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ELEMENTARY PHYSICOCHEMICAL PROCESSES

Genes and Cancer under Magnetic Control

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Abstract—Many experimental observations convincingly demonstrate that the genes and genome as a whole are sensitive to the magnetic fields, permanent and oscillating. The invasion of nuclear magnetic stable isotopes of Mg, Ca, and Zn in enzymatic catalysis disclosed new features of the DNA and gene chemistry; it discovered a new, radical pair mechanism, which substantiated the origin of magnetic effects. This mechanism implies electron transfer between the reaction partners; it is switched on by catalyzing ions and generates magneto-sensitive radical pairs. The key processes of gene functioning – DNA synthesis, DNA damage, and DNA repair – are shown to be magnetically controlled. A new anti-cancer strategy is suggested based on the using of the nuclear magnetic ions of magnesium, calcium, and zinc as a powerful and universal means to selectively kill only cancer cells; they are supposed to be highly promising for medical applications.

Keywords: magnetic isotope effect, genes, DNA synthesis, cancer, anti-cancer effects

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1. INTRODUCTION

Magnetic field as the permanent factor of human environment is generally accepted to influence on the health of people, but it remains to be enigmatic, contradictive, and ambiguous: there are many observations indicating its danger for the health; on the other side there exists a powerful medical technology of trans-cranial magnetic stimulation of brain, which corrects or even prevents neurological deceases (Alzheimer, Parkinson, and others). No doubts that the origin of these contradictions is hidden in the chemistry, in the molecular mechanisms.

This paper summarizes recent observations of magneto-genetic effects; its goal is to suggest and analyze molecular mechanisms underlying magnetic control of genes, to enlighten biochemical and medical consequences of the control and offer means how to deliberately use them in medicine. There are two facets in the magnetic control: the first is the elucidation and understanding new details of the molecular mechanisms; the second is the medical applications of magnetic technologies based on the magnetic effects; both are analyzed below.

2. ELECTROMAGNETIC CONTROL OF GENES

The effect of microwave radiation emitted by mobile phones on the DNA damage in follicle cells of hair in the ear canal was investigated by comet assay [1], which is known to be a rapid, simple and highly sensitive fluorescence microscopic gel electrophoresis technique used to detect DNA damage. The measured comet assay parameters (head length, tail length, comet length, percentages of comet head and tail as the indicators of the DNA damage by fragmentation) were markedly higher in the cells of men (42 persons) subjected to radiation than in the control group of men (14 persons). It was concluded that the radiation produces DNA damage in follicle cells of hair.

The action of radiation emitted from a GSM 900-MHz mobile phone on the proliferation, differentiation and apoptosis of adult murine neural stem cells were studied [2]. The number and size of resulting neuro-spheres and the percentage of cells differentiated into neurons was shown to significantly decrease with increasing exposure duration to electromagnetic field. In contrast, exposure to electromagnetic field at different durations did not effect on the viability, apoptosis and differentiation of astrocytes. These results unambiguously exhibit magnetically induced damage of genes. However, the interrupting regime of electromagnetic irradiation seems to create conditions for the repair of damaged DNA and genes; this observation is important to keep in mind for users of mobile phones. Magnetic control of the DNA damage and repair on the molecular level is a key to realize the

effects of mobile phones, high voltage lines and any electromagnetic sources on the human health.

On the contrary, the long-term (2 years) exposure of murine brains to mobile telephone radiofrequency fields [3] did not produce any astrocyte reaction; however, the exposure has been carried out in the interrupting regime, so that this observation is in agreement with the previous one. The exposure of the rats to long-term radiofrequency radiation at 900, 1800, and 2100 MHz results to the oxidative DNA damage and single-strand DNA breaks in the frontal lobe of brain tissues [4]. In a white-rot fungus *Irpex lacteus* used in medicine and subjected to the electromagnetic treatment there were identified by RNA- and real-time PCR sequencing technologies 3268, 1377, and 941 differentially expressed genes [5]; it was concluded that the global gene expression changes induced by electromagnetic treatment explained the pleiotropic medical effects of *Irpex lacteus*. It was pointed out that a large number of studies have shown that microwave radiation can cause a series of adverse reactions in the central nervous system, including sleep disorders in addition to learning and memory impairments [6]. The elevated risks of dementia, motor neuron disease, multiple sclerosis and epilepsy in relation to exposure to low-frequency magnetic fields was observed [7]. The hazards of electromagnetic fields for the human health and the mortality induced by the fields were also emphasized by statistical analysis [8].

However, trans-cranial magnetic stimulation was shown by numerous works to unambiguously manifest that the magnetic signals stimulate, trigger the expression of brain's genes and production of various enzymes (for review see [9]). Namely these magnetically induced positive effects are supposed to be responsible medical effects of trans-cranial magnetic stimulation as a powerful means to correct or even to prevent cognitive deceases (see Section 5).

At first sight these observations are contradictive: sometimes the effects are positive, sometimes they are negative. However, it is necessary to keep in mind that the magnetic effects are switched on or off as a function of concentration of ions in cells. No needs to remind that the ions are distributed in different cells not homogeneously; moreover, their concentration depends on the physiological state of cells and organisms, on the diet, etc. It means that the electromagnetic effects on the living organisms are hardly certainly predictable but they may be deliberately controlled for medical purposes, particularly in the case when the ions may be delivered on target; molecular mechanisms underlying these effects will be discussed later.

3. DNA DAMAGE INDUCED BY MAGNETIC NUCLEI

The DNA and genes are also subjected to the damage induced by nuclear magnetic ions. The direct evidence follows from the effect exhibited by HL-60 cancer cells: the loading of these cells by $^{43}Ca^{2+}$ ions produces short DNA fragments that count 25–35 nucleotides in length contrasting with the normal 180–210 nucleotides produced by $^{40}Ca^{2+}$ polymerase [10]. The ions $^{25}Mg^{2+}$ and $^{67}Zn^{2+}$ demonstrate the similar effects: they also produce abnormally short (25–35 nucleotides) fragments [11], which are not formed in cells loaded with ions $^{24}Mg^{2+}$ and $^{64}Zn^{2+}$. The abnormally short, an "invalid" DNA segments, are known to be inefficient in the DNA repair. These results indicate that the reactions responsible for the DNA damage are magnetically controlled. Evidently, microwave magnetic fields, acting on the macroscopic level, and internal magnetic fields of magnetic nuclei of catalyzing ions, acting on the atomic level, produce identical effects: they both induce DNA damage.

4. MAGNETIC CONTROL OF THE DNA REPAIR

Among the various DNA damages induced by radiation the DNA double-strand breaks are known to be the most dangerous for the survivability of cell; comet assay was used to detect these breaks and their repairing [12]. The rate of repairing in presence of $^{25}Mg^{2+}$ ions was shown to be slower than in the presence of $^{24}Mg^{2+}$ ions. The decay kinetics of double-strand DNA breaks, induced by radiation, is different for $^{25}Mg^{2+}$ and $^{24}Mg^{2+}$ ions. The decay occurs as a first order reaction; the rate constants for this process are $1.1 \times 10^{-3}\ s^{-1}$ and $1.6 \times 10^{-3}\ s^{-1}$ for $^{25}Mg^{2+}$ and $^{24}Mg^{2+}$ ions respectively. Evidently, the DNA repairing exhibits remarkable isotope effect: in the presence of $^{25}Mg^{2+}$ ions the rate of repair is by 1.5 times lower than in the presence of $^{24}Mg^{2+}$ ions, demonstrating that the repairing is a magnetically sensitive process. This result is in accordance with the effect of suppressing DNA synthesis by nuclear magnetic isotopic ions of Mg, Ca, and Zn (Section 7) and indicates that the DNA synthesis seems to be the important chemical part of the total repairing process.

5. GENES OF BRAIN UNDER MAGNETIC CONTROL

A new technology of brain and cortex neuron stimulation by oscillating magnetic fields is being rapidly invaded in modern medicine, in particular, into neurophysiology; the magnetic fields are supplied to patients' head by means of magnetic coils fed by alternating current. The alternating magnetic field, generated by the coils, penetrates through the cranial bones (this gave rise to the name "trans-cranial") [13–15]. A

new, advanced version of this technology employs trans-cranial stimulation together with brain imaging, which opens up the way for direct targeted stimulation of the specified brain areas (navigational trans-cranial magnetic stimulation) [9].

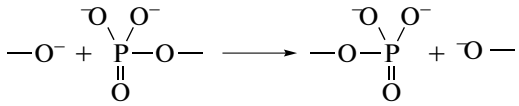
This technology brings about two significant questions: (1) whether or not biological subjects (in particular, neurons) are able to perceive the magnetic field, and (2) whether or not the magnetic reception is significant for the functioning of these subjects. Direct medical experience answers "yes" to both questions: it is possible to treat cognitive disorders and neurological diseases (stroke consequences, epilepsy, Parkinson disease, pain syndromes, paralysis, and schizophrenia). Moreover, there is reliable evidence that trans-cranial magnetic stimulation performs molecular transformations in the cortex, which are remembered and retained for long time (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 (it is considered below).

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, they try to find out what genes act as TMS receivers and what genes are TMS-insensitive; the second group, which will be considered here, deals directly with the TMS-induced changes in the genome. 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 [16]. High levels of the NO neurotransmitter and cGMP (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 morphology changed. The only possible conclusion was drawn: the origin of the effects should be in increased expression of genes responsible for the synthesis of the neuronal NO-synthase in the cerebral cortex of rats subjected to TMS [17]. Trans-cranial magnetic stimulation is also used to modulate astroglial gene expression [18].

These examples do not exhaust numerous observations of magnetically induced modification of genes by TMS signals (for review see [9]); they unambiguously prove that these signals stimulate, trigger gene expression and enhance production of enzymes. They are sought to be responsible for the long-lasting duration of the therapeutic effects of TMS.

6. MOLECULAR MECHANISMS OF GENE CHEMISTRY

It is commonly accepted that the DNA synthesis occurs as a nucleophilic reaction, which implies that the reaction proceeds as an attack of phosphorus atom of the approaching nucleotide by the ribose oxy-anion according to the scheme



This reaction excludes formation of paramagnetic intermediates in the DNA synthesis but it requires to overcome powerful repulsion between reactants, it is energy strongly deficient and needs to overcome the energy barrier 42–46 kcal/mole [19, 20]. This high barrier is a reason, why DNA synthesis does not occur in homogeneous solutions, it is accomplished only by DNA polymerases, special molecular machines. A source of the energy needed to overcome the energy deficit for energy-expensive nucleophilic reaction is thought to be a compression of the catalytic site and reactants overcoming their repulsion by protein mechanical energy.

Enzymatic DNA synthesis is known to be catalyzed by Zn^{2+}, Ca^{2+} and Mg^{2+} ions, which are traditionally considered to coordinate reactants in the catalytic site keeping them on the reaction trajectory to facilitate nucleophilic attack. The prediction [21] and discovery [22] of magnetic isotope effect in chemistry [23–26] stimulated invasion of magnetic isotopes in geological and environmental chemistry [27], in biochemistry and medicine [28]. In enzymatic reactions the effects were first detected in the ATP synthesis by isolated enzymes [29] and then by whole living organisms [30]. Nuclear magnetic ions $^{25}Mg^{2+}$ were shown to strongly, by 3–5 times, increase the yield of ATP in heart muscle preventing ATP deficiency and related deceases.

Magnetic control in chemical genetics occurs by radical pair mechanism (RPM), which is well known in chemistry [31–35]; it implies pair wise generation of radicals by electron transfer between reaction partners. The reactions in the radical pair are controlled by powerful factor, an angular momentum. Conservation of the angular momentum (electron spin) is a fundamental and universal principle: all molecular processes are allowed only for those spin states of reactants whose total spin is identical to that of products. Magnetic fields are universal means to overcome spin prohibition and to control chemistry. The RPM may be also controlled by magnetic fields of isotopic nuclei; the latter is known as the magnetic isotope effect that is the dependence of the reaction rates on the nuclear magnetic moments of reactants.

In the majority of publications, exhibiting magnetic effects on the gene chemistry [36–46], it is recognized that the sources of the effects remain enig-

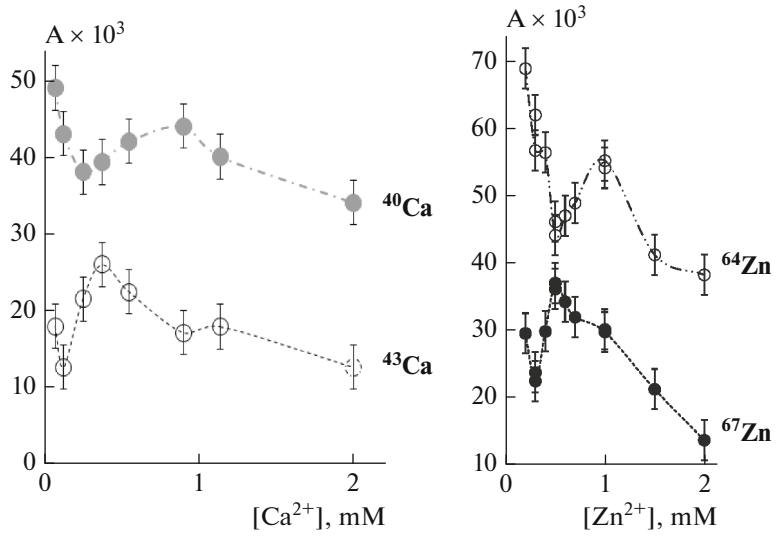


Fig. 1. The rate of the DNA synthesis by polymerase β as a function of the concentration of ions in the pairs $^{40}Ca^{2+}/^{43}Ca^{2+}$ and $^{64}Zn^{2+}/^{67}Zn^{2+}$. Tritium radioactivity A is measured as the number of counts/min/mg of DNA.

matic. In principle one can imply magnetic control of genes in three processes: the DNA synthesis, which elongates DNA chains creating genes; the cleavage, the scission of DNA chains producing DNA damage and destroying genes; and the DNA repair. All three processes are shown to be magnetically vulnerable and result to the total magnetic control of genes; the latter is shown to be a powerful means to kill cancer cells.

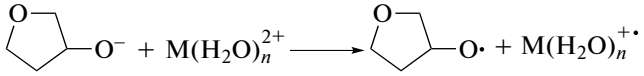
7. MAGNETIC CONTROL OF THE DNA SYNTHESIS

DNA synthesis is generally accepted to occur as a nucleophilic reaction catalyzed by Mg^{2+}, Ca^{2+}, and Zn^{2+} ions. The substitution of these catalyzing ions in polymerases by the ions $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$ with magnetic nuclei was shown to produce a huge isotope effects: nuclear magnetic ions by 3–5 times suppress DNA synthesis with respect to those with nonmagnetic ions [47, 48].

7.1. Calcium and Zinc Ions

Figure 1 illustrates these magnetic effects for Ca^{2+}, and Zn^{2+} ions.

These observations demonstrate that the DNA synthesis occurs by radical pair mechanism (RPM); the idea of the RPM in enzymatic reactions was first prompted and then dictated by observation of magnetic effects. The following steps of the mechanism may be suggested. In the case of DNA synthesis electron is donated by the ribose oxy-anion of the growing DNA chain to the $M(H_2O)_n^{2+}$ ion (M is Mg, Ca, Zn; Scheme 1):



Scheme 1. Generation of the radical pair by electron transfer.

The energy of this reaction was computed [35] to be negative for the large n, i.e. electron transfer is endothermic and forbidden in water. However, it is energy allowed even for the fully completed first hydrated sphere ($n = 6$) of magnesium, zinc, and calcium ions. Again, like in the case of the ATP synthesis [29], the removal of water molecules by compression of the catalytic site in the DNA polymerases dehydrates catalyzing ions switching on energy cheap RPM.

It is remarkable that the isotope effect on the DNA synthesis, certifying radical pair mechanism, appears at very low concentration of the ions. It seemingly evidences that even the first ion, which enters into the enzymatic site, switches on electron transfer and radical pair mechanism (the function of the second and third ions will be discussed later). The appearance of the isotope effect at the low concentration of ions testifies the dominating contribution of the radical pair mechanism in the DNA production.

Note, that the RPM, being on the energy scale by order of magnitude cheaper that the nucleophilic one, is induced by both sorts of ions, magnetic and nonmagnetic, they both decrease the efficiency of DNA synthesis; the only difference is that magnetic ions function more strongly and suppress DNA synthesis by 3–5 times more efficiently than nonmagnetic ones.

7.2. How to Switch on the RPM

Electron transfer as a source of the radical pairs is induced by remarkable property of enzymes to squeeze water molecules out of the catalytic site when the enzyme domains are drawn together to unite reagents [49]. The removal of water partly dehydrates catalyzing ions $M(H_2O)_n^{2+}$ (M is Mg, Zn, or Ca), increasing both positive charge on the core metal and electron affinity of the ion, so that at some threshold value n^* electron transfer becomes exoergic and energy allowed. The water molecule number n^* in complex $M(H_2O)_n^{2+}$ functions as a trigger, it switches over the reaction between endoergic and exoergic regimes. At $n > n^*$ electron transfer is endoergic and energy forbidden, at $n < n^*$ it is exoergic and energy allowed. When n reaches n^* electron transfer becomes inevitable and switches on radical pair mechanism. According to this mechanism the compression energy of enzymatic site is spent on the removal of water out of the ion hydrate shell; it activates this ion as an electron acceptor.

The second step is an addition of the ribose oxy-radical to the P_α–O double bond of the incoming nucleotide. It generates a new oxy-radical OXY, which is decomposed by β-scission mechanism along the three channels. Ultimately the RPM appears to be strongly destructive and almost prevents DNA synthesis; this mechanism is certainly supported by magnetic field effects [48].

In terms of the RPM nuclear magnetic effect arises in the primary radical pair produced by electron transfer. As any pair generated from the diamagnetic molecules, it is in singlet spin state, in which back electron transfer is spin allowed and regenerates reactants. However, if the ion with magnetic nuclei ^{25}Mg, ^{43}Ca, or ^{67}Zn is presented in the catalytic site, the singlet-triplet spin conversion, induced by hyperfine coupling in the radicals $M(H_2O)_n^{+\bullet}$, competes with back electron transfer and transforms short living singlet pair into the long living triplet pair, in which back electron transfer is spin forbidden; it mostly decomposes. As a result the ions with magnetic nuclei stimulate singlet-triplet spin conversion of the primary pair and direct DNA synthesis along the radical, destructive pathway suppressing ultimately DNA synthesis.

7.3. Magnesium Ions

The behavior of magnesium ions is different from that of calcium and zinc ions. It is clearly seen in Fig. 2: in contrast to calcium and zinc ions there is no isotope effect at low concentration of magnesium ions that is DNA synthesis occurs as a nucleophilic process. At the higher concentrations, when the second ion enters into the enzymatic site, the RPM is switched on, resulting to suppression of DNA synthesis; the appearance of isotope effect is an unambiguous indicator of the RPM. Note, that again the RPM is induced by both sorts of ions, magnetic and nonmagnetic, they both decrease the efficiency of DNA synthesis; the only difference is that magnetic ions function more strongly and suppress DNA synthesis by 3–5 times more efficiently than the nonmagnetic ones. Polymerases with $^{24}Mg^{2+}$ and $^{26}Mg^{2+}$ ions exhibit no difference in enzymatic activity; it means that the mass-dependent isotope effect is negligible.

Now the question is why in the case of magnesium the RPM is switched on by the second ion in enzymatic site in contrast to calcium and zinc, where this mechanism is switched on by the first ion. The answer seems to be the following: the first magnesium ion in enzymatic site is tightly adheres to the pyrophosphate residue and is not able to be dehydrated and serve as electron acceptor, only the second ion may be considered as a "free," able to release water molecules and switch on the RPM by electron transfer. The calcium and zinc ions have the lower affinity to the pyrophosphate residue and may be considered as a "free," able to switch on the RPM by electron transfer.

7.4. Polymerase Chain Reaction

The famous polymerase chain reaction (PCR) was shown to be also suppressed by $^{25}Mg^{2+}$ ions [48] convincingly confirming nuclear magnetic control of the DNA synthesis (Fig. 3); the efficiency of the DNA synthesis by PCR enzyme as a function of concentration and isotopes is identical to that of polymerase β (Fig. 2).

7.5. Does DNA Polymerase Need the Third Ion?

The invasion of the metal ions (the first in the case of Ca and Zn and the second in the case of Mg) in enzymatic site switches on radical pair mechanism. What does the third and the next ions? By using an elegant time-resolved technique of x-ray crystallography it was shown [50] that the capture of the third Mg^{2+} ion is required for the DNA synthesis to occur. This conclusion is valid for the reaction in crystallo-catalysis, when the escape of the pyrophosphate ion is restricted in confined space of assembled complex; then the third ion stimulates accelerating departure of the pyrophosphate ion. This conclusion is also valid for the native DNA synthesis as shown in Figs. 4 and 5. After switching on the RPM and decreasing the rate of DNA synthesis it is observed significant increasing the rate assisted by the third ion, both magnetic and nonmagnetic. Evidently, like in the case of crystallo-catalysis, the third ion accelerates departure of pyrophosphate ion; this effect is exhibited by Mg (Figs. 4 and 5) as well as by Ca and Zn ions, both magnetic (^{25}Mg, ^{43}Ca, ^{67}Zn) and nonmagnetic (^{24}Mg, ^{26}Mg, ^{40}Ca, ^{64}Zn) [47]. Note, that the third ion does not change

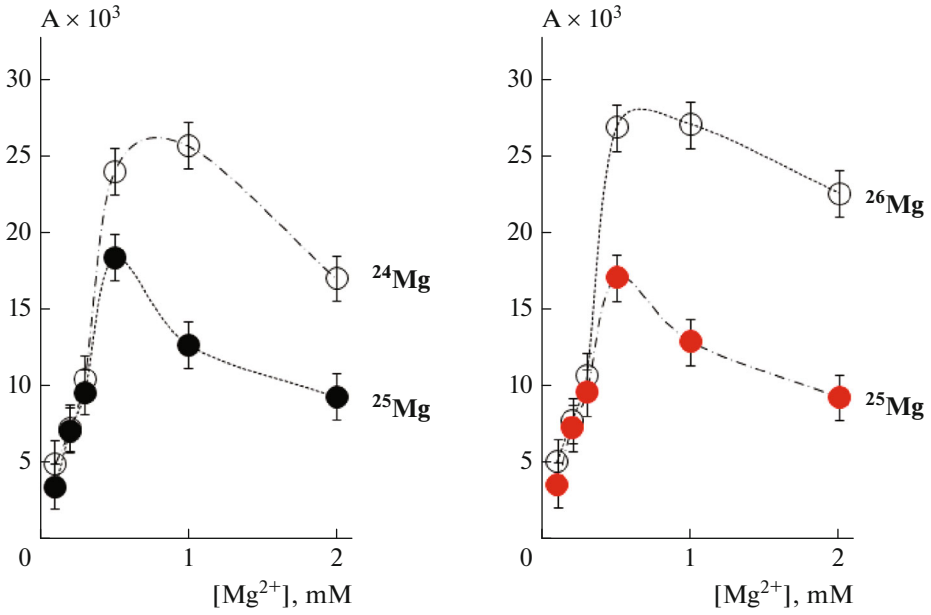


Fig. 2. The rate of the DNA synthesis by polymerase β as a function of the concentration the magnesium ions in pairs $^{24}Mg^{2+}/^{25}Mg^{2+}$ and $^{26}Mg^{2+}/^{25}Mg^{2+}$. The radioactivity A of tritium labeled DNA is measured as the number of counts/min/mg of DNA.

isotope effect; it seems to be an indication that the third ion seats on the pyrophosphate group facilitating its departure and stimulating DNA synthesis. The reason is that the addition of the third ion occurs by noncovalent bonds; this ion does not participate in the spin selective reaction itself and does not produce additional magnetic isotope effect. These considerations are in a perfect agreement with the post-chemistry steps of nucleotide incorporation by DNA polymerase analyzed by Reed et al. [51]. Thus, the efficiency of DNA-polymerases depends on the number of ions in the catalytic site: the first ion of calcium and zinc induces magnetically sensitive radical pair mechanism, in the case of magnesium it makes the second ion; the third and the following ions are accepted by pyrophosphate residue facilitating its departure and stimulating DNA synthesis.

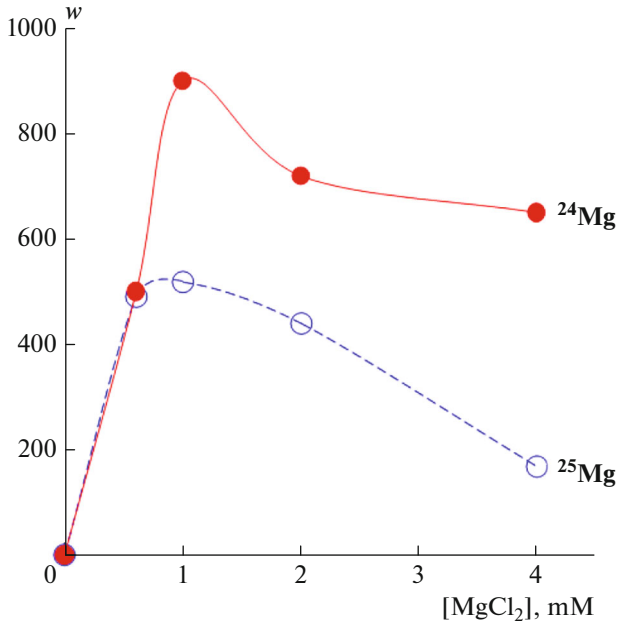


Fig. 3. The rates of the DNA synthesis by polymerase chain reaction in pairs $^{24}Mg^{2+}/^{25}Mg^{2+}$.

7.6. Summarizing Comments on the DNA Synthesis

The invasion of nuclear magnetic isotopes in the DNA synthesis has disclosed the new facets of this process. The most important result seems to be the discovery of the magnetic isotope effect of the catalyzing metal ions on the DNA synthesis. It certifies the new, radical pair mechanism, which is induced by electron transfer from the ribose ring of the growing DNA strand to the metal ion. The effects of magnetic nuclei and magnetic fields on the DNA synthesis are reliable evidences that the radical pair mechanism is an unambiguous phenomenon. The second important result is that the efficiency of DNA synthesis depends on the number of metal ions in enzymatic site and these dependences are different for the different ions. It compels to accept the following statements.

First, the radical pair mechanism is destructive, it suppresses DNA synthesis; this effect is produced by any metal ion, either magnetic or nonmagnetic, but

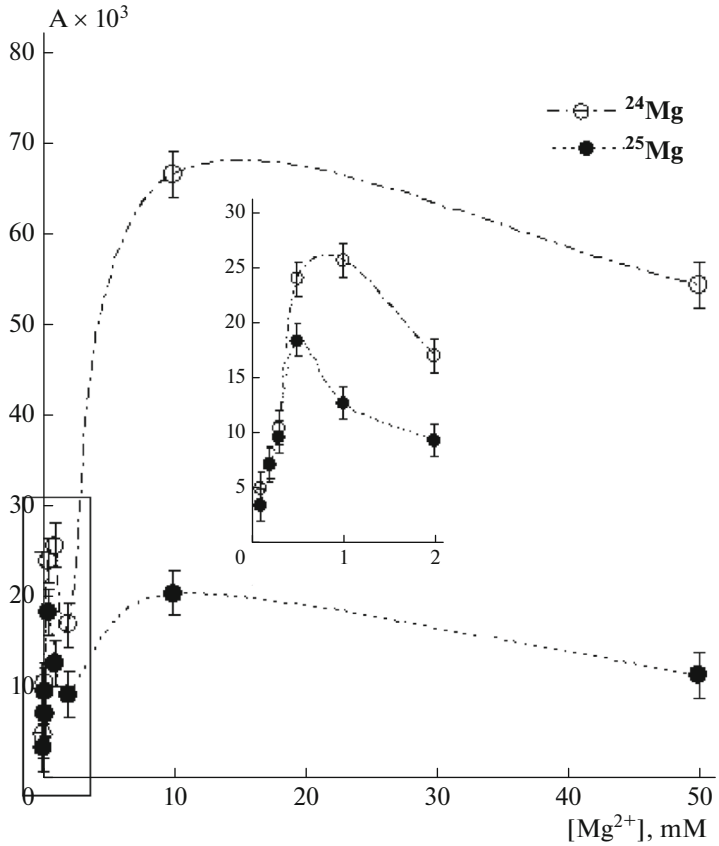


Fig. 4. The rate of the DNA synthesis as a function of concentration of the catalyzing ions in the isotopic pair $^{24}Mg^{2+}/^{25}Mg^{2+}$. The inserted fragment refers to low concentrations and reproduces Fig. 2.

the suppression ability of the former is by 3–5 times stronger than that of the latter (Figs. 1–5).

Second, DNA synthesis may occur in the absence of metal ions. Indeed, in the case of Ca and Zn the very low concentrations of the ions switch on the destructive radical pair mechanism which suppresses DNA synthesis; nevertheless, even at these conditions the yield of the DNA is rather high (Fig. 1).

Third, the addition of the metal ions to the pyrophosphate residue is an important process for the efficiency of DNA synthesis. This was suggested and established by Gao and Yang (ref. 50) for the crystallocatalysis, however it is valid also for the "homogeneous" DNA synthesis. Indeed, the increase of the ion concentration is accompanied by increasing the DNA yield, however neither isotope effect, nor magnetic field effect are changed, that is radical pair mechanism continues to function, but the adhered to the pyrophosphate residue metal ions stimulate DNA synthesis, even compensating destructive function of the radical mechanism.

Fourth, in the case of Ca and Zn even the first ion seems to switch on the radical pair mechanism, but in the case of Mg the first ion seems to adhere to the pyrophosphate residue stimulating DNA synthesis without isotope effect (Fig. 2); only the second ion Mg^{2+} in enzymatic site switches on the radical mechanism resulting to the magnetic effects and decreasing DNA yield.

Fifth, the concentration dependences of the DNA yield are almost identical for magnetic and nonmagnetic ions (Figs. 1–5); it supports the idea that after switching on radical pair mechanism the subsequent ions, which enter in enzymatic site, are seemingly sitting on the pyrophosphate residue and do not interfere in the radical pair mechanism.

Despite the fact that some details of the mechanism are not clear it is unambiguous that the radical pair mechanism functions in synthesis, fragmentation, and repair of genes; it is a powerful means to understand and deliberately use magnetic effects in medicine, particularly in the trans-cranial magnetic stimulation and cancer killing.

8. CANCER UNDER MAGNETIC CONTROL

According to the WHO reports cancer remains to be one of the two leading causes of death worldwide; the representative data of cancer induced mortality in the large Macheng City (China) were collected and

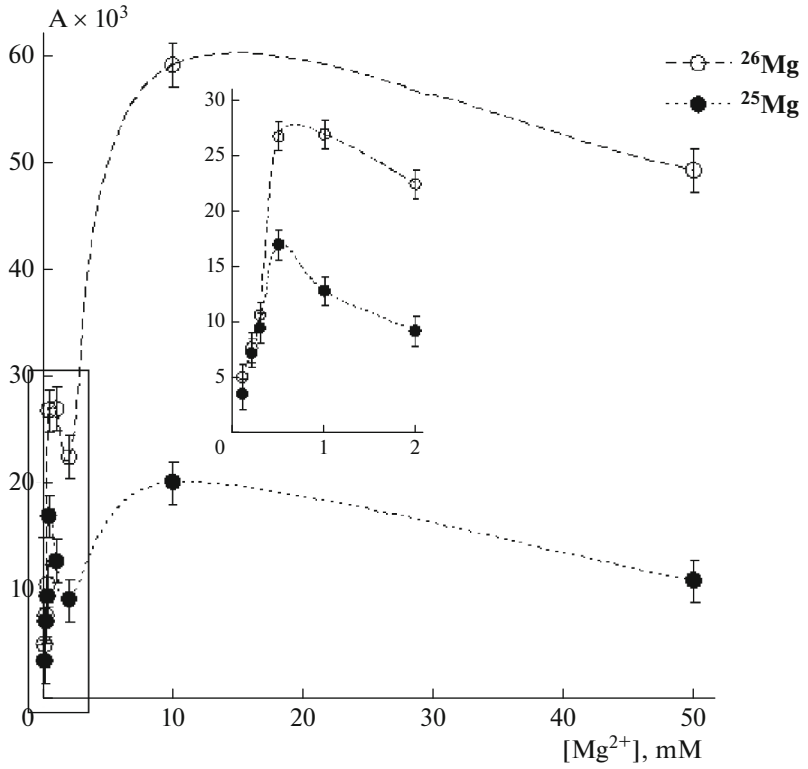


Fig. 5. The rate of the DNA synthesis as a function of concentration of the catalyzing ions in the isotopic pair $^{26}Mg^{2+}/^{25}Mg^{2+}$. The inserted fragment refers to low concentrations and reproduces Fig. 2.

summarized by Li et al. [52]. They certify some clearly expressed tendencies.

1. The cancer induced mortality increases as the age increases, and then reaches a maximum and decreases. The peak of mortality depends on the period when the mortality data were collected: for the period of 1984–1988 it is at the age group of 45–49, for the period of 2009–2013 it is at the group 40–44. It clearly indicates that the cancer mortality over the period of 25 years (the lifetime of one generation) is shifted to the more young age by 5 years, i.e. cancer kills more young generations.

2. This unfavorable trend becomes even more convincible by comparing the curves *1* and *2*: cancer induced mortality over the period of 2009–2013 is almost doubled with respect to the period of 1984–1988.

3. The mortality of the young age group 20–24 is by almost twice larger than that of the age group 80–84. It does not mean that the cancer induced mortality decreases for the elderly people; it is just the evidence that other deceases become more important and dominating.

8.1. Magnetic Effects on the Cancer

There are several hundred publications concerning antitumor magnetic effects; their collection is out of the aims of this paper. Only the recent publications will be considered as the examples. Low frequency magnetic field (0–0.15 T, 4.2 Hz) has been shown to inhibit by over 30% melanoma, liver and lung cancer growth in mice bearing MDA-MB231 and MCF7 human breast cancer cells [53]. The authors claim that this effect has clinical potentials to inhibit breast cancer growth. A different effect of electromagnetic irradiation on viability of cancer and noncancerous cells was found [54].

In another study the antitumor effect of the magnetic field against neuroblastoma and nephroblastoma is reported [55]. After 2 h per day exposure to the magnetic field of the cells their viability decreased significantly after 2 days. After 3 days, inhibition rates of 17–22% in these cells were achieved. Exposure to the field was shown to decrease cell proliferation and induce apoptosis. Electromagnetic fields of low frequencies 7.83 and 60 Hz were shown to inhibit B16F10 cancer cells [55]; exposed to sweep frequencies for 24 hours these cells were inhibited by 17–26% compared with those of the control group. There are many other similar observations cited in references [36–46].

8.2. Nuclear Magnetic Anti-Cancer Effects

Nuclear magnetic control of the DNA synthesis and gene repair may appear to be important for vitality

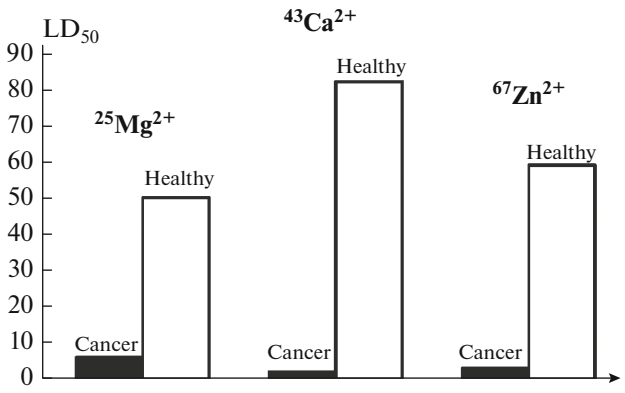


Fig. 6. The LD_{50} of the cells loaded with $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$ ions for the cancer (left columns) and healthy (right columns) cells.

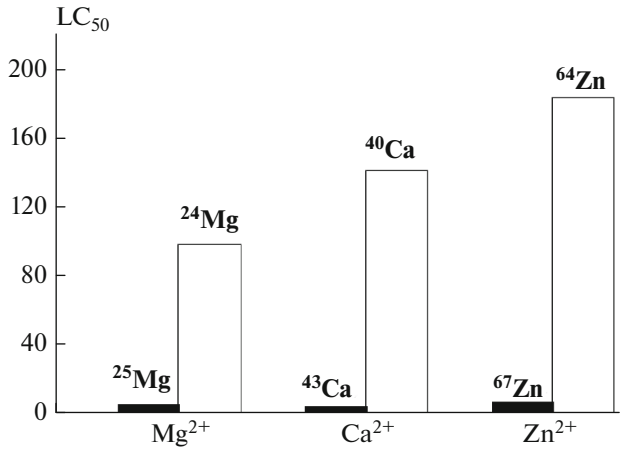


Fig. 7. The LD_{50} magnitudes for the retinoblastoma cancer cells loaded with magnetic (left columns) and nonmagnetic (right columns) ions Mg^{2+}, Ca^{2+}, and Zn^{2+}.

of cancer cells. Indeed, as shown in Section 7 nuclear magnetic ions $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$ control DNA synthesis and strongly, by 3–5 times, suppress catalytic activity of polymerases. These ions were tested as a means to kill cancer cells HL-60; the results are presented in Fig. 6; they unambiguously demonstrate different survival of both sorts of cells: cancer cells are much more vulnerable with respect to nuclear magnetic ions than the healthy cells [10, 56, 57]. It means that magnetic control of the DNA synthesis by nuclear magnetic ions of magnesium, calcium, and zinc is a powerful and universal anti-cancer means; they strongly, by 20–40 times, increase mortality of cancer cells.

The remarkable anti-cancer effects were discovered by Bukhvostov et al. [58, 59]. The inhibition of DNA synthesis by polymerase β from the retinoblastoma cancer cells Y70 and WERI-RB loaded with $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$ ions is accompanied by the sharp increasing the cell mortality: the LC_{50} values are significantly, by 10–40 times, less for the cells with $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$ ions than for the cells with $^{24}Mg^{2+}$, $^{40}Ca^{2+}$, and $^{64}Zn^{2+}$ ions. Decreasing catalytic activity of polymerase by 3–5 times, nuclear magnetic ions $^{25}Mg^{2+}$, $^{43}Ca^{2+}$, and $^{67}Zn^{2+}$ even more strongly, by 10–40 times, increase mortality of cancer cells (Fig. 7). No doubts that the same mechanism operates in other polymerases, which accomplish replication of DNA and transcription of RNA, because DNA and RNA synthesis are chemically absolutely identical. It means that the nuclear magnetic ions suppress synthesis of DNA, m-RNA, and t-RNA, controlling all three key processes in cell – replication, transcription, and translation; these ions may be considered as a powerful and universal anti-cancer means [60].

The large effect was found for the HL60 cells: the LD_{50} for leukemia cells loaded with $^{67}Zn^{2+}$ ions was 20 times less than LD_{50} for the healthy cells; it means that the nuclear magnetic ions are 20 times more efficient as the cancer cell killers [61]. The extreme vulnerability of cancer cells to the ions with magnetic nuclei may be considered as a powerful and universal means to kill only cancer cells.

9. COVID-19

It is worth noting that the widely spread in the world COVID-19 is recently proposed to be manifestation of the magnetically induced transformation of pathogenic coronavirus from endogenous virus within the human genome via chiral symmetry breaking and magnetic catalysis, which is mediated by magnetic anomalies [62, 63]. At first glance this idea seems to be speculative but there are some arguments, which do not allow to ignore it; of course, this hypothesis needs to be deliberated and analyzed.

10. CONCLUSION

Both isotope and magnetic field effects reliably certify that the key processes of gene modification – DNA synthesis, DNA damage, and DNA repair – are magnetically controlled. It is worthy to emphasize that the key to the understanding and deliberately using magnetic control in gene and cancer chemistry is the radical pair mechanism; it is inevitably switched on when metal ion (the first one in the case of Ca and Zn, the second one in the case of Mg) enters into the enzymatic site, no matter is it nonmagnetic or magnetic. But magnetic ions function much more efficiently than nonmagnetic ones due to the violation of angular momentum forbiddance by electron-nuclear magnetic interaction.

No doubts that the same mechanism operates in replication of DNA and transcription of RNA, because DNA and RNA synthesis are chemically absolutely identical. It means that the nuclear magnetic ions suppress synthesis of DNA, m-RNA, and t-RNA, controlling all three key processes in cell – replication, transcription, and translation; these ions induce mortality of cancer cells and may be consid-

ered as the safe, powerful and universal anti-cancer means. Both nuclear magnetic effects and electromagnetic effects are in perfect consistency, they are seemingly the most promising in the two medical applications: trans-cranial electromagnetic stimulation of brain neurons and synapses as a means to correct or even prevent cognitive deceases (Parkinson, Alzheimer), and nuclear magnetic stable isotopes as a powerful anti-cancer means.

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