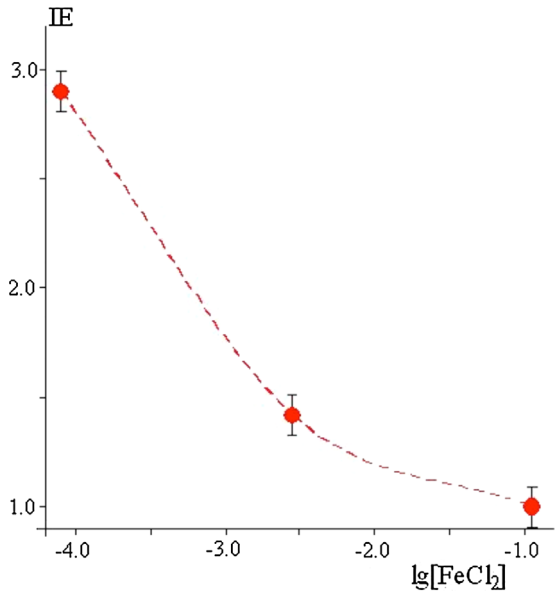

Fig. 9. Magnesium isotope effect IE on the ATP synthesis by creatine kinase as a function of $FeCl_2$ concentration (the latter is given in mM) [Buchachenko and Kouznetsov, 2014].

Magnetic field sensitivity was not detected in flavoenzyme-catalysed reactions [Messiha et al., 2014]; it was concluded that the magnetic field effects are unlikely in redox enzymes. It seems to be valid for all iron- or cobalt-containing enzymes. This is a reason why neither magnetic field effect, nor ^{17}O magnetic isotope effect were detected in the oxidation of linoleic acid, catalyzed by soybean lipoxygenase [Hwang and Grissom, 1994; Glickman et al., 1997]. In these cases it is expectable, because paramagnetic ferrous ions presented in enzyme catalytic site destroy nuclear spin selectivity and prevent observation of the magnetic isotope and magnetic field effects but do not delete radical mechanism, which is certainly known to function in these reactions. The possible presence of uncontrollable, even trace amounts of paramagnetic ions (iron, cobalt, manganese, etc.) in the reaction medium may result in irreproducibility and contradictions of experimental observations in magneto-biological studies.

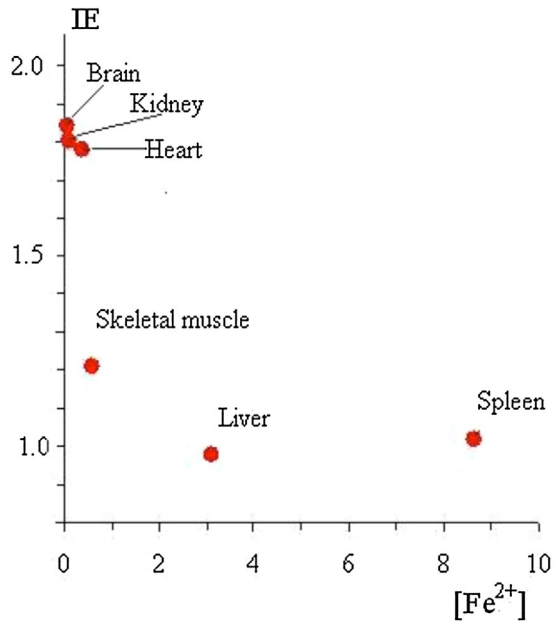

Fig. 10. Magnesium isotope effect IE on the ATP production by mitochondria from different tissues as a function of iron contents in these mitochondria. $[Fe^{2+}]$ is expressed in μg per g of mitochondria [Svistunov et al., 2013].

Concentration of the catalyzing metal ions. A general property of the magnetic effects on the enzymatic reactions is that they are not observed at very low concentration of the catalyzing metal ions. Thus, for the phosphoglycerate kinase with magnesium ions, magnetic effect on the ATP synthesis appears at $\geq$10 mM; for the DNA synthesis, it is switched on at ~0.5 mM for magnesium and at even less, <0.1 mM for the zinc ions (Figs. 5 and 6). At small concentrations nucleophilic mechanism dominates; the absence of magnetic effects is a definite proof of this statement. At these conditions each catalytic site has at least one ion, tightly bound with phosphate groups. Further increasing concentration of the catalyzing ions (Mg^{2+}, Zn^{2+}) results in appearance of the second ion in catalytic site; it is not bound with phosphate groups and acts as an electron acceptor, it switches on magnetically vulnerable radical pair mechanism.

It is necessary to keep in mind that the concentration of ions in the different elements of cells is also different and mostly unknown; but it is a critical parameter, which controls switching on the radical mechanism and, therefore, the chance to detect or not detect magnetic effects. This seems to be the second important source of numerous contradictions and inconsistencies in the experimental magneto-biological observations. On the other side, it is worth noting that intra-cell concentration of ions in living organisms is supposed to be rather low and hardly overcome boundary when at least two ions happen to appear in enzymatic site. Perhaps it gives some grounds for thinking that in living organisms radical mechanism is not dominating. However, this argument is not universal; moreover, radical mechanism may be artificially switched on for the medical purposes [Buchachenko, 2015] and it is a great privilege of the mechanism for medical purposes.

Kinetics and the radical pair spin dynamics. The third factor that prevents detection of the magnetic effects, even if radical mechanism is certainly known to function, is the kinetics of the intra-pair reactions: magnetic effects are observable if the rates of singlet-triplet conversion and decay of the pair are comparable. The former is a purely physical process controlled by magnetic (Zeeman or Fermi) interactions, the latter is dominated by intra-pair reactions (annihilation of radicals into the molecule or their escape). The favorable competition of these two processes imposes a rather strong restriction on the observation as well as on the magnitude of magnetic effect; quantitative theory is given by Buchachenko et al. [2012].

Which Magnetic Field Is Important, Permanent or Oscillating?

The time required for the spin change in the radical pair, that is, the time of singlet-triplet spin conversion, is determined by the relation

$$\tau_S = (\Delta g \beta H + \Sigma a_i m_i)^{-1}, \quad (1)$$

in which the first term corresponds to the contribution of the Zeeman interaction into the spin conversion, although the second one characterizes the contribution of the hyperfine coupling of unpaired electron with magnetic nuclei (Fermi interaction). Here, Δg is the difference between g-factors of the radical partners in the pair, a_i is the hyperfine coupling constant, m_i is the projection of the magnetic nucleus spin; the sum is taken for all i nuclei of the pair. Usually τ_S are 10^{-7}–10^{-10} s; it is comparable with the chemical lifetime of the pair itself.

A permanent magnetic field, both external and internal nuclear-magnetic field, performs spin conversion by means of precession of the electrons of the pair in these fields; the difference between the precession frequencies of electrons belonging to the partners is $(\Delta g \beta H + \sum a_i m_i)\, s^{-1}$. This is exactly the process of spin dephasing, which transforms triplet pair into the singlet one (or vice versa); the time of complete dephasing (i.e., dephasing of the spins through the angle π) is the time of the singlet-triplet spin conversion τ_S.

The effect of oscillating magnetic field on the electron spins of the pair depends on the field frequency ω, that is, on the oscillation period $\tau_0 = \omega^{-1}$. Low-frequency fields (such that the oscillation period is much longer than the time of singlet-triplet spin conversion, i.e. $\tau_0 >> \tau_S$) perform only spin dephasing, that is, they act as the permanent fields. In other words, a radical pair "sees" any low-frequency field that oscillates at frequency $\tau_0^{-1} << \tau_S^{-1}$ as a permanent field. Practically it means that all magnetic fields oscillating with frequency less than 100 MHz can be considered as the permanent fields.

High-frequency fields, such that $\tau_S^{-1} << \tau_0^{-1}$, produce no effect on the spin conversion, no influence on the magnetic effects. However, at the resonance, when the frequency of oscillation coincides with the Zeeman electron frequency, spin flip (reorientation) may occur that results to the spin conversion. But the spectral density of the resonance fields is low, being only a minor part of all background fields; therefore, the effect of the resonance fields on the magnetobiology can certainly be neglected (except for exotic cases, where the frequencies are specially tuned in resonance). Practically, it means that all oscillating magnetic fields with the frequency less than 100 MHz can be regarded as the permanent fields.

Conclusion and Perspectives

Radical pair mechanism of enzymatic ATP synthesis, DNA replication, and enzymatic phosphorylation of proteins—three cornerstones of the life chemistry—was discovered by using pure isotope forms of metal (magnesium, zinc, calcium) ions, catalyzing enzymatic phosphorylation. This mechanism is convincingly proved by magnetic isotope and magnetic field effects on these processes. It is worth emphasizing that the most reliable proofs follow from the magnetic isotope effect because internal magnetic field created by magnetic nucleus is subjected to influence neither macroscopic magnetic susceptibility nor Lorentz forces.

The physical essence of mechanism is founded on the remarkable property of enzymes as molecular machines: in the reactive state, when the enzyme domains are drawn together to unite substrates, they squeeze water molecules out of the catalytic site [Lahiri et al., 2001; Wyss et al., 1993] and partly dehydrate $M(H_2O)_n^{2+}$ ions (M is a catalyzing metal ion). The removal of water molecules increases both positive charge on the metal ion and its electron affinity, that is, electron transfer becomes energy allowed, switching on radical mechanism. According to this mechanism, compression energy of enzymatic site is spent on the removal of water out of the ion hydrate shell, which activates this ion as an electron acceptor. In order to make electron transfer allowed it is merely enough to remove weakly bound water out of the external hydrate shell [Pavlov et al., 1998]. In this process a total energy deficit does not exceed 3–5 kcal/mol, that is, it takes by order of magnitude less energy than the nucleophilic synthesis. For this

reason ion-radical mechanism seems to predominantly function in enzymatic reactions carried out by compressing molecular machines.

As pointed out on the start of the paper, radical pair mechanism manifests itself in the ATP synthesis in isolated mitochondria and in the living organisms as well as in the widely used polymerase chain reaction of the DNA replication. It can potentially be used to stimulate ATP synthesis and eliminate ATP deficiency in cardiac diseases, to control cell proliferation, to kill cancer cells, and control trans-cranial magnetic stimulation against cognitive deceases. In principle it is known how it can be switched on (by using the ions of magnetic isotopes), how it can be switched off (by using the iron or other paramagnetic ions) and in which organs of the body this mechanism is the most efficient. Moreover, there is an understanding of what factors prevent detecting magnetic effects as an indicator of the radical mechanism.

It is also worth noting that the ion-radical concept is a key to understanding many intriguing phenomena in magneto-biology [Buchachenko, 2015]. In magneto-biology it seems to be the most reasonable and significant concept for explaining biomedical effects of electromagnetism, for the progress of the new trans-cranial magnetic stimulation of cognitive activity, for the nuclear magnetic control of biochemical processes, and for the search of new magnetic effects in biology and medicine.

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