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Magnetic field-dependent molecular and chemical processes in biochemistry, genetics and medicine

A L Buchachenko

Institute of Problems of Chemical Physics, Russian Academy of Sciences
prosp. Akademika Semenova 1, 142432 Chernogolovka, Moscow Region, Russian Federation

The molecular concept (paradigm) in magnetobiology seems to be most substantiated and significant for explaining the biomedical effects of electromagnetic fields, for the new medical technology of transcranial 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. The key structural element of the concept is a radical ion pair as the receiver of magnetic fields and the source of magnetic effects. The existence of such pairs was recently detected in the two life-supporting processes of paramount importance — in enzymatic ATP and DNA syntheses.
The bibliography includes 80 references.

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I. Is magnetobiology a science?

Magnetobiology is a field of knowledge considering the phenomena that accompany the interaction of magnetic fields, constant and alternating, with biological systems at all levels: molecular, cellular, and body levels. Very few people doubt that magnetic fields do affect the human health and feeling of well-being, and this is the key factor stimulating the interest in magnetic biology. There are also other factors: the influence of the electromagnetic fields of cell phones and high-voltage power transmission lines; magnetoreception, orientation and navigation of migrating animals; the relationship between the suicide statistics and the Solar magnetic activity and professional activity of people (it was found that the suicide level in electricians dealing with electromagnetic fields is twice the average level). This means that magnetobiology has gained a social meaning.

It should be admitted, however, that observations in magnetobiology are ambiguous, non-reproducible and contradictory; and this is not due to the lack of diligence or knowledge of the observers. As noted by A Yu Grosberg,[1] the whole magnetobiology demonstrates a 'sad picture of contradictory and non-reproducible experiments'. If we add here the unrestrained activities of quacks selling, on behalf of medicine, magnetic bracelets, sheets and belts that cure everything and everybody, it is not surprising that magnetobiology is listed among the disreputable branches of science;[2] at best, it is considered to be illusive.

The physical ideas used in magnetobiology are sensible and rely on the common knowledge of magnetism and electromagnetism physics;[3,4] however, they are often fruitless or improper (for example, it is hardly reasonable to discuss the cyclotron resonance in living organisms, consider a DNA molecule as a resonator or analyze the mythical states of water in a magnetic field). Thus, a very large body of observations has been accumulated in magnetobiology without being converted to proofs or theories. If there are no explanations to facts or understanding of facts, then there are no ways to regulation and control of magnetic field-sensitive processes in biology, medicine and

A L Buchachenko Academician, Doctor of Chemical Sciences, scientific supervisor of the Theoretical Department at the IPCP RAS.
Tel. (7-495) 939 71 28, e-mail: abuchach@chph.ras.ru
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social life. This level of magnetobiology has been retained for decades.

The blind and vain search for the truth, the route from hypothesis to proof, *i.e.*, to understanding, is faced with a barrier: the lack of description of the molecular mechanisms that form the foundation of the chemistry of biologically significant magnetic field-dependent processes. Analysis of these mechanisms constitutes the subject of this review.

II. Facts and artefacts

A discouraging circumstance for magnetobiology is the inconsistency and mystery of the observed phenomena. For example, for *Escherichia coli*, out of the 18 studies undertaken to detect magnetic field effects, one-third 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. A similar situation was observed for enzymes, bacteria and fungi (see the review [5]). This relates to both constant and alternating fields. Indeed, a 2–6 G (50 Hz) alternating field changes the rate of *lac* transcription in *E.coli* as follows: a 3 G magnetic field suppresses the transcription but a 5.5 G field stimulates it.[6] A magnetic field of 14 100 G increases the transcription rate of 21 genes but decreases this rate for 44 other genes in *Shewanella oneidensis*.[7] Weak fields of 0.8–8.0 G (60 Hz) stimulate the transcription of the *c-myc* gene both in mice and in humans.[8] A 1000 G static field does not affect the HL-60 cells or the content of calcium ions in them.[9] The mentioned review [5] contains a multitude of such examples.

As noted by Galland and Pazur,[10] the pitiful condition of magnetobiology is due to incomplete investigation and the absence of systemic analysis of the dose–response relationships. Kumar and Galland [11] obtained the desired dose–response curves for the expression of genes producing phenylalanine ammonia lyase, chalcone synthase and tubulin. As the investigation subject, they used the popular plant *Arabidopsis thaliana* subjected to illumination with blue light (10 W m^{-2}). The dose–response curve was found to exhibit four maxima of stimulation of gene expression in a 15, 40, 60 and 90 μT constant fields (1 μT = 10^{-2} G), and the amplitude of the effect, *i.e.*, the difference between the maximum and minimum values, was as large as two orders of magnitude. Similar effects were observed in the synthesis of anthocyanins.[11] It was concluded that the magnetic field intrudes into the genome functioning at the gene expression level (magnetic field-induced expression), although the origin of the effects still remains obscure.

In the photosynthetic bacterium *Rhodobacter sphaeroides*, the porphyrin yields and the production of 5-aminolevulinic acid by the enzyme dehydratase increased 5-fold in 1300–3000 G fields [12] — all this was due to expression of the corresponding genes.

A magnetic field effect was observed in the enzymatic decomposition of hydrogen peroxide by horseradish peroxidase;[13] The transformation of ethanolamine into acetaldehyde by the bacterial enzyme ethanolamine ammonia lyase [14] was also affected by the magnetic field.† However, later, the magnetic field effects observed in horseradish peroxidase and lyase reactions were not reproduced,[16, 17] for unknown reasons. The influence of a 5 G magnetic field on the growth of the seedlings of *Arabidopsis thaliana* reported in one work [18] could not be reproduced in another work.[19]

The oxidation of nicotinamide adenine dinucleotide (NADH) with molecular oxygen is catalyzed by the enzyme peroxidase and occurs as an oscillating reaction in which the concentrations of the reactants (NADH and O_2) change with a ~100 s period. Both the oscillation frequency and amplitude for this reaction depend non-monotonically on the magnetic field intensity (in the 1000–4000 G range); both the frequency maximum and amplitude minimum being attained in a field of ~1500 G and being equal to 10%–15%.[20] The detection of the pronounced magnetic-field effect reliably indicates that this intricate reaction comprising 15–20 intermediate steps has steps involving radical pairs formed by radicals with different g-factors.

A noticeable influence of the magnetic field (550 and 800 G) on the synthesis of adenosine triphosphate (ATP) by creatine kinase was reported.[21] Simultaneously, a huge isotope effect was found: the enzyme with $^{25}Mg^{2+}$ ions (with a magnetic ^{25}Mg nucleus) produced 2–3 times more ATP than the $^{24}Mg^{2+}$ enzyme (with a non-magnetic ^{24}Mg nucleus). This result received strict physical substantiation in terms of spin chemistry and spin-selective chemical reactions.[22] Later the described experiment [21] was repeated [23] but neither magnesium isotope effects nor magnetic field effects were found. It is demonstrated below that this failure is caused by significant biochemical reasons.

III. Transcranial 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 patient's head by means of magnetic coils. The alternating magnetic field generated by the coils penetrates through the cranial bones (this gave rise to the name 'transcranial') and acts on the neurons through electric potential modulation.[24–26] A new, advanced version of this technology employs transcranial stimulation together with brain imaging, which opens up the way for direct targeted stimulation of the specified brain areas (navigational transcranial magnetic stimulation).[27]

This technique brings about two significant questions:

— whether or not biological subjects (in particular, neurons) are able to perceive the magnetic field and

— whether or not the magnetic reception is significant for functioning of these subjects.

Direct medical experience answers 'yes' to both questions: it is possible to increase the efficiency of treatment of cognitive disorders and neurological diseases (stroke consequences, epilepsy, Parkinson disease, pain syndromes, paralysis, schizophrenia). Moreover, there is reliable evidence that transcranial magnetic stimulation (TMS) induces molecular transformations in the cortex, which are remembered and retained for long periods (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. This, however, brings about the question: what are the molecular mechanisms of the effect (for the answer, see below).

Most of TMS works pursue purely medical, therapeutic goals. Two types of biochemical studies performed at the molecular level should be mentioned. One type deals with analysis of the effect of gene polymorphism on the sensi-

† Full analysis of magnetic-field effects in biochemical reactions is given in a review.[15]

tivity to TMS (in other words, the researchers try to find out what genes act as TMS receivers and what genes are TMS-insensitive). The second type of works are those dealing directly with the TMS-induced changes in the genome.

An example of the first type is the study of the effect of the 5-HT_{1A} serotonin receptor polymorphism on TMS signals (in 99 patients).[28] It was found that C/C patients were much more susceptible to TMS than the C/G and G/G subjects, who were less sensitive. One more vivid example is the different susceptibility of genetic polymorphism to TMS caused by the difference between the Val66Met and Val66Val alleles of the genetic neutrotrophic factor BDNF, one of many genes that affect the synapse plasticity.[29] The effect of mutations in the γ-aminoglutamic acid ($GABA_A$) receptor on the cortex susceptibility to TMS signals was investigated.[30] Studies of this type combining therapy and genetics indicate reliably and unambiguously that the genome, being the key factor governing the TMS effects, determines both the genome susceptibility to TMS and the scale of TMS-induced effects.

Works of another group 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 encoding the *c-fos* and *zif/268* proteins in the rat cortex was demonstrated.[31] In the low-frequency (0.1 Hz) but high-amplitude (5000–100 000 G) TMS mode, significant changes in the proliferation and differentiation of the neural stem cells in the cortex of neonatal rats were detected,[32] the most pronounced effect being attained in a 40 000 G field.

High levels of the NO neurotransmitter and cyclic guanosine monophosphate in the cerebral cortex, grooves and hippocampus were detected in rats that have been exposed to electromagnetic radiation for 5 days (frequency 60 Hz, amplitude 20 G); moreover, neither the number of neurons nor the neuron morphology changed. The only possible conclusion was drawn: the origin of the effects is to be sought in the increased expression of genes responsible for the synthesis of the neuronal NO-synthase in the cerebral cortex of rats subjected to TMS.[33]

Numerous works of this type prove unambiguously that the TMS magnetic signals trigger the gene expression and production of some enzyme proteins — and this accounts for the long-term therapeutic effect of TMS.

IV. Magnetoreception: cell phones

A consequence of the civilization development is filling of the environment with electromagnetic fields of various frequencies and amplitudes (generated by power transmission lines, telecommunications, domestic appliances and so on). The high density and the permanent presence of these fields brought about concern of what are their biomedical effects and possible hazards.[34–37] In terms of magnetobiology, two topics are discussed most actively:

— the orientation and navigation of migrating animals (see below);

— the impact of microwave fields employed by cell phones and space navigation systems on humans.

The latter problem is of much higher social significance, being discussed in a multitude of sociological and biomedical investigations but the conclusions are contradictory: some works state the enhanced risk of cancer, while other works notice no such risk. The papers lack extensive statistical substantiation and, hence, they are unreliable and are of low value.

However, there exists a statistically reliable and professionally trustworthy study[38] in which animals (rats of a particular genetic line) housed free in open-air cages were continuously exposed to radiofrequency signals that simulated cell phone signals. In experiments with continuous radiation for 17 and 24 months, no macroscopic effects detrimental to health (with respect to the control group not subjected to radiation) were observed; also, no effects were detected at the pathologic anatomy level.

In another series of experiments, irradiation lasted for years (36 and 37 months for two groups of test animals up to their natural death). The life span of irradiated animals reduced, on average, by 9% (*i.e.*, by 72 days for the total life span of 799 days in the first group and by 77 days for the life span of 852 in the second group). There was not any effect of irradiation on the stimulation of carcinogenesis.[38]

These results reliably indicate that the detrimental effect of microwave magnetic fields of cell phones on the human health and survival has been overstated. The effects are insignificant and, certainly, they do not rank among the top dangers that threaten humans and the mankind.

V. Magnetic compass: orientation and navigation of animals

The discovery of spin-selective and, hence, magnetically sensitive chemical reactions introduced new ideas into studies of the orientation in space and navigation of migrating animals.[39–45] One idea considers, as the biomagnetic compass, nano-sized magnetic particles, magnetosomes, which arise in living bodies as products of metabolism; it is believed that the magnetic field of these particles makes the migrating species orient themselves along the Earth magnetic field. This idea is highly discredited as physically non-realistic. Indeed, animals — birds, insects, amphibians, crabs, fish and mammals (altogether more than 50 species) — migrate in different directions and hardly ever along the magnetic force lines of the Earth. This raises the questions of how the migrating animals find the angle between the magnetic field and migration route and what is the physiological sensor for this angle. There is no answer to these questions, no answer is even expected, and this makes the idea senseless.

Another idea based on the achievements of spin chemistry states that radical pairs act as receivers of magnetic fields and as sources of magnetic effects. There is no direct evidence that this idea operates in living organisms. There are only examples of photosynthetic molecules whose reactions depend on the magnetic field. Indeed, the photosynthetic molecules extracted from the bacteria *Rhodobacter sphaeroides* diminish the photoinduced production of singlet oxygen by 50% even in a weak magnetic field of 20 mT (this is still 400 times as large as the Earth magnetic field). The CPF molecule consisting of carotenoid (C), porphyrin (P) and fullerene (F) moieties is converted upon photolysis to a biradical state, *i.e.*, an intramolecular radical pair, the lifetime of which depends on the magnetic field ($\leqslant 50$ μT).[46] Yet another result is even more significant: if a CPF molecule is fixed in place in a liquid crystal, the lifetime of the pair depends on the orientation of its axes relative to the field direction, *i.e.*, an anisotropic part of magnetic sensitivity appears (through the anisotropy of the Zeeman interaction). And this is exactly what is required of

a magnetic compass: a dependence of any signal on the orientation of its sensor. Presumably, this mechanism may operate in reactions of light-sensitive proteins — cryptochromes, which have been found in birds' eyes.[46]

The proper idea of magnetic chemical navigation is perceived as non-trustworthy; it is even called pseudoscientific (see a reported discussion [46]). A significant argument for discredit is the fact that humans, being at the top of biological evolution, have no ability to magnetoreception and no field- or field orientation-biosensors. However, even this fact is not convincing as the evolutionary pathways of humans and migrating animals separated many million years ago and the animals had time to create their own magnetic compass. A group of authors [39–41, 43] are steadily developing this idea. No unambiguous answer to the question of whether or not the magnetic biological compass exists is given; all ideas remain hypothetical.[47, 48]

It is quite likely that the navigation and orientation of animals have nothing to do with magnetoreception; possibly, the magnetic contribution to navigation and its role are substantially overstated with respect to other means such as vision and memory. Indeed, there are much more reliable things to control the navigation of living beings, the internal and external memory, the internal memory being more universal, as it is determined by the biological clock of the body, position of the Sun, and degree of their mutual correlation; numerous pieces of evidence for these statements have been obtained.[48, 49]

VI. Biological clock

Biological clocks operate in every cell of a living body; they define the daily periodicity in the life of every living being including plants. It was shown that the clock is not related to metabolism; even full termination of metabolic processes does not violate the rhythm. However, poisons that disrupt the read-out of genetic information (for example, actinomycin D, which prevents the synthesis of mRNA by RNA polymerases) distort functioning of the clock. According to a number of observations, the mechanism of operation of biological clock is inherent in the genome. Indeed, the gene *Per* determining the circadian periodicity was detected in particular sites of chromosomes of the fruit fly. Mutations of this gene were found to result in heritable change in the biological clock rate. Similar genes were found in the lower fungus neurospora and in the plant *Arabidopsis thaliana*.

To date, seven genes (*Per1*, *Per2*, *Per3*, *Cry1*, *Cry2*, *Clock*, *Bmal1*) that provide self-sustained stable rhythms of functioning and metabolisms in living organisms have already been detected. It was found that the rhythmicity is maintained by the photosensitive Master Clock, which is located in the vicinity of hypothalamus and sends control signals to local clocks, which tick in all organs and in every cell. The family of circadian genes *Per* encodes the *Per* proteins; violation of the synthesis of these proteins by various inhibitors stops the biological clock.[50–52] A unique feature of the *Per* proteins is their ability to ensure the temperature independence of the clock rate, and it is this property that has always been enigmatic. The amino acid chains of the *Per* protein form a loop and some protein molecules are connected to one another to form dimers. The intra- and intermolecular interaction processes follow opposite temperature dependences thus counterbalancing each other, so that the protein activity remains constant and the clock functioning is not affected by temperature. The biological clock is present in every organism being a universal product of evolution. There are numerous clues (although no direct evidence) that the biological clock is susceptible to a magnetic field;[48, 53, 54] it is obvious that both the biological clock and its magnetic field dependence are significant for the medical-physiological condition of living organisms, first of all, the health and feeling of well-being of humans.

VII. Two physical mechanisms in magnetobiology

Two types of physical mechanisms, macroscopic and molecular ones, can be distinguished in magnetobiology as being responsible for magnetic effects. The former can be manifested in processes involving coarse particles — microcrystals, mitochondria, membranes. If these particles have large anisotropy of magnetic susceptibility, then the energy of their interaction with a constant magnetic field may be comparable with the thermal energy (kT). In this case, these particles can be oriented or deformed in the magnetic field (similarly to liquid crystals). As a result, the properties and the chemical reactivity of deformed particles (*e.g.*, membranes) change. However, magnetic effects of this type are significant only in strong and durable magnetic fields, *i.e.*, under exotic conditions. Therefore, the contribution of macroscopic mechanisms to magnetobiology can be ignored. Magnetic resonance imaging is not an exception, as the action of field is short-term in this case.

Chemical processes involving generation or participation of free radicals, radical ions or paramagnetic particles make a much more pronounced (and, most likely, the only) contribution to the magnetic dependence of biosystems. The unpaired electrons in these species carry spin magnetism and it is them that interact with both constant and alternating magnetic fields.

There is a naive belief that the appearance of paramagnetic particles in chemical (biochemical) reactions is a sufficient condition for magnetic-biological effects to appear. A constant magnetic field can only align the electron spin, and microwave radiation can change spin orientation; however, chemistry does not depend on the spin orientation of a single radical. Being the receiver for microwave radiation, a spin cannot ensure a magnetic-field- or electromagnetic biological effects. These effects can be manifested only in multispin systems, *i.e.*, when at least two spins are present. A radical pair or a radical-ion pair can exist in two spin states: the singlet (the total electron spin is zero) or triplet state (the spin is unity). These states are chemically identical but markedly differ in reactivity. Magnetic fields can induce triplet–singlet spin transitions in these pairs and change their spin state and reactivity. It is this physically clear and experimentally substantiated concept that underlies the spin chemistry and spin biochemistry.[55–58]

VIII. Energetic dogma

Observations of magnetic effects in chemistry or biochemistry have always faced disbelief irrespective of their reliability. The effects themselves were announced to be pseudoscience and the authors were accused to be ignorant in view of the fact that the magnetic energies are negligibly low; they are 4–6 orders of magnitude lower than the kT value, *i.e.*, they are much lower than the thermal background energy and, hence, their influence should be neglected — this is the essence of the energetic dogma.

The difficulties of the energetic dogma in the description of magnetoreception are commonly known and have been summarized.[59] To overcome these difficulties, the authors [59] proposed a physical model of the interaction of an oscillating magnetic field with molecular protein complexes bearing charges that are unevenly distributed throughout the complex bulk. According to authors' idea, this interaction may give rise to displacements, turns or even rotation of the complex, thus promoting its conformational rearrangements, which are able to change the biochemical functioning of proteins.

A flaw of the model is that the alternating field interacts only with moving charges giving rise to the Lorentz forces

$$F = \frac{e}{c} \boldsymbol{v} \boldsymbol{B} \sin \alpha$$

where $\boldsymbol{v}$ and $\boldsymbol{B}$ are the moving 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 magnetic Lorentz forces do not operate in biological media, and the proposed model [59] does not provide a magnetoreception mechanism.

One more model proposed in the same publication considers nano-sized magnetic particles (mainly crystalline magnetite), which are known to be metabolic products; they are called magnetosomes.[48, 59] In particular, the concentration of magnetosomes in the human brain is $\sim 10^8$ g^{-1}. An alternating field can move or rotate these particles but this motion is unlikely to affect biochemistry. The magnetosome field itself can produce an effect but the problem is again reduced to mechanisms of magnetoreception. It can be stated with confidence that no relationship was found between the existence of magnetosomes and their possible functioning.

The energetic dogma was detrimental for magnetobiology and spin chemistry, as it removed the incentives for their development and thus retarded their progress for decades. A false problem of why so weak magnetic interactions have a pronounced influence on the chemical and biochemical processes is still being debated. The reason is that, apart from overcoming the energy barrier (as is reasonably asserted by the energetic dogma), any reaction also requires retention of the full angular momentum (spin) of the reactants, and this condition is being neglected by the energetic dogma. All reactions obey the spin retention law: if the electron spins of the reactants and the products do not coincide, the reaction is strictly forbidden. This law, which establishes the spin control of any reaction, has been proved experimentally.[60]

Magnetic interactions are unique: only they are able to control the spin of the reactants and can change the spin. Being negligibly small in energy, they can eliminate spin prohibition by switching reactions in radical pairs from spin-forbidden to spin-allowed channels; and this is the way they control the reactions. The radical (radical ion) pairs are the spin nanoreactors that function as magnetic field receivers for both constant and alternating fields. The molecular and chemical processes controlled by magnetic fields in such nanoreactors are sources of all magnetic effects both in chemistry and in biochemistry.

IX. Magnetic field-dependent reactions in biochemistry and genetics

Many reactions that are accompanied by generation or participation of paramagnetic species (radicals or radical ions) are known in biochemistry but they do not exhibit any significant (experimentally detectable) magnetic-field dependence; perhaps, the contribution of spin pairs as spin nanoreactors is minor in these reactions and has no substantial influence on the outcome. However, recently, radical ion mechanisms were discovered for two enzymatic reactions that play a fundamental, life-supporting role in biology, namely [61–65]

— synthesis of ATP, the key energy carrier in living organisms;

— DNA replication by polymerases, which is directly relevant to the gene chemistry and genetics.

Both reactions provide functioning of living organisms; they are both catalyzed by metal ions (magnesium, zinc), and for both reactions, the catalytic activities of ions with magnetic nuclei (^{199}Hg, ^{25}Mg, ^{67}Zn, ^{43}Ca) were found to be considerably different. This phenomenon is known as a magnetic isotope effect; [66–68] detecting this effect is a reliable indication of a radical ion mechanism in which the key role belongs to radical ion pairs. Exactly these pairs in which the spin conversion is controlled by the magnetic fields (both external fields and internal fields of magnetic nuclei) are responsible for magnetic effects.

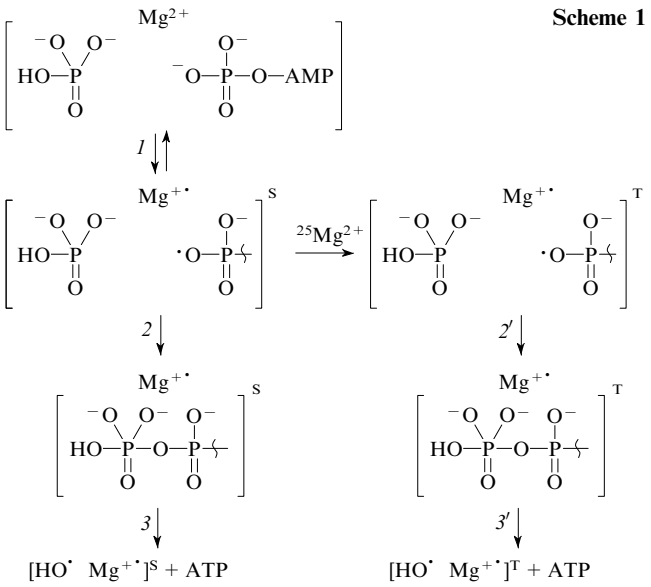
1. Magnetic field-dependent synthesis of ATP

The ATP synthesis by kinases, mitochondria and even *in vivo* in living organisms depends on what magnesium isotope is present in the catalytic site. The rate of ATP synthesis by enzymes in which the magnesium cation has the magnetic ^{25}Mg nucleus is 2–3 times higher than the rate of ATP generation by the same enzymes under the same conditions but with spin-free non-magnetic ^{24}Mg and ^{26}Mg nuclei.[62] The rates of ATP synthesis by ^{24}Mg- and ^{26}Mg-containing enzymes do not differ. The discovery of this giant nuclear magnetic isotope effect provides reliable and unambiguous evidence that the synthesis of ATP is a radical ion reaction involving paramagnetic intermediates: radical ions and radical ion pairs. This mechanism is implemented in oxidative (Scheme 1) and substrate phosphorylation of adenosine diphosphate (ADP) by ATP synthase.

The first (key) stage of the synthesis is electron transfer from the ADP phosphate group to Mg^{2+} (reaction *1*, AMP is adenosine monophosphate) giving rise to a radical ion pair formed by the ADP oxy radical and magnesium radical cation. It is this pair that a serves as a receiver of all magnetic fields (the internal field of the magnetic ^{25}Mg nucleus, external magnetic field and microwave radiofrequency field) and the source of magnetic effects.

In the radical ion pair (it exists in the singlet spin state, like any thermally generated radical pair), the oxy radical adds to the P=O double bond of the phosphate (reaction *2*); and the new oxy radical undergoes β-cleavage (reaction *3*). This reaction affords ATP and the secondary radical pair composed of the Mg^+ ion and the hydroxyl radical. The back electron transfer from Mg^+ to the hydroxyl radical recovers the Mg^{2+} ion, while the hydroxyl radical is converted to HO^- and then to H_2O.

Scheme 1



The rate of ATP synthesis along the singlet channel (the left-hand part of Scheme 1, reactions *1*–*3*) is limited by the back electron transfer, which is spin allowed. The transfer recovers the initial reactants and sharply decreases the ATP yield. However, if the $^{25}Mg^{2+}$ isotope ion is present in the catalytic site, coupling of the unpaired electron in the $Mg^{+\bullet}$ radical cation with the magnetic ^{25}Mg nucleus changes the spin of the pair and thus switches it to the triplet state from which the back electron transfer is spin-forbidden. This implies an additional irreversible triplet channel of ATP synthesis (right-hand part of Scheme 1, reactions *2*′, *3*′), which surpasses the singlet channel in efficiency.

The essence of the magnetic isotope effect of magnesium in the ATP synthesis is as follows: magnetic interaction of the unpaired electron of the $Mg^{+\bullet}$ radical cation with the magnetic nucleus changes the electron spin of the pair inducing conversion from the singlet to triplet state. The change in the spin opens up a new reaction channel in the radical pair, indicating the nuclear-spin control of the chemical reaction: the magnetic nucleus controls the electron spin and reactivity of the radical pair.

This control can be performed also by an external magnetic field. Analysis of the dependences of the rate of magnesium-catalyzed ATP synthesis by creatine kinase (Fig. 1) demonstrated that the rate of the synthesis actually does depend on the magnetic field: the $^{25}Mg^{2+}$ enzyme is activated by a magnetic field, while the catalytic activity of the $^{24}Mg^{2+}$-containing enzyme somewhat decreases in a magnetic field.[21]

The radical ion pair serves as a receiver of a microwave field; the relevant quantitative theory was considered in a publication,[69] which also presents quantitative characteristics of the magnetic effect. The full theory was reported in other studies.[70, 71]

The radical ion magnetic field-dependent mechanism of ATP synthesis functions at rather high concentrations of magnesium ions that are higher than physiological magnesium concentration in mitochondria and cells.[72] However, a contribution of magnesium present in physiological concentrations to ATP synthesis also cannot be ruled out: it can be minor but act permanently and be accompanied by significant magnetic biological effects particularly during the synthesis of ATP — the principal energy carrier.

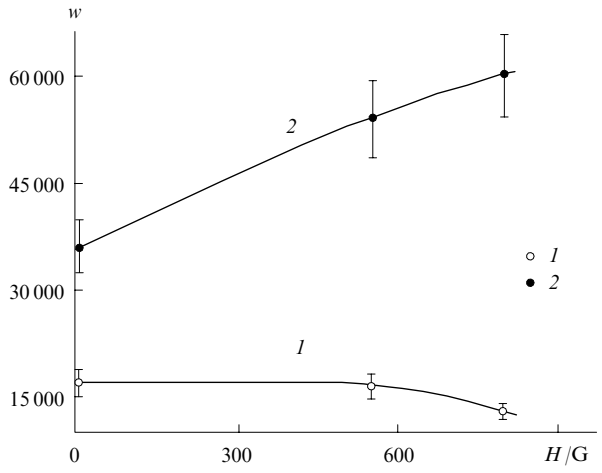


Figure 1. Rates of ATP synthesis (w) by creatine kinase catalyzed by $^{24}Mg^{2+}$ (*1*) and $^{25}Mg^{2+}$ (*2*) ions as a function of the magnetic field.[21]

The results of direct measurements of ATP synthesis parameters in rats, rabbits and goats [73, 74] proved the radical ion mechanism *in vivo*. The dependences of the yield of ATP in the cardiac muscle of living rats on the concentration of the introduced isotope forms of magnesium chloride (Fig. 2) indicate that the rate of ATP synthesis with $^{25}Mg^{2+}$ isotope ions is substantially (3–6 times) higher than the rate of synthesis with non-magnetic $^{24}Mg^{2+}$ ions. With allowance for this effect, drugs against hypoxia and heart failure were proposed and means for targeted delivery of these drugs to the cardiac muscle were developed.[22] This also opens prospects for the control of the growth of microorganisms in biotechnology.

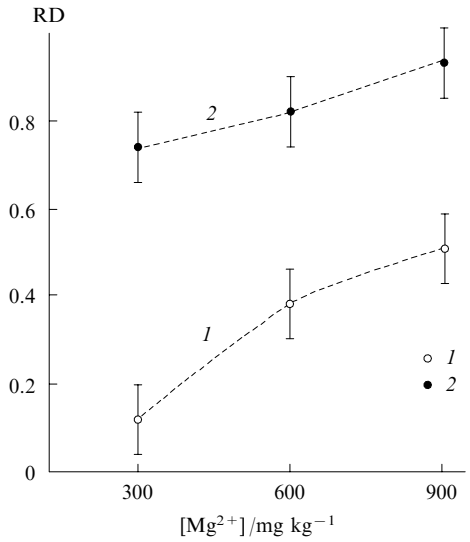


Figure 2. Yield of ATP in the cardiac muscle of living mice *vs.* the amount of $^{24}MgCl_2$ (*1*) and $^{25}MgCl_2$ (*2*).[73]
Recovery degree (RD) is the recovery degree of the ATP level with respect to the normal level after the animals have been brought to a condition with reduced ATP level (hypoxia) and introduction of isotope forms of $MgCl_2$.

2. Which route of ATP synthesis, magnetic or non-magnetic, is more important?

It was noted above (see Section IX.1) that magnetic field has a pronounced effect on the ATP synthesis by creatine kinase;[21] a giant isotope effect was detected for the same reaction: the enzyme with magnetic ^{25}Mg ions produced 2–3 times more ATP than the enzyme with non-magnetic ^{24}Mg nuclei. Later, however, the described [21, 61] experiments were repeated,[23] and neither magnesium isotope effects nor magnetic-field effects were detected. This result is remarkable because both magnesium chloride samples ($^*MgCl_2$ with natural magnesium isotope abundance and $^{25}MgCl_2$ with 97.7% $^{25}Mg^{2+}$) that were used by the researchers cited [23] contained quite a lot of impurity iron, 14.6 and 9.7 μg ml^{-1}, respectively. More recently, however, these authors [23] admitted that these values were erroneous and reported new values: 0.05 μg ml^{-1} in $^*MgCl_2$ and 0.36 μg ml^{-1} in $^{25}MgCl_2$ (see Ref. 75). In any case, one may suspect that the Fe^{2+} (or Fe^{3+}) impurity ions destroy the nuclear-spin selectivity and eliminate the magnetic isotope and magnetic field effects.

In order to elucidate the intriguing role of iron ions, the catalytic activity of creatine kinase was measured in two series of experiments: in one series, creatine kinase was loaded with $^{25}MgCl_2$ while in the other series it contained $^*MgCl_2$. The amounts of deliberately added $FeCl_2$ were equal in the two experimental series. The results are summarized in Table 1.

It can be seen that that the magnetic effect shows itself only in the presence of the purest magnesium chloride containing only traces of $FeCl_2$ (the first row of the Table): the chloride containing magnetic ^{25}Mg nuclei is almost three times more active than the natural chloride. As the content of $FeCl_2$ increases (the second and subsequent rows of the Table), the isotope effect rapidly diminishes (Fig. 3), *i.e.*, even a 10^{-2} mmol litre^{-1} iron admixture completely eliminates the magnetic isotope effect.

Table 1 presents also one more important result. The activity of $^*MgCl_2$-containing creatine kinase is relatively low and barely depends on the presence of $FeCl_2$ (except for the first portion of $FeCl_2$ equal to 4×10^{-4} mmol litre^{-1}, which reduces the creatine kinase activity by only 10%). Conversely, the activity of $^{25}MgCl_2$-containing creatine kinase is almost three times higher than the activity of creatine kinase with $^*MgCl_2$ containing almost no $FeCl_2$ (the first line of Table 1); the activity is markedly suppressed by $FeCl_2$ additives (Fig. 3). The isotope effect defined as the ratio of the rates of ATP synthesis by creatine kinase with

Table 1. Rate of the ATP synthesis by creatine kinase [(mmol of ATP) litre^{-1} min^{-1} (g of creatine kinase)$^{-1}$] catalyzed by $^*MgCl_2$ and $^{25}MgCl_2$ in the presence of different amounts of $FeCl_2$.

$[FeCl_2]/10^{-4}$ mmol litre^{-1}	$^{25}MgCl_2$	$^*MgCl_2$
0.8	27.9	9.6
3.9	–	8.6
28.0	12.2	8.5
754.8	7.9	–
1135.6	–	8.5

Note. The rate of ATP synthesis was measured to an accuracy of 6%; the ^{25}Mg contents in $^{25}MgCl_2$ and $^*MgCl_2$ were 98.6% and 11%, respectively. The amounts of $FeCl_2$ added were the same as used in other works.[23, 75]

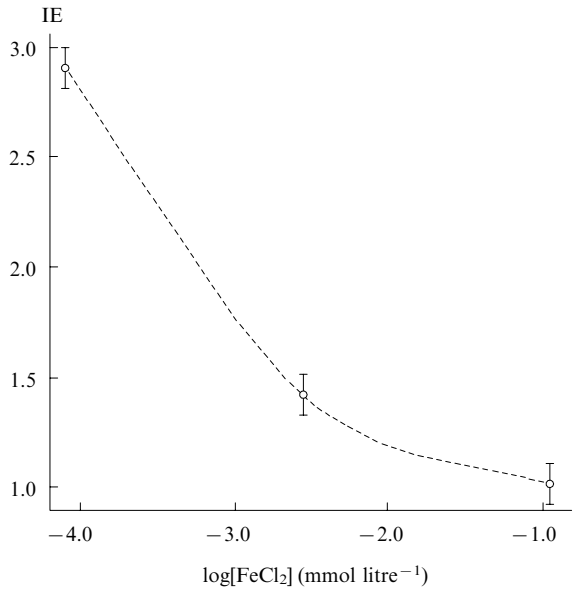


Figure 3. Magnesium isotope effect (IE) as a function of $FeCl_2$ concentration.[76]

$^{25}MgCl_2$ and $^*MgCl_2$ disappears (approaches unity) even when the $FeCl_2$ concentration is about 10^{-2} mmol litre^{-1}. This implies that under these conditions, ATP is synthesized only by the nucleophilic mechanism, the radical ion mechanism being switched off. This provides the quantitative ratio: the radical ion (magnetic) mechanism is three times more efficient in the ATP synthesis than the nucleophilic (non-magnetic) mechanism. In other words, the magnetic channel of the synthesis is three times more efficient than the non-magnetic channel.

A significant question is why the Fe^{2+} ions suppress the magnetic channel of ATP synthesis but do not affect the non-magnetic channel. First of all it should be borne in mind that Fe^{2+} cations are bound to the phosphate groups in the catalytic site much more strongly than Mg^{2+} ions and, therefore, they displace magnesium from the active site. Yet another circumstance is even more important: the Fe^{2+} cation strongly holds the water molecules in the hydration shell and, unlike the Mg^{2+} ion, it cannot be dehydrated upon compression of the catalytic site. This means that in the presence of Fe^{2+}, the electron transfer is impossible and, hence, the radical ion mechanism cannot be switched on; meanwhile, the nucleophilic channel functions irrespective of which ion, Fe^{2+} or Mg^{2+}, resides in the catalytic site.

The suppression of the radical ion channel of the ATP synthesis by Fe^{2+} ions was confirmed by investigations of the mitochondria isolated from various organs of rats.[76] In the experiments, the iron content and ATP production by mitochondria with $^{25}MgCl_2$ and with $^{24}MgCl_2$ were measured simultaneously. The ratio of the rates of ATP synthesis by these mitochondria (isotope effect) depends appreciably on the amount of iron in them (Fig. 4). In kidney, brain and cardiac muscle mitochondria in which the iron content is low (<0.5 μg per g of mitochondria), the isotope effect is large (~1.8), *i.e.*, the ATP synthesis occurs by both mechanisms. Conversely, in the liver and spleen mitochondria containing a lot of iron, the isotope effect is equal to unity, *i.e.*, the ATP synthesis occurs by the nucleophilic,

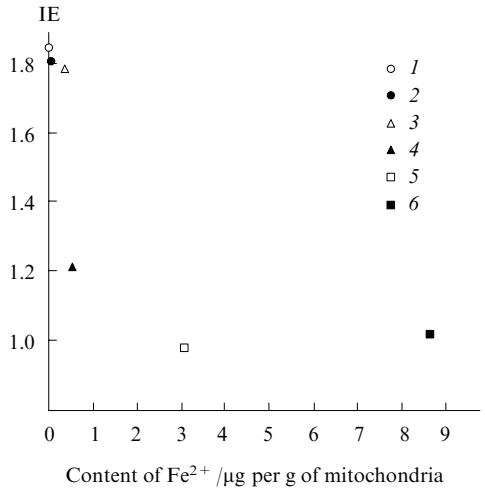


Figure 4. Isotope effect in the ATP synthesis by mitochondria from various rat organs *vs.* iron content in them.[76]
Organ: (*1*) brain, (*2*) kidney, (*3*) heart, (*4*) skeletal muscle, (*5*) liver, (*6*) spleen.

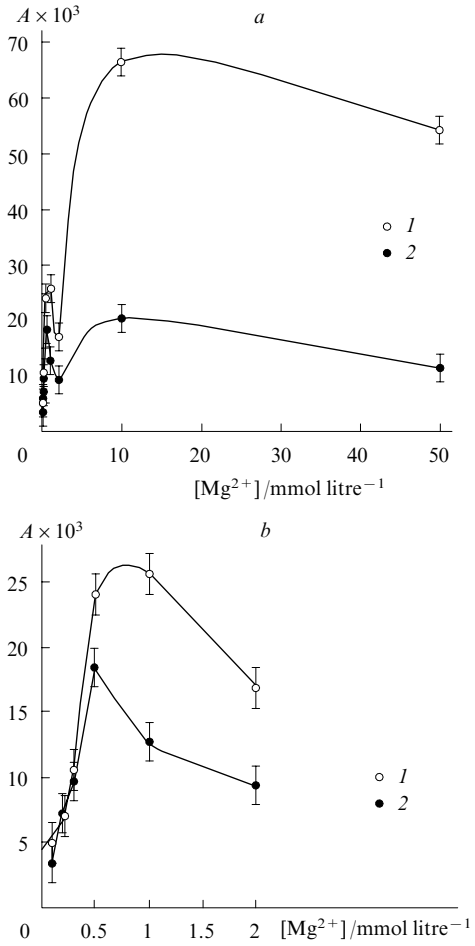


Figure 5. Rates of DNA synthesis *vs.* concentration of $^{24}MgCl_2$ (*1*) and $^{25}MgCl_2$ (*2*).[78]
The rate was measured from radioactivity A [pulses min^{-1} (mg of DNA)$^{-1}$] of the synthesized DNA with the introduced tritium-labelled dTTN nucleotide. The plots in panels *a* and *b* are given on different scales.

non-magnetic mechanism; the presence of iron switches off the radical ion (magnetic) channel of synthesis. The considerable stimulation of the ATP synthesis *in vivo* in the cardiac muscle (see Fig. 4) by the $^{25}Mg^{2+}$ ions is achieved particularly due to the fact that the iron content in cardiac mitochondria is low.

The 'facts and artefacts' story (see Section II) provides two important conclusions. First, the detection of magnetic effects indicates unambiguously that biochemical reactions involve paramagnetic intermediates; conversely, if reactions follow radical or radical ion mechanisms, they do not always show magnetic-field or magnetic-isotope dependence. Second, magnetic effects can be hidden or even eliminated by the presence of paramagnetic impurities (iron, copper, cobalt, manganese and other cations). This was proven experimentally for the ATP synthesis by creatine kinase and in mitochondria (see above). It cannot be ruled out that in other cases, too, the lack of reproducibility is caused by paramagnetic impurities. The presence of impurities does not necessarily switch off the radical or radical ion mechanisms; they can just hide the effect.

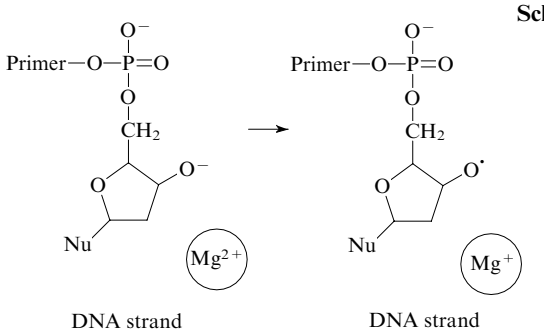
3. Magnetic field-dependent synthesis of DNA

The generally accepted mechanism of DNA replication implies successive nucleophilic addition of nucleotides (Nu) to the growing DNA chain; this mechanism does not allow for any paramagnetic intermediates. The DNA synthesis is performed by DNA polymerases and catalyzed by magnesium ions. It was found [77, 78] in experiments with pure magnesium isotopes, $^{24}Mg^{2+}$, $^{25}Mg^{2+}$ and $^{26}Mg^{2+}$, that the rate of the DNA synthesis by β-polymerase depends on what magnesium isotope resides in the enzyme catalytic site. As in the case of enzymes that synthesize ATP, a magnetic isotope effect was detected: the magnesium cation of magnetic ^{25}Mg isotope appreciably (3–5-fold) suppressed the DNA synthesis as compared with $^{24}Mg^{2+}$ and $^{26}Mg^{2+}$ ions (Figs 5 and 6). The rates of the DNA synthesis by β-polymerases for $^{24}Mg^{2+}$ and $^{26}Mg^{2+}$ being present in the catalytic site were indistinguishable.

A similar effect was found for β-polymerases bearing Zn^{2+} ions in the catalytic site: ions with magnetic ^{67}Zn nuclei substantially (2–3-fold) suppressed the catalytic activity of the enzyme as compared with ions having non-magnetic nuclei (Fig. 7).

The nuclear magnetic dependence of the DNA synthesis unambiguously indicates that the mechanism of the synthesis includes radical ion steps in which radical ion pairs are generated. It is these pairs that serve as the source of magnetic isotope effects. Presumably, electron transfer from the ribose anion of the growing DNA chain to the magnesium ion is the key reaction of the radical ion mechanism (Scheme 2):

Scheme 2



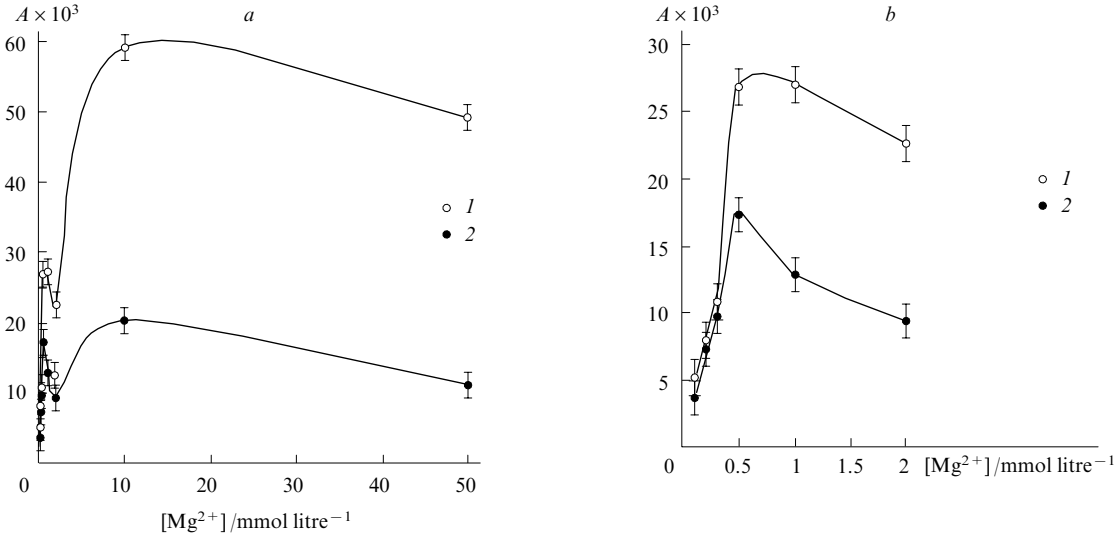


Figure 6. DNA replication rate *vs.* concentration of $^{26}MgCl_2$ (*1*) and $^{25}MgCl_2$ (*2*).[79]
The rate was measured from radioactivity A [pulses min^{-1} (mg of DNA)$^{-1}$] of the synthesized DNA with the introduced tritium-labelled dTTN nucleotide. The plots in panels *a* and *b* are given on different scales.

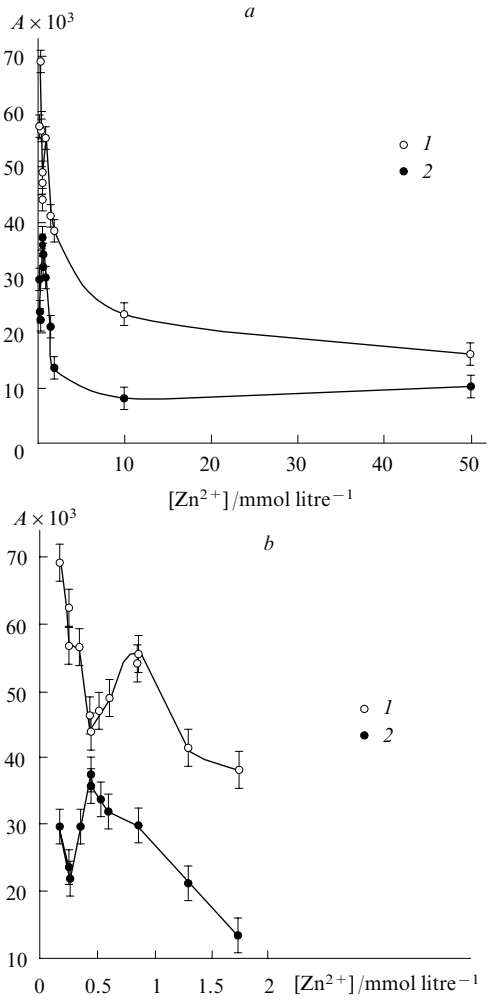
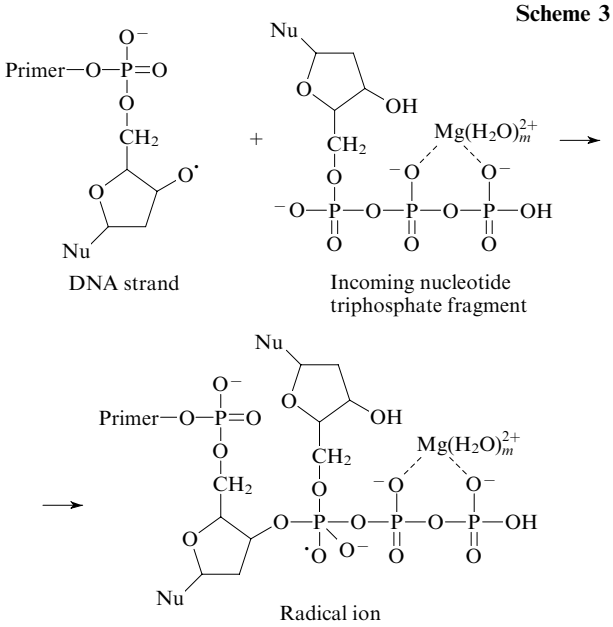


Figure 7. Rates of DNA synthesis *vs.* concentration of $^{64}ZnCl_2$ (*1*) and $^{67}ZnCl_2$ (*2*).[78]
The rate was measured from radioactivity A [pulses min^{-1} (mg of DNA)$^{-1}$] of the synthesized DNA with the introduced tritium-labelled dTTN nucleotide. The plots in panels *a* and *b* are given on different scales.

Then the ribose oxy radical adds to the P=O double bond at the nucleotide α-atom thus giving a new oxy radical (Scheme 3):

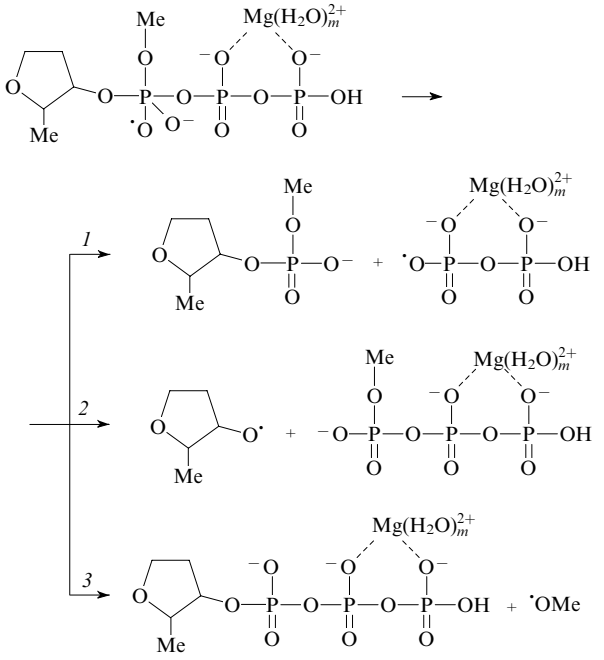
Scheme 3



The oxy radical can decay along three channels (the model reactions are shown in Scheme 4) two of which (channels *2* and *3*) terminate the DNA synthesis; only in the first channel, the pyrophosphate anion is eliminated and the nucleotide adds.

It can be seen rather easily that the radical ion mechanism mimics the nucleophilic one. The only difference is that, instead of the one-step nucleophilic addition of the ribose oxy anion to the α-phosphorus atom with liberation of the pyrophosphate anion, the radical ion mechanism includes a sequence of three steps: electron transfer, addition of the ribose oxy radical to the α-phosphorus atom and decay of the new oxy radical.

Scheme 4



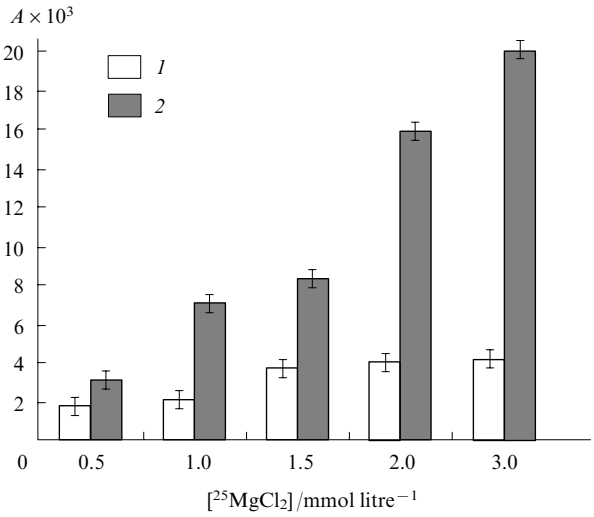


Figure 8. Magnetic field effect in the rate of $^{25}MgCl_2$-catalyzed DNA synthesis.[79]
The rate was measured from radioactivity A [pulses min^{-1} (mg of DNA)$^{-1}$]. (*1*) Magnetic field of the Earth, (*2*) 1600 G magnetic field.

The source of magnesium and zinc isotope effects is the primary radical ion pair, which exists in the singlet spin state. The back electron transfer recovers the initial reactants and shortens the lifetime of the pair thus suppressing the subsequent reactions of the oxy radicals. However, in the presence of magnetic nuclei, ^{25}Mg or ^{67}Zn, spin conversion of the radical ion pair occurs: the short-lived singlet pair is converted to the long-lived triplet pair. In the latter, the back electron transfer is spin forbidden; this stimulates the subsequent reactions of oxy radicals, thus directing the reaction along channels *1–3*. However, the addition of a nucleotide (and, hence, the the DNA synthesis) occurs only along the first channel, which is endothermic, *i.e.*, energetically unfavourable (as opposed to the exothermic channels *2* and *3*). The suppression of the DNA synthesis by the ions with magnetic ^{25}Mg and ^{67}Zn nuclei is due exactly to the fact that magnetic isotope ions switch on the triplet channel of the radical ion mechanism, which competes with the nucleophilic mechanism.

These views are consistent with the ideas of spin chemistry — a reliable and soundly substantiated science. Moreover, they predict the dependence of the DNA synthesis on the magnetic field,[78] which is supported by the diagram shown in Fig. 8. A magnetic field considerably (severalfold) increases the rate of the DNA synthesis. The physical cause of the effect is obvious: the magnetic field switches off the triplet channel of the radical ion mechanism, which competes with the nucleophilic mechanism. In other words, the magnetic field stimulates the DNA synthesis and, hence, counterbalances the suppressing effect of magnetic nuclei. In terms of spin chemistry, this outcome results from competition between the magnetic electron–nuclear interaction, which switches on the triplet channel, and the Zeeman magnetic interaction, which partly switches off this channel.

The radical ion mechanism is incompatible with the generally accepted nucleophilic mechanism and, therefore, it seems improbable; one may think than this is artefact, a mistake of unknown origin. However; both effects, *viz.*, the magnetic field and nuclear magnetic ones, prove unambiguously its existence. Among numerous mechanisms we considered, only one that is presented above can explain and cover both the DNA synthesis and magnetic effects. Moreover, the discovery of the radical ion mechanism is simultaneously a reliable proof for the nucleophilic mechanism: at low concentrations of ions, the isotope effect is not observed, the nucleophilic mechanism being responsible in this case for the DNA synthesis.

The question of whether the radical ion mechanism is significant *in vivo*, in living organisms, has not been answered. From the fact that the nuclear magnetic isotope effect is immeasurably small at low concentrations of ions (see Figs 3–5), it follows that the contribution of the radical ion mechanism to the *in vivo* synthesis of DNA is moderate. However, considering the uneven distribution of ions and their local concentrations exceeding average concentrations, one may be doubtful about this conclusion. It is only clear that both mechanisms coexist and that the nucleophilic mechanism predominates at low concentrations of ions, while the radical ion mechanism is switched on at significant ion concentrations. This feature should be used in medicine (for the control of malignant growth, therapy of cognitive disorders by transcranial stimulation, cell prolifeation, *etc.*).

X. Which magnetic field is more important, constant or alternating?

The time required for spin change in the radical (radical ion) pair, *i.e.*, the time of spin conversion is determined by the relation

$$\tau_s = (\Delta g \beta H + \sum a_i m_i)^{-1}$$

where the first term corresponds to the contribution of the Zeeman interaction to the spin conversion, while the second one characterizes the contribution of the hyperfine electron–nuclear coupling. Here Δg is the difference between the radical g-factors 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 is $10^{-7}-10^{-10}$ s, this is comparable with the chemical lifetime of the pair itself.

A constant magnetic field, both external and internal nuclear-magnetic field, performs the spin conversion by means of precession of electrons of the pair. The difference between the precession frequency of electrons belonging to the partners, which is given by $(\Delta g\beta H + \sum a_i m_i)$, accounts for the process of spin dephasing, the time of complete dephasing (rotation of the pair spins through the angle π) is the time of spin S–T conversion τ_s.

The effect of alternating (oscillating) magnetic field on the electron spins of the pair depends on the field frequency ω, *i.e.*, on the oscillation period

$$\tau_0 = \omega^{-1}$$

Low-frequency fields (such that $\tau_0 \gg \tau_s$) perform only the spin dephasing, *i.e.*, act as constant fields: the oscillation period is much longer than the time of spin S–T conversion. In other words, a radical pair 'sees' any low-frequency field that oscillates at ${\tau_0}^{-1} \ll {\tau_s}^{-1}$ frequency as a constant field.

High-frequency fields (such that $\tau_0 \ll \tau_s$) function according to two mechanisms: they perform spin conversion at any frequency through spin dephasing and at resonance frequencies, where the alternating field frequency coincides with the Zeeman electron frequency, also through spin flip (reorientation). The density of such resonance fields is low, being only a minor part of all background fields; therefore, the effect of the resonance high-frequency fields in magnetobiology can certainly be neglected (except for the exotic cases where the frequencies are specially tuned to resonance). Practically this means that all oscillating magnetic fields with <100 MHz frequency can be regarded as constant with respect to a short-lived receiver — radical (radical ion) pair. The oscillating magnetic fields with frequencies of >100 MHz (if they are not resonance fields) act on electron spins like constant fields but their efficiency is low because the slow spin system weakly responds to fast high-frequency magnetic field oscillations.

XI. Conclusion

The radical ion mechanism of the ATP and DNA syntheses is a prologue to a new biochemical paradigm; it is unfamiliar and unusual and, hence, it is met with disbelief. D MacArthur [80] is right saying, on the occasion of false discovery of the longevity gene, that the more surprising a result seems to be, the less likely it is to be true. In the first glance, the radical ion paradigm deserves a similar attitude and, therefore, almost all biochemists are suspicious about it.

It should be borne in mind, however, that this paradigm was convincingly proven by the magnetic isotope effect (for the mercury, magnesium, zinc and calcium magnetic nuclei); it was indisputably confirmed by the magnetic field effect on the ATP and DNA synthesis. Finally, it is steadily finding its place in mitochondria and in living organisms. The conditions and the extent of functioning of the radical ion mechanism and the way to switch it on and off by means of isotope ions and iron ions were established reliably and unambiguously. It is also known in which organs of the body the radical ion mechanism is most efficient.

It is clear as well how this mechanism can be used to stimulate the ATP synthesis and eliminate the ATP deficiency at cardiac diseases and how to use the magnetic isotope ions as medical agents against hypoxia and heart failure, as means for controlling the cell proliferation and cancer cell destruction.

The discovery of the radical ion and, hence, magnetic field-dependent mechanisms of two key life-supporting processes, the ATP synthesis and DNA replication, forms a physically clear molecular chemical concept in the magnetobiology as the base for further development. The key element of the concept is a radical ion pair in which the competition between chemical and physical processes (forward and back electron transfer, magnetic field-induced spin conversion and radical decay and addition reactions) is controlled by magnetic interactions. The ATP synthesis and DNA replication play a crucial role in functioning of living organisms: in cell division, in the operation of the genetic apparatus, in gene expression and synthesis of the encoded enzymes and in control of biological clock. The molecular concept in magnetobiology appears most substantiated and practically significant in both medical applications and the use of biomedical effects of electromagnetic fields. It is beyond doubt that a radical ion pair can serve to receive microwave radiation used in the transcranial magnetic stimulation. The radical ion mechanisms form the key to the understanding of numerous phenomena of magnetobiology and medicine. Moreover, they prompt ideas for new quests along the route of transformation of magnetobiology into a respected science.

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