Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2023**; 28(10): 252
https://doi.org/10.31083/j.fbl2810252

Original Research

8-Oxoguanine-DNA-Glycosylase Gene Polymorphism and the Effects of an Alternating Magnetic Field on the Sensitivity of Peripheral Blood

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Academic Editor: Ricardo Jorge Pinto Araujo
Submitted: 14 July 2023 Revised: 24 August 2023 Accepted: 6 September 2023 Published: 20 October 2023

Abstract

Background: The production of reactive oxygen species (ROS) in animals and cells often results from exposure to low-intensity factors, including magnetic fields. Much of the discussion about the initiation of oxidative stress and the role of ROS and radicals in the effects of magnetic fields has centered on radical-induced DNA damage. **Methods**: The DNA concentration in the final solution was determined spectrophotometrically. Typing of the polymorphic variant rs1052133 of the 8-oxoguanin DNA glycosylase (*hOGG1*) gene was performed by polymerase chain reaction. An enzyme immunoassay was performed to determine the level of 8-oxyguanine in DNA. To process samples exposed to an alternating magnetic field, the authors developed a device for the automated study of biological fluids in an alternating magnetic field. The content of hydrogen peroxide in aqueous solutions of DNA was determined using the spectrophotometric method. **Results**: It was experimentally determined that an increase in the concentration of hydrogen peroxide in an aqueous medium by 3–5 times under the action of a low-frequency magnetic field reduces the resistance of the genomic material to oxidative modification and the accumulation of 8-oxyguanine in DNA. A model is proposed for the mechanism of action of a low-frequency magnetic field on aqueous solutions of nucleic acids and proteins, which satisfies the model of a chemical oscillator for the transformations of reactive oxygen species in an aqueous medium. The model illustrates the oscillating nature of the processes occurring in an aqueous solution of DNA and makes it possible to predict changes in the concentration of hydrogen peroxide in an aqueous solution of biopolymers, depending on the frequency of the acting low-intensity magnetic field. **Conclusions**: The key element in the mechanisms involved in the effects of low-intensity magnetic field on living systems is the occurrence of ROS generation in the aquatic environment of chemical oscillators, in which the competition of physical and chemical processes (electron transfers, reactions of decay and addition of radicals, spin magnetically induced conversion, synthesis, and decay of the longest-lived form—hydrogen peroxide) is controlled by a magnetic field.

Keywords: low-frequency magnetic field; 8-oxoguanine-DNA-glycosylase; polymorphism; hydrogen peroxide; reactive oxygen species; chemical oscillator

1. Introduction

The most common product of oxidative DNA damage under oxidative stress is 8-oxo-7,8-dihydroguanine (8-oxoG), which is the main biomarker of genome conformational rearrangements [1]. According to ESCODD (European Standards Committee on Oxidative DNA Damage), the level of endogenous 8-oxoG in DNA is about one 8-oxoG per 10^6 G. Under genotoxic stress, this indicator can increase several fold [1]. It has been noted that the level of 8-oxoG increases in smokers and in a number of diseases [2]. The appearance of 8-oxoG in the hereditary material of the cell indicates destabilization of the genome, resulting from changes in the antioxidant system of the body or its individual tissues and cells. The accumulation of 8-oxoG in biological fluids is one of the best biomarkers of genotoxic oxidative stress in various pathophysiological conditions.

During excisional repair, damaged areas are cut out of the DNA strand and the gaps are filled with intact material. In humans, 11 glycosylases have been isolated and described. These are 8-oxoguanine-DNA-glycosylases (hOGG1, EC 3.2.2.23), which remove 8-OH-guanine, leaving behind a single-strand break [3,4]. As a result of the 8-oxoguanine-DNA-N-glycosylase (hOGG1, EC 3.2.2.23) enzymatic function, the sequential hydrolysis of the N-glycosidic bond occurs from the 3′ end of the damage and the binding of 8-oxoG to the active center [5]. Simultaneously, the enzyme exhibits a highly specific β-lyase activity against the remaining AP sites, thereby "reversing" the 8-oxoG from the DNA molecule.

The production of reactive oxygen species (ROS) in animals and cells often results from exposure to low-intensity factors, including a magnetic field [6–15]. ROS

cause a shift in the state of the pro-/antioxidant system, thereby contributing to the formation of varying degrees of oxidative stress, which is one of the reasons for the disruption in the hereditary material structure [16,17]. The corresponding hypotheses and experimental data are summarized and discussed in several reviews on this topic [6,18–21]. Much of the discussion about the initiation of oxidative stress and the role of ROS and radicals resulting from the effects of magnetic fields is focused on DNA damage caused by radicals [20,22,23].

Biological systems are constantly under the influence of natural and artificial sources of magnetic fields (MFs). In the course of evolution, they have developed mechanisms for perceiving information about the state of the environment through interactions with the Earth's magnetic field. Indeed, biological systems are highly sensitive to changes in the magnetic background as an evolutionarily justified factor that contributes toward their survival. At present, there are a sufficient number of experimental studies on the impact of low-frequency MFs on biological systems; nevertheless, the nature of these phenomena is not completely clear [18,24–26].

The impact of MFs on living systems, especially those in the low-frequency and extremely low-frequency ranges, can be two-fold in nature. On the one hand, the negative effect of magnetic fields is associated with the need to protect the human body since its effect on living systems can lead to DNA damage: it can initiate oxidative modification of nitrogenous bases and increase the number of single- and double-strand breaks [22,27,28]. On the other hand, in recent decades, extremely low-frequency MFs have occupied a special place in medical research, especially in the field of cancer treatment and in combination with chemotherapeutic drugs and pain relief [29,30]. It is assumed that the rate of diffusion through biological membranes, the orientation and conformation of biological macromolecules, and the concentration of free radicals can all change under the action of MFs [22,31,32]. In neurophysiology, transcranial magnetic stimulation (TMS)—technology that stimulates the brain and cortical neurons using alternating magnetic fields—is increasingly being used [33]. Studies, where TMS therapy is combined with genetics, have clearly indicated that the genome is the main factor that controls the effects of TMS (neuronal susceptibility and exposure strength) [34,35]. In addition, in recent studies, the presence of natural oscillation frequencies in genes was established, depending on the nucleotide sequence, which may be the reason for the presence of individual frequencies that cause biological effects [36]. In our opinion, one of the objectives of research being conducted in this area should be to study the effect of gene polymorphisms and their sensitivity to low-intensity, variable MFs, which are used in medical practices.

Currently, there are no generally accepted hypotheses in the field of low-frequency MF that depict how they influence biological systems or theoretical models describing the mechanisms of these influences [37]. However, detailed physicochemical processes that determine the parameters of biochemical reactions and form the body's response to external influences are not taken into account in theoretical models [19,21,22]. Low-frequency MFs cannot cause thermal effects directly and make significant changes in the rate constants of biochemical reactions due to temperature effects. We believe that these fields can act indirectly by changing the concentrations of some kinetically significant molecules, such as ROS.

In this work, the 8-oxoguanine-DNA-glycosylase (*hOGG1*) gene polymorphism was studied, and the nature of oxidative damage to DNA was revealed before and after exposure to an alternating magnetic field *in vitro* by determining the level of 8-oxoG in DNA in groups of donors with different polymorphisms. A model of the low-frequency magnetic field action mechanism on aqueous solutions of nucleic acids and proteins has been developed.

2. Materials and Methods

For an experimental, non-randomized study, donor blood samples were acquired and genomic DNA was isolated. The study involved 93, apparently, healthy donors, including men aged 21–23 years, who were university students and, according to the survey, did not have any previous pathologies or diseases. Donors provided written consent to participate in the experiment. Blood was taken from the cubital vein and placed into test tubes with an EDTA anticoagulant.

DNA from bioassays was isolated using reagents from ready-made commercial AmpliSense kits—"DNA-Extran-1" (Cat. EX-509, FSUE TSNIIE Rospotrebnadzor, Moscow, Russia)—using the sorption method [38]. The DNA concentration in the final solution was determined spectrophotometrically, the extinction coefficient was E_{260nm} 200.

Typing of the rs1052133 polymorphic variant of the 8-oxoguanin DNA glycosylase (*hOGG1*) gene was carried out by real-time polymerase chain reaction using TaqMan probes on a Rotor-Gene Q amplifier (S/N: R0812156, Qiagen, Germany), with reagents for determining the polymorphism of the 8-oxoguanin DNA glycosylase gene (rs1052133) (Cat.No.NP-465-100, Syntol LLC, Moscow, Russia). The reaction mixture for determining the Pro332Ala polymorphism of the 8-oxoguanin DNA glycosylase (*hOGG1*) gene (rs1052133) was prepared, according to the protocol from 32 test samples plus 4 additional samples (3 positive and 1 negative sample).

Using the Rotor-Gene Q software (version 2.3.5, Qiagen, Germany), the temperature regimes, the duration of each cycle, and the number of repetitions in each stage were set; their values are shown in Table 1.

After the amplification was completed, the results of the study were analyzed using the Rotor-Gene Q software (version 2.3.5, Qiagen, Germany), with the threshold line set to 0.1, and the areas of the corresponding genotypes

Table 1. Operating modes of Rotor-Gene Q during PCR to determine polymorphic variants of rs1052133 Pro332Ala of the 8-oxoguanin DNA glycosylase (*hOGG1*) gene.

PCR steps	Temperature, °C	Duration, sec	Number of cycles
Melting	94	180	1
Cycling 1	94	20	10
	58	20	
	61	30	
Cycling 2	94	20	30
	58	20	
	61	30	

were highlighted (i.e., define genotype, wild type, heterozygous, and mutant). The results were interpreted according to Table 2.

The flanking sequence was considered, and the frequency of the minor allele G was taken as equal to 30.21%, which corresponded to 1000 genomes.

The correspondence of the distribution of genotypes to the Hardy–Weinberg equilibrium was assessed using the WpCalc online service (https://wpcalc.com/en/equilibrium-hardy-weinberg/). Criterion χ^2 was used to compare the allele and genotype frequencies between the analyzed groups.

The level of 8-oxyguanine in the DNA was determined by enzyme immunoassay using monoclonal antibodies to 8-oxoG with DNA damage—kit (determination of 8-OH-2-deoxyguanosine, catalog number EC-360, Immun diagnostics, Berlin, Germany), according to the protocol. Antibody solutions to 8-oxoG were preliminarily prepared at a dilution of 1:250 and at a dilution of 1:500 for the conjugated mouse IgG antibodies. A total of 50 µL of 8-oxoG antibodies were added to the wells, incubated for 1 hour, and washed 6 times with wash buffer. Next, 50 µL of mouse IgG antibody conjugate was added, similarly incubated and washed. Then, 50 µL of tetramethylbenzidine substrate (chromogen) was introduced and after instant coloring, the mixture was incubated for 15 min in the dark, and the reaction was completed by adding the stop solution. After the addition of the stop solution, the optical density of the samples was measured at a wavelength of 450 nm using a Thermo Fisher Scientific Multiskan FC microplate reader (Type: 357; S/N: 357-902375, Thermo Scientific, MA, USA). In each experiment, measurements were recorded at least three times, and the average value was determined. The content of 8-oxoG DNA was quantified using a prebuilt calibration curve, which was linear over the 8-oxoG concentration range of 0.94–60 ng/mL. The sensitivity was 0.59 ng/mL.

The samples were treated with an alternating magnetic field using a device developed by us for the automated study of biological fluids, a detailed description and structural diagram of the device is provided in [38,39]. The scheme of the device is shown in Fig. 1.

To increase the homogeneity of the alternating magnetic field during the processing of biological objects, an emitter 7 was manufactured in the form of a solenoid. The coil resistance was 20 ohms; wire type PEV-1, wire diameter with insulation of 0.81 mm; 2735 coil turns; 12 layers; wire length of 485.309 m; coil inductance of 84 mH. The coil was placed in a shielded chamber 6, which was made of structural steel, 3 mm in thickness. The weakening of the external electromagnetic field by the chamber in the range from 3 Hz to 300 kHz reached 100 times. The constant magnetic field (geomagnetic field) was measured using an Aktakom ATT-8701 magnetic induction meter (Russia). The magnitude of the magnetic field strength in the open space was 40.00 $\pm$ 2.00 A/m and 0.40 $\pm$ 0.02 A/m inside the shielding chamber. Samples were treated (experiments were carried out in three repetitions) with an alternating magnetic field at room temperature (22 $\pm$ 1 °C) in a chemically clean and sterile plastic container, with a layer thickness of 2 mm, according to the procedure described in [21]. The sample was placed at the center of the solenoid; the magnetic field at the location of the sample can be considered homogeneous since the size of the solenoid is 50 times larger than the size of the sample. The Ekofizika-110A spectrum analyzer, with the P6-70 antenna, acted as the electromagnetic field strength sensor 8. At the location of the sample, the effective field strength was 450 $\pm$ 10 A/m and the magnetic field frequency varied from 3 to 50 Hz. The initial MF frequency and the corresponding field strength were set, and each sample was processed for 30 min.

The hydrogen peroxide content in the aqueous DNA solutions was determined using the spectrophotometric method, while the PerOx method was used to determine the peroxides in the plasma EDTA samples (Immun Diagnostic AG, Germany), using a Thermo Fisher Scientific Multiskan FC microplate reader (Type: 357; S/N: 357-902375, Thermo Scientific, MA, USA). The calibration graph is linear in the range $1 \times 10^{-5} - 5 \times 10^{-2}$ M.

The test the hypothesis and determine if the data followed a normal (Gaussian) type of distribution the Shapiro–Wilks test was used. Additionally, the ordinates of the normalized Gaussian distribution function were determined according to the recommendations outlined in the monograph [40]. The significance of the degree of oxidative damage to DNA was assessed by the nonparametric Mann–Whitney U-test. Differences in all studied parameters were considered statistically significant at $p \leq 0.05$. StatPro software (version 8, Frankfurt, Germany) package was used for statistical processing.

The study was approved by the Independent Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education "Kuban State Medical University" of the Ministry of Health of the Russian Federation (4 Mitrofan Sedin St., Krasnodar, Russia), protocol No. 89 of June 26, 2020.

Table 2. Interpretation of PCR results to determine the Pro332Ala polymorphism of the *hOGG1* gene.

Allele 1 (green)	Allele C	Genotype C/C
Heterozygote (green + yellow)	Allele C + Allele G	Genotype C/G
Allele 2 (yellow)	Allele G	Genotype G/G

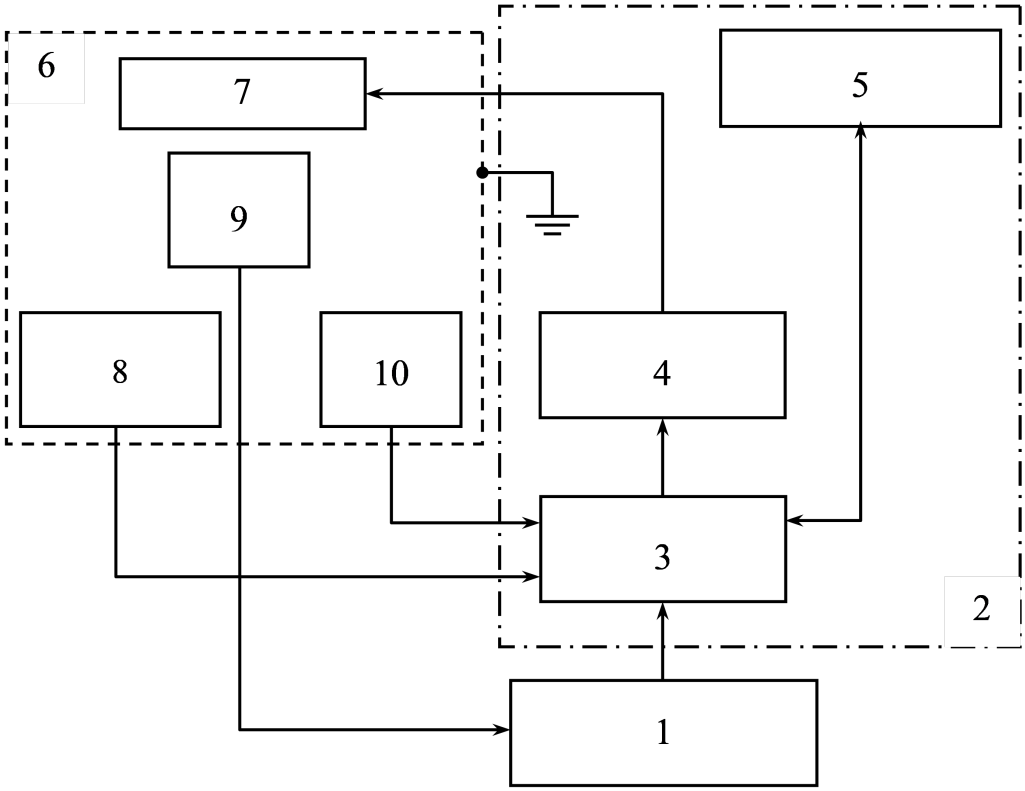

Fig. 1. Structural diagram of a device for automated search for optimal parameters for processing biological fluids in an alternating magnetic field. 1: personal computer; 2: generator unit; 3: microcontroller; 4: power amplifier; 5: control and indication unit; 6: grounded shielded chamber; 7: emitter; 8: electromagnetic field strength sensor; 9: measuring module with a sample; 10: temperature sensor.

3. Results

When analyzing the polymorphism of the 8-oxoguanine-DNA-glycosylase (*hOGG1*) gene in healthy donors, genotypes were divided into homozygotes (wild type), heterozygotes, and homozygotes for the recessive allele (mutant type).

The distribution of genotypes for the rs1052133 locus in the *hOGG1* gene is shown in Table 3. As can be seen from Table 3, in healthy donors, the homozygous CC genotype of the *hOGG1* gene was mainly observed; however, heterozygous CG and homozygous GG genotypes were also observed. From the data presented in Table 3, it can be seen that in the control group of conditionally healthy donors, the CC genotype is predominant, with it identified in 68 people, which is 73% of the participants. The CG genotype accounts for 25% (23 people) and the GG genotype for 2% (2 people). From the ratio of allele frequencies, calculated according to the Hardy–Weinberg equation, it was found that the differences in the frequency of the C allele between the two groups are not significant: this indicator in the first group was 0.94, while in the second it was 0.83. The G allele frequency in the second group of donors was 0.15, which is significantly higher than in the first group, which demonstrated an allele frequency of 0.05 ($p < 0.05$).

According to the results of the PCR analysis, the donors were divided into two groups: those with the C/C genotype *hOGG1* (68 people; group 1) and C/G and G/G genotypes (25 people; group 2). The accumulation of 8-oxoG in the blood serum and a decrease in the stability of the genetic material with an increasing oxidative load can act as an indicator of genome destabilization.

3.1 Determination of the Degree of Oxidative DNA Damage Following Exposure to an Alternating Magnetic Field

To determine the resistance of the genetic material to external influences, further studies were carried out on the effects of an alternating magnetic field (MF) on the appearance of oxidative DNA damage in conditionally healthy donors.

Table 3. Distribution of allele and genotype frequencies for the rs1052133 polymorphic locus of the *hOGG1* gene in donors with the Pro332Ala polymorphism.

Genotypes, alleles	Group, n = 93 people
	abs, %
CC	68 73%
CG	23* 25%*
GG	2 2%
C	0.85
G	0.15

*df = 2; χ^2 = 8.898, critical value of χ^2 at p = 0.05–5.991, $p < 0.05$. Significance level p = 0.012.

The degree of oxidative DNA damage was assessed by changes in the concentration of 8-oxoG in the blood serum of donors. The concentrations of 8-oxoG in DNA from the blood serum of healthy donors in the first and second treatment groups are shown in Fig. 2, for both before and after the *in vitro* treatment of blood samples with a magnetic field, at frequencies of 3, 30, and 50 Hz. These frequencies were selected based on previous studies [21,41]. The initial level in the control samples, without exposure to the field, was 7.4 $\pm$ 1.9 ng/mL in the first group and 6.3 $\pm$ 1.5 ng/mL in the second group. After treatment of MF samples with frequencies (f) of 3, 30, and 50 Hz, a significant increase was observed in the levels of 8-oxoG in blood serum DNA in both treatment groups compared to the untreated blood samples. Thus, after exposure to an MF at a frequency of 3 Hz, the concentration of 8-oxoG increased in the first and second groups, reaching 14.8 $\pm$ 2.2 ng/mL and 24.9 $\pm$ 2.8 ng/mL, respectively. Exposure to an MF with a frequency of 30 Hz also resulted in an increase in the concentration of 8-oxoG in the first group, up to 14.1 $\pm$ 2.1 ng/mL, and in the second group, up to 22.0 $\pm$ 2.6 ng/mL. Finally, the level of the studied indicator in the blood samples of donors also turned out to be comparable in both groups after exposure to a magnetic field with a frequency of 50 Hz (Fig. 2). Therefore, the obtained results for the donors in the second group indicate the maximum modification susceptibility to oxidative DNA modifications under conditions associated with a normally functioning antioxidant protection.

As noted in a number of studies [6–14,19,20,23], magnetic fields affect animals and cells by promoting the generation of reactive oxygen species (ROS), potentially leading to oxidative stress at the cellular and systemic levels. An increased level of ROS generation, mediated by physical, chemical, or biological environmental factors, is the most genotoxic process affecting DNA [20,22,23].

To study the mechanisms involved in the process of magnetic fields causing the formation of free radicals in the blood, we developed a mathematical model. However, to simplify calculations, the model was used to study an aqueous solution of DNA isolated from the blood of apparently healthy donors.

3.2 Model of the Mechanism of Action of a Low-Intensity Alternating Magnetic Field on Aqueous Solutions of Biopolymers

In dilute solutions of biopolymers, the processes of ROS formation proceed as a chemical oscillator [42]. To describe the chemical oscillator in the conversion of hydrogen peroxide, the longest-lived ROS in an aqueous solution, we used chemical equations with known simplifications.

The initial stage is the initiation of the process, i.e., the attachment of an electron from e-c Rydberg excited levels of macromolecules (for example, DNA) [43], to free protons of water, to the formation of a hydrogen radical:

$$H^+ + e^-{}_{Rg} \rightarrow H^\bullet \quad (1)$$

at neutral pH, the hydrogen radical interacts with dissolved oxygen molecules, the concentration of which is 3 orders of magnitude higher than the concentration of protons and hydroxide ions (10^{17} versus 10^{14} molecules/cm^3) [44], to form a hydroperoxide radical:

$$H^\bullet + O_2 \quad \rightarrow HO_2\_^\bullet \quad (2)$$

further formation of peroxide occurs in two ways:

$$HO_2\_^\bullet + H^\bullet \rightarrow H_2O_2 \quad (3)$$

or

$$2HO_2\_^\bullet \rightarrow H_2O_2 \quad + {}^1O_2 + h\nu \quad (4)$$

as the concentration of hydrogen peroxide increases, according to Eqns. 3–4, the pH of the solution increases. When the aqueous environment is at a neutral and alkaline pH, hydroperoxide radicals decompose to form superoxide ions:

$$HO_2\_^\bullet \rightarrow H^+ + O_2{}^-\_^\bullet \quad (pK_a \sim 4,8) \quad (5)$$

the released proton can again interact with the Rydberg e-$_{Rg}$ of the macromolecule. Then, with an increase in hydrogen peroxide, the superoxide ions contribute to its decomposition through the formation of hydroxyl radicals [45]:

$$H_2O_2 + O_2{}^-\_^\bullet \rightarrow OH^- + OH^\bullet + O_2 \quad (6)$$

the presence of a singlet oxygen in a neutral and weakly alkaline medium leads to the further formation of superoxide ions:

$$OH^- + {}^1O_2 \rightarrow OH^\bullet + O_2{}^-\_^\bullet \quad (7)$$

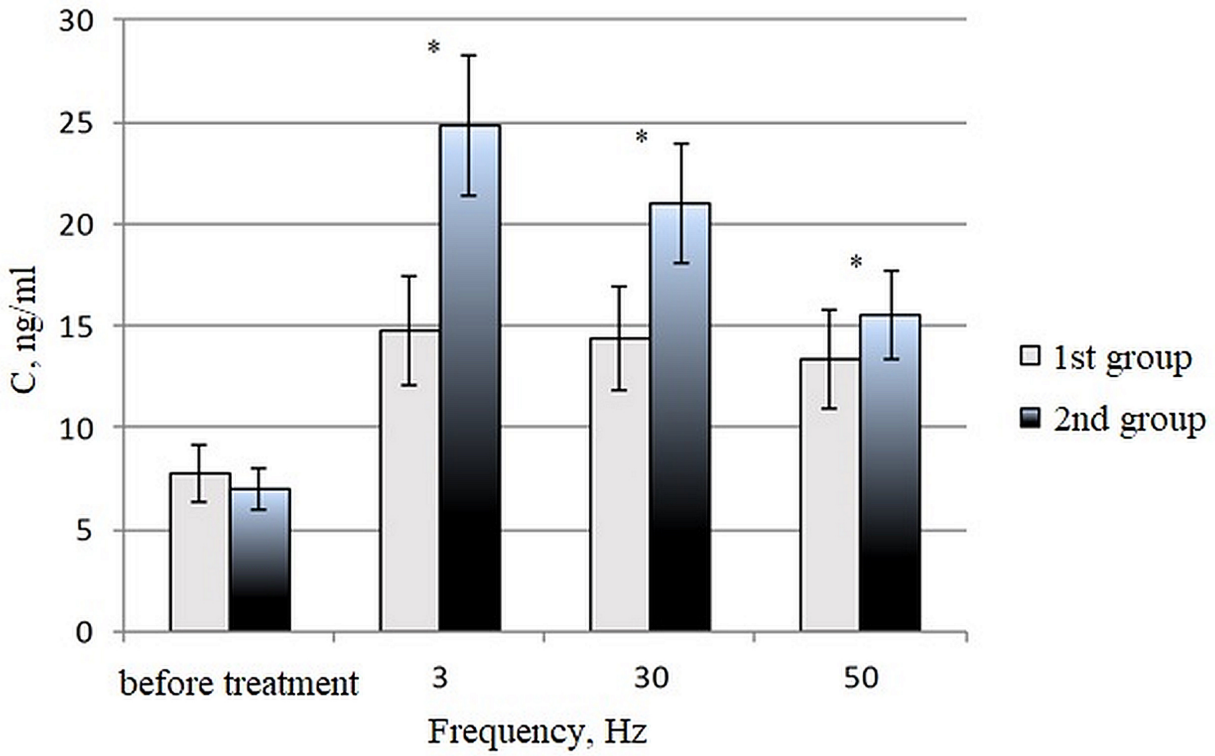

Fig. 2. The 8-oxoG content in the blood serum of healthy donors in the first group (C/C polymorphism of the *hOGG1* gene) and the second group (C/G and G/G polymorphisms of the *hOGG1* gene) after treating blood samples *in vitro* with a magnetic field at frequencies of 3, 30 and 50 Hz for 30 min. U = 1.5; U critical = 3 for $p \leq 0.01$; U critical = 7 for $p \leq 0.05$. *: statistically significant differences compared with the control (blood samples not treated with a magnetic field) at $p < 0.05$.

dismutation of the hydroxyl radical leads to the formation of hydrogen peroxide:

$$2OH^{\bullet} \rightarrow H_2O_2 \tag{8}$$

where the hydroxyl radical can interact with the resulting hydrogen peroxide:

$$^{\bullet}OH + H_2O_2 = H_2O + H^{+} + {}^{-}O_2{}^{\bullet} \tag{9}$$

As the pH increases, peroxide is able to spontaneously decompose with the acidification of the medium:

$$H_2O_2 \rightarrow H^{+} + HO_{2\_}{}^{-} \quad (pK_a \sim 11,5) \tag{10}$$

or with the formation of singlet oxygen:

$$H_2O_2 \rightarrow 2H_2O + {}^{1}O_2 \tag{11}$$

self-decomposition of peroxide, according to for the rate constants of Eqn. 10, has an order of magnitude from 1 to 2 and leads to the formation of singlet oxygen $^{1}O_2$, which again participates in the cycle of ROS interconversions.

By introducing the notation k_i for the rate constants of reactions (1)–(11), we can obtain the corresponding kinetic equations for the rates of formation of various ROS biopolymers in dilute aqueous solutions. Using the condition of constancy for the intermediate products in the system (1)–(11) and simplifying the kinetic model of production and loss of hydrogen peroxide, we can obtain an expression for the rate of hydrogen peroxide formation:

$$\frac{d}{dt}\left[H_2O_2\right] = \frac{k1}{2}\left[OH\_^{-}\right]\left[e^{-}{}_{Rg}\right] + \frac{k4}{2}\left(\frac{k2}{k3}\right)^{2}\left[O_2\right]^{2} - k_{10}\left[H_2O_2\right] \tag{12}$$

from Eqn. 12, it follows that in dilute solutions of biopolymers, the rate of accumulation of hydrogen peroxide depends on the pH of the solution, the concentration of electrons $e^{-}{}_{Rg}$ at the Rydberg excited levels of macromolecules, and the concentration of dissolved oxygen, which coincides with the conclusions presented in [46]. Periodic accumulation and decomposition of hydrogen peroxide determine the frequency of the entire cycle of interconversions in the chemical oscillator of ROS.

Let us consider the formation of a chemical oscillator involved in ROS interconversions in aqueous solutions of biopolymers. Fig. 3 shows a simplified schematic of H_2O_2 transformations, in the course of chemical reactions (1)–(11), in aqueous solutions of biopolymers (the main chem-

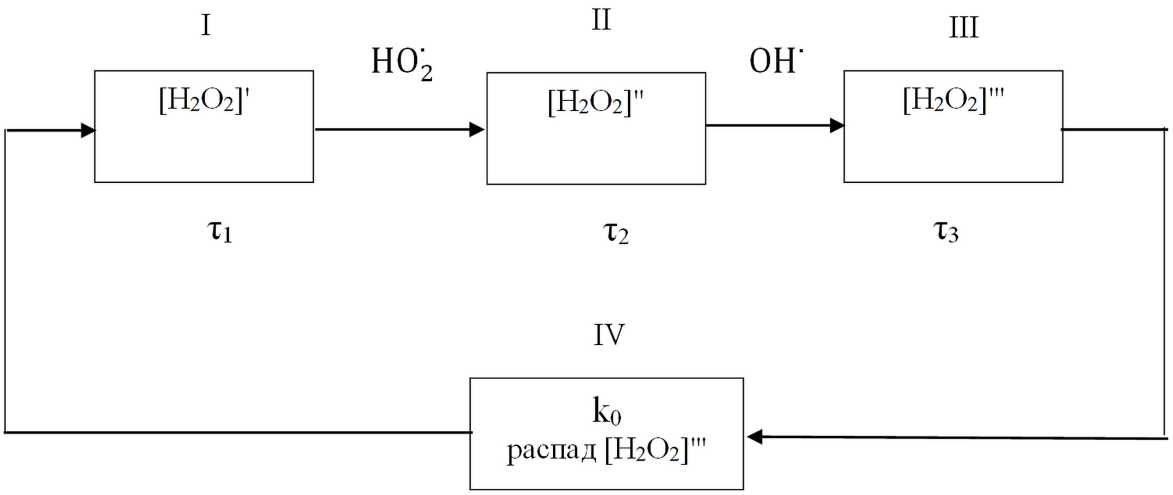

Fig. 3. Schematic of interconversions of hydrogen peroxide in a biopolymer aqueous solution for reactions (1)–(11).

ical oscillator). Taking into account the fact that several more oscillators of hydrogen peroxide can exist in the solution in addition to the main oscillator, the reactions involved in the formation of hydrogen peroxide, which proceed according to Eqns. 1–11, will be divided into three groups. Each of which has feedback: the first group is the initiation of the cycle and the initial formation of H_2O_2, which is described by Eqns. 1–5, in Fig. 3, marked I; the second group are reactions involving dissolved and singlet oxygen and are described by Eqns. 2,4, and 6–7, in Fig. 3, marked II; the third group are reactions involving the hydroxide radical, which are described by Eqns. 6–9, and are designated by III in Fig. 3. A separate block, depicted by IV, highlights the processes involved in hydrogen peroxide decomposition, illustrated by reactions (10)–(11), which proceed efficiently when a sufficient amount of H_2O_2 is accumulated in the solution: k_0 represents the degree of hydrogen peroxide decomposition. Within each of the selected groups, hydrogen peroxide transformations occur within their own periods of oscillation. In solutions of biopolymers, several parallel chemical oscillators of H_2O_2 interconversions can exist simultaneously, each of which can have its own frequency of fluctuations in the concentration of hydrogen peroxide. Thus, we have a system of coupled oscillators with positive feedback.

Let us introduce the value τ—the time involved in increasing the concentration of (H_2O_2) in each cycle of reactions by e times. The value of τ considers both the time of accumulation of hydrogen peroxide and the lifetime and diffusion of the corresponding ions and radicals in each group of reactions. Then, the rate of change in the concentration of hydrogen peroxide in the chemical oscillator can be written as below, while the schematical depiction is also shown in Fig. 3:

$$\frac{d\left[\mathrm{H_2O_2}\right]^{II}}{dt}+\frac{1}{\tau_1}\left[\mathrm{H_2O_2}\right]^{II}=\frac{1}{\tau_1}\left[\mathrm{H_2O_2}\right]^{I} \tag{13}$$

$$\frac{d}{dt}\left[\mathrm{H_2O_2}\right]^{III}+\frac{1}{\tau_2}\left[\mathrm{H_2O_2}\right]^{III}=\frac{1}{\tau_2}\left[\mathrm{H_2O_2}\right]^{II} \tag{14}$$

$$\frac{d}{dt}\left[\mathrm{H_2O_2}\right]^{IV}+\frac{1}{\tau_3}\left[\mathrm{H_2O_2}\right]^{IV}=\frac{1}{\tau_3}\left[\mathrm{H_2O_2}\right]^{III} \tag{15}$$

$$\left[\mathrm{H_2O_2}\right]^{I}=-k_0\left[\mathrm{H_2O_2}\right]^{IV} \tag{16}$$

taking into account the occurrence of hydrogen peroxide decomposition reactions and a decrease in its concentration, the index k_0 in Eqn. 16 has the "–" sign. Transforming the system for Eqns. 13–16 and discarding the term containing the third derivative, due to its smallness, we can obtain the final equation for changing the concentration of hydrogen peroxide in an aqueous solution of a biopolymer:

$$\frac{d^2}{dt^2}\left[H_2O_2\right]+\frac{\tau_1+\tau_2+\tau_3}{\tau_1\tau_2+\tau_1\tau_3+\tau_2\tau_3}\frac{d}{dt}\left[H_2O_2\right]+\frac{k_0+1}{\tau_1\tau_2+\tau_1\tau_3+\tau_2\tau_3}\left[H_2O_2\right]=0 \tag{17}$$

Eqn. 17 is a differential equation for free oscillations that arise in a harmonic oscillator [47]. The expression in front of $[H_2O_2]$ is the square of the frequency of natural oscillations in the chemical oscillator:

$$\omega_0^2=\frac{k_0+1}{\tau_1\tau_2+\tau_1\tau_3+\tau_2\tau_3},$$

and the expression before $\frac{d}{dt}\left[H_2O_2\right]$ is the damping index of the fluctuations in hydrogen peroxide concentrations in a chemical oscillator.

$$\delta = \frac{\tau_1 + \tau_2 + \tau_3}{\tau_1\tau_2 + \tau_1\tau_3 + \tau_2\tau_3}.$$

Then, Eqn. 17 will take the form:

$$\frac{d^2}{dt^2}\left[\mathrm{H_2O_2}\right] + \delta\frac{d}{dt}\left[\mathrm{H_2O_2}\right] + \omega_0^2\left[\mathrm{H_2O_2}\right] = 0 \qquad (18)$$

3.3 Influence of the Low-Intensity Magnetic Field Frequency on the Formation of Hydrogen Peroxide in Aqueous Solutions of Biopolymers

Let us consider the influence of a low-intensity and low-frequency magnetic field, which sine changes and is described by the equation $H = H_m \sin\omega t$, on the yield of hydrogen peroxide in a dilute aqueous solution of biopolymers.

According to Eqn. 12, in biopolymer solutions, the rate of hydrogen peroxide accumulation depends on, among other things, the concentration of electrons at the Rydberg excited levels of macromolecules. A low-intensity magnetic field can affect the magnetic moments of these electrons. In addition, in aqueous solutions of biopolymers, there are radical pairs with different g-factors of partners (for example, $H^{\bullet}$, $HO_{2\_}{}^{\bullet}$, and $OH^{\bullet}$). The magnetic field apparently orients the spins of biradical pairs (for example, $H^{\bullet}$ и O_2), changing their mobility, which brings us back to the theory of the interaction of triplet–singlet pairs [33].

All of the above suggests that under the influence of a magnetic field, the increment in the concentration of hydrogen peroxide changes in proportion to its strength:

$$\Delta\left[H_2O_2\right] = \alpha H_m \sin\omega t$$

where α is the coefficient of proportionality.

As a result, the oscillations arising in the chemical oscillator will become forced, causing the following equation to become valid for them:

$$\frac{d^2}{dt^2}\left[H_2O_2\right] + \delta\frac{d}{dt}\left[H_2O_2\right] + \omega_0^2\left[H_2O_2\right] = \alpha H_m \sin\omega t \qquad (19)$$

the solution of such an inhomogeneous equation is equal to the sum of the general solution of a homogeneous equation that characterizes the decaying process of hydrogen peroxide formation, which occurs after the application of an external influence, as well as a particular solution that describes a steady oscillatory process under the action of an applied driving force.

If the losses in the chemical oscillator are small, and the frequency of the driving force differs slightly from the natural frequency of the oscillations in the hydrogen peroxide concentration in the chemical oscillator, then, we can obtain the solution for Eqn. 19 in the following form:

$$\left[H_2O_2\right] = \left[H_2O_2\right]_{\mathrm{M0}} \mathrm{e}^{-\delta t}\sin\left(\omega_0 t + \varphi\right) + \left[H_2O_2\right]_{\mathrm{M}}\sin(\omega t + \varphi) \qquad (20)$$

additionally, the value of the amplitude of the forced fluctuations in the concentration of hydrogen peroxide under the action of an alternating MF is described by the expression:

$$\left[H_2O_2\right]_{\mathrm{M}} = \alpha H_m\left(\left(\omega_0^2 - \omega^2\right)^2 + 4\delta^2\omega^2\right)^{-1/2} \qquad (21)$$

thus, it follows from Eqn. 20 that natural oscillations in the hydrogen peroxide concentration decay with time in the chemical oscillator, and only forced oscillations in the H_2O_2 concentration are present; the amplitude of which depends on the frequency of the external magnetic field. The process has a quasi-resonance character, whereby resonance occurs when the frequency of the external field coincides with the natural frequency of the chemical oscillator of fluctuations in the concentration of hydrogen peroxide in solution. Thus, it is possible to, first, convert a weak magnetic field signal into a chemical one, and then, in a complex system, into a biochemical response.

Theoretical dependences for the content of hydrogen peroxide in an aqueous solution of DNA relying on the frequency of an alternating magnetic field have been constructed. The calculation considered the strength of the magnetic field –450 A/m and the attenuation index of the fluctuations in the hydrogen peroxide concentrations in the chemical oscillator was 0.7–2.5 (Fig. 4).

3.4 Comparison of Model Calculations using Experimental Data

To verify the model, the theoretically calculated and experimentally obtained values for the hydrogen peroxide concentrations were compared after treatment of aqueous DNA solutions with a low-intensity MF at the corresponding frequencies. The results are shown in Fig. 5. The H_2O_2 content in the aquatic environment without MF treatment was less than 7.0 μM/dm^3. In the control DNA solution, at a concentration of 2.5 μg/mL, the content of H_2O_2 reached 94.5 ± 8.3 μM/dm^3. The DNA control solution was kept in the measuring module for 30 min without MF treatment. As can be seen from Fig. 5, a significant increase (3–5 times) in the content of H_2O_2 in the DNA solutions can be observed after their treatment with variable MF frequencies: f = 3, 4, 8, and 50 Hz.

4. Discussion

The kinetic mechanism of interaction between the enzyme 8-oxoguanine DNA glycosylase hOGG1 and the damaged site in DNA consists of several stages [21]. The first step in the interaction between the hOGG1 enzyme and DNA is the formation of a nonspecific complex. The

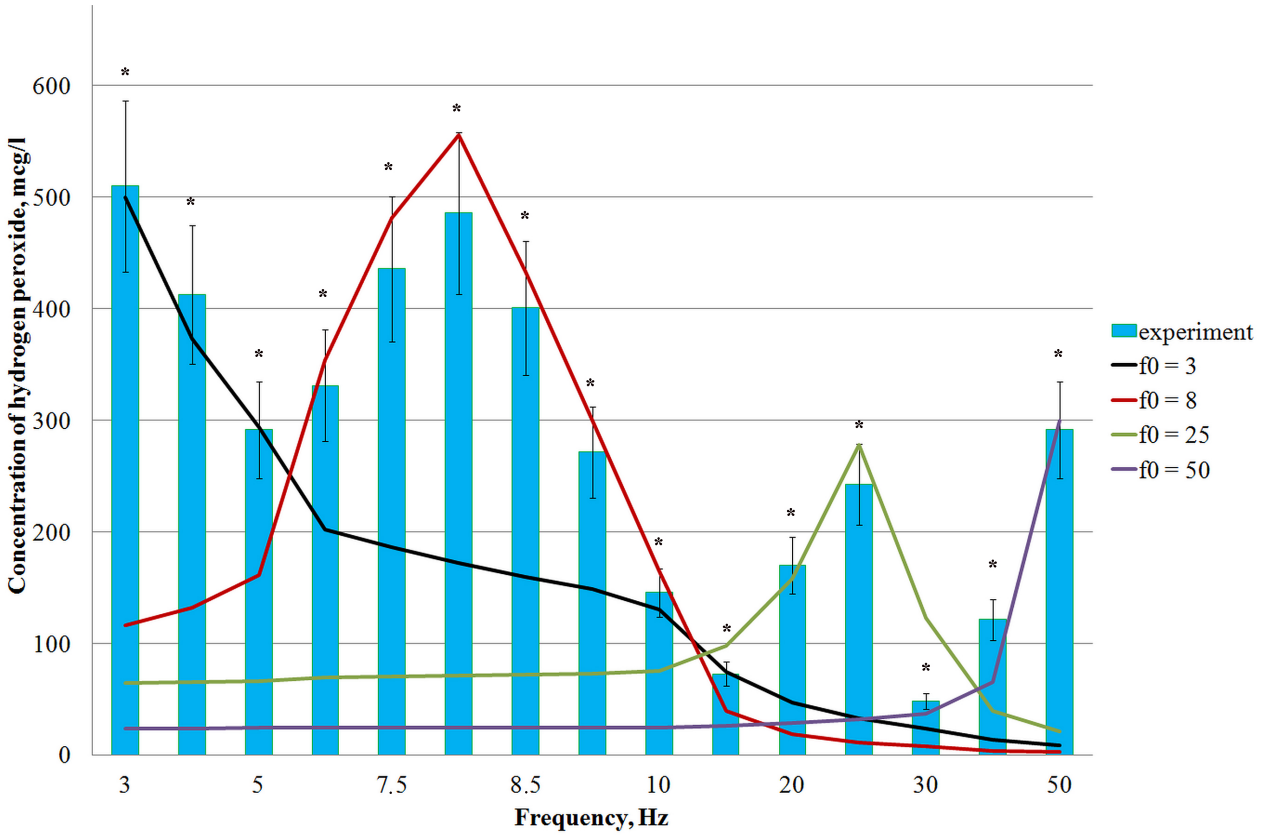

Fig. 4. The content of hydrogen peroxide in an aqueous solution of DNA depends on the frequency of the magnetic field, calculated by Eqn. 21, and the experimentally determined content of hydrogen peroxide in aqueous solutions of DNA with a concentration of 0.025 µg/mL after exposure to different magnetic field frequencies at a temperature of 21 °C and tension of 450 A/m. The exposure time for each solution was 30 min. *: statistically significant differences compared with the control (samples not treated with a magnetic field) at $p < 0.05$.

process of primary binding of the oxoG substrate leads to the rapid inversion of 8-oxoG from the double helix, first into the "precatalytic", and then, into the catalytic center of the enzyme. In the second stage of the binding process, the formed cavity in the DNA duplex is filled with specific amino acid residues and the ribose phosphate backbone of the substrate begins to bend. However, as was shown using the 8-oxoG–aPu substrate, the third stage also reflects the process of the incorporation of amino acid residues into the DNA duplex. Only in the third complex is the bending of the duplex completed and a complete system of contacts is formed between the enzyme and DNA substrate, which is necessary for the catalytic stage of the process to proceed [21]. Apparently, the functioning of the enzyme 8-oxoguanine DNA glycosylase hOGG1 in C/G and G/G polymorphisms of the 8-oxoguanine DNA glycosylase (*hOGG1*) gene is sharply reduced, which does not allow for the restoration of the DNA structure. Conversely, the accumulation of 8-oxoG in DNA, which occurs upon exposure to a low-frequency MF, can lead to the appearance of new mutations, including those that generally weaken the processes of reparative regeneration.

DNA-binding proteins protect chromosomes from oxidative damage. This is due both to the compact packaging of the DNA molecule and the interaction of proteins with the resulting ROS. However, it was found in [48], that long-lived protein radicals are sources of long-term ROS formation and are capable of transferring radical damage to DNA, for example, by histone H1 hydroperoxides, which can induce the formation of 8-oxoguanine in DNA [49]. All ROS and protein radicals, which are formed upon the exposure of blood samples to low-intensity MFs, can attack the DNA molecule, thereby leading to oxidative damage of nitrogenous bases and the accumulation of 8-oxoG in DNA.

This conclusion is in accordance with the results of previous work by Blank and Goodman, who found DNA sequences in the promoters of the *c-myc* and *HSP70* genes, which they called response elements to electromagnetic field exposure [50]. They argue that the activation of these genes, which depends on the impact of an electromagnetic field, is associated with the destabilization of hydrogen bonds in these response DNA elements under the influence of the field [51]. A number of researchers believe that MFs affect biological systems by enhancing (or creating) ROS [23,24]. ROS are known to cause a wide variety of biolog-

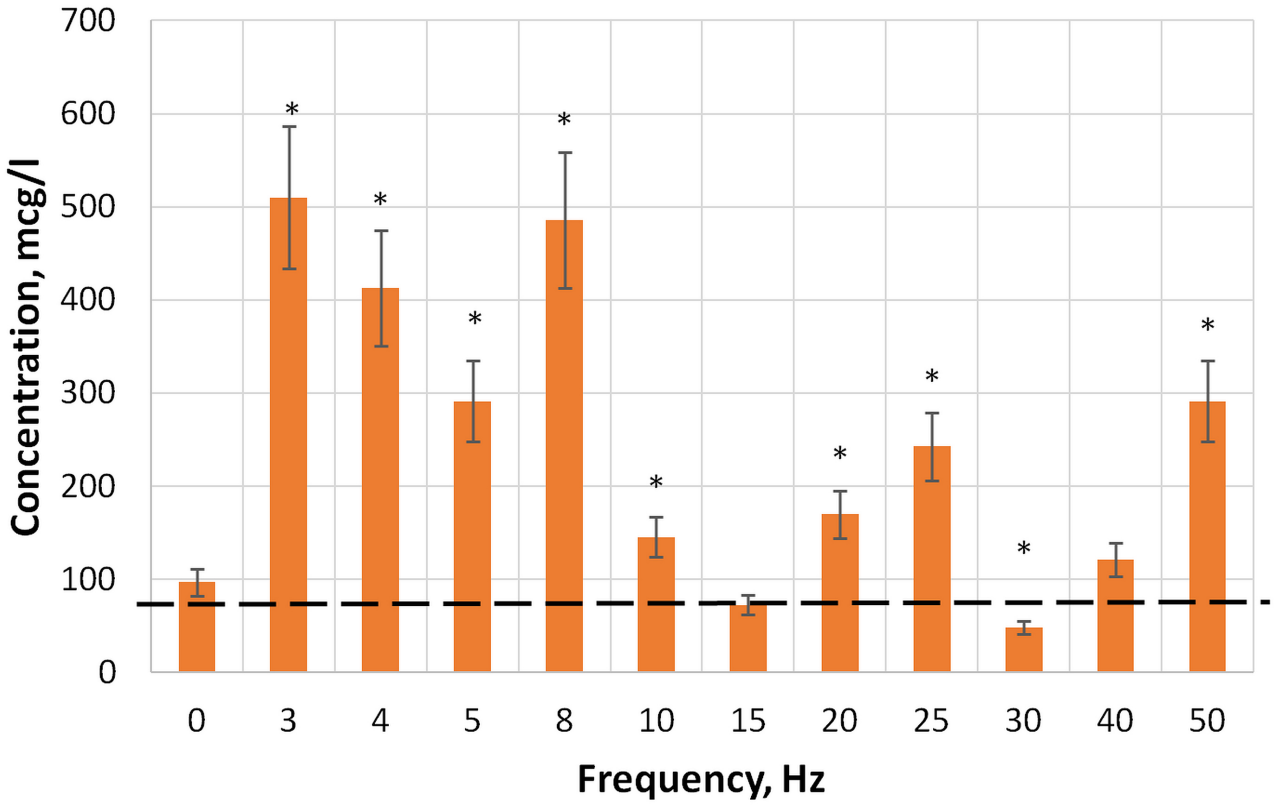

Fig. 5. The content of hydrogen peroxide in aqueous solutions of DNA with a concentration of 0.025 μg/mL, before (0 Hz) and after exposure to magnetic fields of different frequencies at 21 °C, with an exposure time for each solution of 30 min.*: statistically significant differences compared with the control (samples not treated with a magnetic field) at $p < 0.05$.

ical consequences, including DNA damage and the possible induction of mutations. Simko and Mattsson presented some evidence indicating that exposure to extremely low-frequency MFs increases free radical levels in cells through several mechanisms, yet mainly through the activation of macrophages (or other cell types that produce ROS) [52]. It is known that the body has developed a multilevel system of protection to repair any damage to DNA that occurs under the action of ROS. Obviously, DNA damage repair resulting from ROS requires not only antioxidant defense enzymes but also excision repair enzymes [53–55]. To describe the possible mechanism of action in biological systems following exposure to a low-frequency MF, we have developed a model that considers changes in hydrogen peroxide concentration in aqueous media under the action of an MF.

Using an example of an aqueous solution of DNA with a known concentration, the theoretical dependences of the hydrogen peroxide content are compared to the experimental results. Fig. 4 shows the theoretically calculated dependences of the hydrogen peroxide content on the frequency of a low-intensity magnetic field (solid lines), using Eqn. 21, and the experimentally determined concentrations of hydrogen peroxide in aqueous DNA solutions with a concentration of 0.025 μg/mL after their exposure to an MF with the corresponding frequencies (bars). It can be seen that each theoretical dependency presents a maximum concentration of hydrogen peroxide in the solution, while four dependencies were identified in the frequency range from 3 to 50 Hz: at frequencies (f) of 3, 8, 25, and 50 Hz. Each maximum H_2O_2 concentration corresponds to a separate chemical oscillator of hydrogen peroxide transformations in an aqueous DNA solution under the action of a magnetic field. The experimentally determined concentrations of hydrogen peroxide in the DNA solutions after exposure to an alternating magnetic field of different frequencies coincide with the theoretically calculated maxima (Fig. 4). Thus, the developed model for the mechanism of action by low-intensity and low-frequency magnetic fields on aqueous solutions of biopolymers, based on nucleic acids, is in accordance with the experimentally obtained frequency dependencies. Based on the theoretical calculations and the obtained results, it can be concluded that it is possible to increase/decrease the yield of hydrogen peroxide in aqueous solutions of biopolymers during exposure to low-intensity and low-frequency MFs.

A change in the hydrogen peroxide concentration in an aqueous solution of biopolymers makes it possible to explain the observed effects as a result of the influence of the low-frequency alternating MF on biochemical pro-

cesses. Thus, a significant increase in the content of hydrogen peroxide in DNA solutions following exposure to alternating magnetic fields with frequencies of 3–8 and 50 Hz (Fig. 5) leads to an increase in the level of oxidatively modified nitrogenous DNA bases. This is interesting since a significant (1.5 times) increase in the level of 8-hydroxy-2-deoxyguanosine in genomic DNA is a key biomarker of oxidative damage to nucleic acids mediated by ROS generation.

Considering that H_2O_2 plays a central role in regulating the redox balance, its accumulation, which leads to, among other things, the appearance of oxidized DNA sites can cause further changes at the systematic, cellular, and behavioral levels of a whole organism [40,48,56–58]. For example, Ding *et al*. [59] exposed HL-60 cells simultaneously to an ultra-low frequency magnetic field (60 Hz, 5 mT) and H_2O_2 (85 or 100 mM). Co-exposure significantly reduced the number of viable cells compared to cells treated with H_2O_2 alone, thereby establishing low-frequency MFs as promoters of apoptosis. A two-fold increase in the intensity of chemiluminescence was observed by the authors [60] following the joint stimulation of mononuclear cells with MF and H_2O_2 compared with stimulation by H_2O_2 only. Based on theoretical calculations and the obtained results, it can be concluded that it is possible to increase/decrease the yield of hydrogen peroxide in aqueous solutions of biopolymers under the influence of a low-intensity and low-frequency MF.

The proposed model of the mechanism of action of a low-intensity alternating magnetic field on aqueous solutions of biopolymers does not consider the biophysical nature of the target and takes into account only the nature of its interaction with the aqueous environment. Despite the fact that water is considered stable and relatively inert, reports of its exceptional behavior have attracted considerable interest recently. Thus, water molecules are spontaneously oxidized with the formation of hydrogen peroxide near the water-air interface of micron-sized water droplets [61,62]. This process does not require any chemical reagent, catalyst, applied electrical potential, or radiation, and is associated, according to the authors, with the presence of a superstrong electric field at the air-water interface. Similar phenomena were also observed by the authors of [63], although they explained them not by the interfacial effect of drops, but by ultrasonic treatment. Thus, water should be considered as a non-equilibrium active dynamic system, which is very sensitive to weak external influences of physical (low-intensity and low-frequency MF) and chemical (presence of a biopolymer) nature. On the whole, the processes of ROS formation in the aquatic environment, which occur like a chemical oscillator, gradually fade if not supported by external energy of low-intensity factors.

Under the action of a low-intensity and low-frequency MF on aqueous solutions of biopolymers, a significant role is played by collective dynamic and structural rearrangements, in which ROS are both regulatory and control elements. As the authors of the works [64,65] found, periodic rhythms involving ROS depend on fluctuations in the external field as a control (or modulating) signal. Under normal physiological conditions, the production of ROS and the action of chemical oscillators on fluctuations in the concentration of hydrogen peroxide occur rhythmically, while all other cellular processes are balanced and synchronized. The impact of low-intensity MFs affecting the pro-oxidant–antioxidant system in the body, changes with the intensity of free-radical oxidations and the potential of the endogenous antioxidant system of the body.

Thus, although the action of an MF does not directly affect DNA, under some circumstances it produces a biological effect reminiscent of heat shock and/or stress [37]. This effect is mild and depends on the state of cellular homeostasis prior to exposure and the polymorphism of genes that are sensitive to the low-intensity variable MF being emitted.

5. Conclusions

Donors with C/G and G/G polymorphisms in the 8-oxoguanin DNA glycosylase (*hOGG1*) gene are more sensitive to the effects of low-frequency magnetic fields, while donors with a C/C polymorphic *hOGG1* are much less susceptible to the actions of low-frequency MFs, as evidenced by the elevated levels of 8-oxoG in the blood serum of donors in the second group after the *in vitro* treatment of their blood samples with MF, compared with the first group.

A model has been proposed for the mechanism of action by low-frequency magnetic fields, with extremely low energies, on aqueous solutions of biopolymers containing nucleic acids and proteins. The key element in this concept is the chemical oscillators of ROS generation in the aqueous medium, in which competition by the physical and chemical processes (electron transfers, reactions of decay and addition of radicals, spin magnetically induced conversion, synthesis, and decay of hydrogen peroxide) is controlled by the magnetic field. Changes in the concentration of hydrogen peroxide in aqueous solutions of biopolymers make it possible to explain the experimentally observed effects of the low-frequency magnetic field on the biochemical processes. The resulting increased ROS attacks on the nucleophilic centers of proteins and DNA molecules, ultimately, change their states. Thus, damage to biopolymers in aqueous solutions resulting from exposure to low-intensity magnetic fields is similar to damage that occurs during oxidative stress.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

ET, MB, SD, AD, VM and GI jointly conceptualized, searched available literature, wrote the original draft and edited the final draft. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study was approved by the Independent Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education "Kuban State Medical University" of the Ministry of Health of the Russian Federation (4 Mitrofan Sedin St., Krasnodar, Russia), protocol No. 89 of June 26, 2020.

Acknowledgment

Not applicable.

Funding

This work was financially supported by the state assignment of the Ministry of Education and Science to the Kuban State University FZEN-2023-0006.

Conflict of Interest

Given their role as Guest Editors, Anna Dorohova and Stepan Dzhimak had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Amedeo Amedei.

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