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# Interaction of Anticancer drug Doxorubicin with Tumor DNA Irradiated by Nonionizing Millimeter Electromagnetic Waves

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**Abstract** Convenience of usage of non-thermal coherent millimeter electromagnetic waves has been studied in tumor chemotherapy. DNA released from sarcoma 45 tumor (tDNA) and healthy rats in water-saline solution was irradiated during 90 min by frequencies of both resonant for oscillations of water molecular structures (50.3 GHz and 64.5 GHz) and non-resonant (48.3 GHz). Experiments showed that at the irradiation by resonant frequencies DNA thermostability increases: tDNA thermostability enhances more than hDNA thermostability. Non-irradiated and irradiated tDNA and hDNA binding thermodynamics with anti-tumorous drug doxorubicin (DX) was studied as well. By spectroscopic method absorption spectra of non-irradiated and irradiated complexes of DNA with doxorubicin were obtained. From the absorption spectra, binding constants at 290, 300 and 310 K temperatures have been determined. According to our calculations doxorubicin with irradiated DNA forms a more stable complex and much stronger with tDNA irradiated with resonant frequencies. Summarizing the thermodynamic binding parameters (binding constant and enthalpy) we can affirm that doxorubicin forms more stable complex with irradiated tDNA by resonant frequencies for oscillations of water molecular structures: in vitro experiments it was observed doxorubicin binding selectivity to irradiated tDNA. The obtained data make it possible to assume that the treatment by millimeter therapy of complex with anti-tumorous preparations is perspective for clinical oncology at curing of malignant neoplasms.

***Keywords:*** *non-ionizing millimeter radiation, DNA, sarcoma-45, doxorubicin, binding constant, antitumor effect*

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## 1. Introduction

Studies in recent decades have shown that low intensity millimeter electromagnetic waves (MMEWs) without causing a significant increase in temperature in the tissues and cells, promote activation of a number of physical and chemical processes taking place in biological systems [1,2,3,4]. Therefore MMEWs currently are widely used in several fields, including biology and clinical medicine [4,5,6]. In particular, in recent years, due to the combined use of MMEWs with anticancer drugs, it became possible with experimental animals in chemotherapy significantly to reduce toxic side effects of anticancer drugs without reducing their antitumor activity [1,7]. The anthracycline-doxorubicin (DX) is widely used in chemotherapy due to its efficacy in fight against a wide range of cancers such as carcinomas, sarcomas and hematological cancers [8]. Despite extensive clinical use, the mechanisms of DX action remain under intense debate [9,10,11,12]. Although the molecular mechanisms of DX action has not yet been completely revealed, it can be considered proven that DX molecules, penetrating the cell, bind to DNA. This binding takes place mainly by intercalation and groove binding mechanism [10]. At high DX concentrations, exceeding the concentration of base-pairs of DNA it is also possible formation of an external aggregate complex with DNA [10]. Recent years studies carried out in experimental animals have shown [13] that when DX is injected into tumor-bearing animals with sarcoma-45 almost by 40% reduction the size of tumors takes place and significant (about 2-3 times) decrease in content of 5-methylcytosine isolated from sarcoma-45 DNA is observed, which is known [14], as a molecular indicator of the malignancy process in solid tumors. The aim of this work is to identify the features of interaction of antitumor drug DX with DNA isolated from sarcoma-45 tumor pre-irradiated by resonant frequencies of oscillations of molecular water structures.

## 2. Materials and Methods

In our experiments DNA samples were used, which were isolated from liver of healthy white rats (hDNA) and

from tumor of affected with sarcoma-45 animals (tDNA). Inoculation of the tumor into animals and DNA isolation are described in detail in [15,16]. DX was obtained from Carlo Erba Reagents and used without further purification. The extinction coefficient of 11500 $M^{-1}\cdot cm^{-1}$ at 480 nm was used [9]. All the measurements were performed in 0.1 M NaCl, 0.01 M Tris, 0.5 mM EDTA (pH 7.4). Binding isotherms were determined by means of spectrophotometric titrations using a CARY 219 (Varian) spectrophotometer equipped with stoppered quartz cells, temperature-controlled cell holder and a HAARE F3 thermostat provided with a temperature programmer HAAKE PG 10. Thermal denaturation profiles for hDNA and tDNA were followed through the variation with temperature of the absorbance at 260 nm. Heating rates were $0.2^0$ C/min. In all optical measurements in which changes in the spectrum of DX were recorded as a function of DNA concentration, DX concentration was maintained constant by addition of DNA solution containing DX in the same concentration as that contained in the cell. In general, DX concentration in all experiments was kept as low as possible (Co $\leq 5x10^{-5}$ M). Calculation has shown that the self-association process of DX molecules was negligible in most of the cases [9]. Binding isotherms of DX-DNA were obtained at 290, 300 and 310K. At these temperatures and ionic strength hDNA and tDNA are in a double helix B-conformation [16]. DNA concentration was determined from the extinction coefficient, which made up $\varepsilon_{260}$ (p) = 6550 $M^{-1}\cdot cm^{-1}$. The irradiation of DNA solutions with millimeter waves was performed in special glass vessels, which tops were covered with poly(vinyl chloride) thin films transparent to radiation. The thickness of irradiated sample was of the order of a millimeter. As a source of MMEWs radiation the generators of coherent Extremely High Frequency oscillations G4-141 and G4-142 (Russian made) were used, operation in a range of 38.5-78.8 GHz frequencies. The incident power density at the location of object was about 20 $\mu W/cm^2$. hDNA and tDNA solutions were irradiated for 90 min at frequencies of 50.3 GHz and 64.5 GHz (which coincide with the resonant frequencies of oscillations of the water molecular structures) and at a frequency of 48.3 GHz, which does not coincide with resonant frequencies [17]. In [15,18] were shown that irradiation *in vitro* with resonant 50.3 GHz and 64.5 GHz frequencies for 90 minutes the greatest change in the DNA melting parameters was observed. Therefore, in further experiments hDNA and tDNA solutions were irradiated for 90 min.

## 3. Results and Discussion

*In vitro* effect of non-ionizing, coherent millimeter waves on DNA was investigated by thermal denaturation of DNA molecules [15,19]. Experiments have shown that irradiation with resonant frequencies of 50.3 GHz and 64.5 GHz for 90 minutes changes the values of the melting parameters: melting temperature ($T_m$) and melting interval ($\Delta T$) characterizing structure of DNA molecule. As a result of irradiation $T_m$ increases by about 1°C, $\Delta T$ decreases by about 0.2°C. [19]. By the method of thermal denaturation of DNA the thermal stability of hDNA and tDNA non-irradiated and irradiated with resonant 50.3 GHz and 64.5 GHz as well as non-resonant 48.3 GHz frequencies was studied. Table 1 shows the values of the DNA melting parameters during irradiation with resonant and not-resonant coherent millimeter waves. As seen from the Table, when irradiated with resonant frequencies similar regularities of changes of the melting parameters are observed, however $T_m$ greatest change occurs during irradiation with frequency of 64.5 GHz, which coincides with the resonant frequency of oscillations of water triad structures [17]. At the same time experiments show that as a result of irradiation the melting parameters of tDNA undergo more changes than hDNA (Table 1). In all likelihood, these changes of the melting parameters of tDNA compared with hDNA are due to the structural features of tDNA (caused by 5-methylcytosine) [14,16,19], owing to which the degree of tDNA hydration in hypermethylated sites may significantly differ from hydration in other parts [19]. It should be noted that irradiation with non-resonant frequency of 48.3 GHz melting parameters of hDNA and tDNA also show some changes, which, however,are within the experimental error (Table 1).

**Table 1. The values of the parameters thermal denaturation of DNA exposed to the millimeter waves for 90 minutes**

| Frequency of radiation, GHz | hDNA | | tDNA | |
|---|---|---|---|---|
| | $T_m$, °C | $\Delta T$ , °C | $T_m$, °C | $\Delta T$ , °C |
| 0 | 83.0 ± 0.1 | 5.7 ± 0.1 | 82.0 ± 0.1 | 6.6 ± 0.1 |
| 64.5 | 84.1 ± 0.1 | 5.6 ± 0.1 | 83.5 ± 0.1 | 6.2 ± 0.1 |
| 50.3 | 83.8 ± 0.1 | 5.6 ± 0.1 | 83.2 ± 0.1 | 6.3 ± 0.1 |
| 48.3 | 83.2 ± 0.1 | 5.7 ± 0.1 | 82.3 ± 0.1 | 6.5 ± 0.1 |

Notificftion: The melting temperature ($T_m$) is the midpoint of the hyperchromic transition as determined by the maxima of the first derivative plots.The interval width ($\Delta T$) is determined as difference between temperatures in points where absorbance of DNA solution changes from 17% to 83%. The results are the average of 6 to 8 different experiments.

It is known that the resonant frequencies of DNA absorption are within 2÷9 GHz range [20]. Therefore, summarizing the literature and our experimental data, it can be assumed that DNA thermostability growth by irradiating with resonant frequencies of oscillations of the water molecular structures probably is caused by indirect influence of millimeter waves on DNA, namely, by affecting the water, waves cause quantitative and qualitative changes of water associated with DNA and NaCl [15,21].

It is known that in the process of malignation (neoplastic transformation) the content of 5-methylcytosine significantly increases in DNA extracted from solid tumors [14]. Relatively recently it has been shown [22] that the cytosine methylation contributes to the binding of a number of anthracycline antibiotics to DNA. Because a combination of anticancer drugs with radiation increases the effectiveness of drugs action [1,7], we can assume that the interaction DX with tDNA can to some extent be changed and be selective if tDNA was prior irradiated with resonant frequencies of vibrations of the water molecular structures.

By spectrophotometric method we investigated the changes of the thermodynamic parameters values of the system due to the interaction with DX of irradiated and unirradiated hDNA and tDNA. We studied the behavior of the change in the absorption spectra of DX in the visible region, due to the interaction of DNA with DX. Since in

the visible region DNA doesn't absorb so the changes of the absorption spectra of DX in the visible region are caused only by complexing with DNA. From Figure 1 it follows that by adding DNA to DX solution (at constant concentration of DX) hypochromism and shift of the curve maximum to the long wavelength region (red shift) is observed. In the investigated range of the temperature and ionic strength in the absorption spectra isosbestic point with a wavelength of 538 nm clearly is identified, which remains unchanged until the total binding of DNA with DX is completed. Consequently, in these environments there is only one type of a bound state of DX-DNA, distinguishable by spectrophotometric absorption spectra. The experimental data shows that, starting from a certain value of the relative concentration of $C_p/C_0$ (where $C_p$ is a molar concentration of DNA for base pairs, and $C_0$ is a molar concentration of DX), absorption spectra of the complexes DX-DNA in the visible region no longer are changed, which means that all DX molecules in the solution are in bound state. From the absorption spectra of DX-DNA complexes the values of the basic quantitative parameters characterizing the complexation were determined: binding constant (K) and a parameter determining the complex stoichiometry at saturation of the interaction (n). The absorption spectra were obtained for unirradiated and irradiated complexes of hDNA- DX and tDNA-DX for three different temperatures. From these spectra by equation (1) the concentrations of free ($C_f$) and bound ($C_b$) DX were determined in the solution.

$$C_f / C_o = A - A_b / A_f - A_b, C_b = C_o - C_f \qquad (1)$$

where $A_f$ and $A_b$ are respectively free and bound DX absorption values at $\lambda = 480$ nm, which corresponds to the maximum of the absorption spectrum, A is absorption value of DX-DNA complexes in intermediate states. $A_b$ is determined by linear extrapolation of $A=f(1/c_p)$ dependence, when $1/c_p \rightarrow 0$. Taking into account the values of $C_f$ and $C_b$ calculated by equation (1), the binding isotherms of DX with non irradiated and irradiated hDNA and tDNA in Scatchard coordinates were drawn ($r/C_f$ dependence on r, where $r = C_b/C_p$).

The binding isotherms were described by (2), which more precisely describes the binding of biologically active compounds with nucleic acids [23].

$$r / C_f = K(1 - nr)^n \left[1 - (n-1)r\right]^{1-n}. \qquad (2)$$

In equation (2) n is equal to number of base-pairs with which one DX molecule binds at the saturation.

Figure 2, Figure 3 show the binding isotherm at 290, 300 and 310K for non-irradiated and irradiated tDNA-DX complexes at a frequency of 64.5 GHz. The solid line is the theoretical curve drawn through the experimental points, according to equation (2) by the method of least squares, and where the values of K and n parameters were determined. Table 2 shows the values of K and n complexation parameters of DX for non-irradiated and irradiated hDNA and tDNA at three different frequencies, calculated using equation (2). Using the obtained values for K, according to formula (3) it is possible to calculate the change in the Gibbs free energy due to complexation:

$$\Delta G = -RT\ln K \qquad (3)$$

where R is the universal gas constant, and T is the absolute temperature.

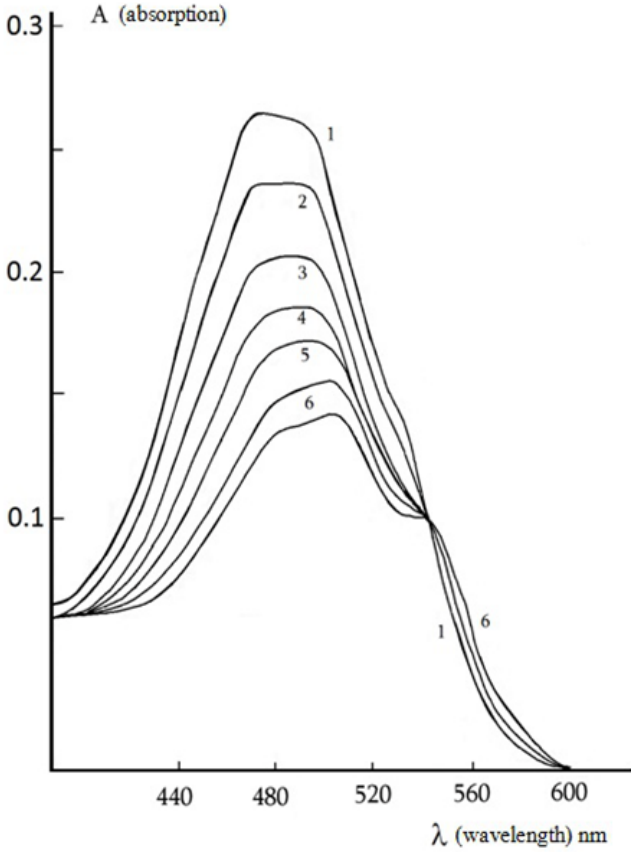


**Figure 1.** Changes in the absorption spectra of doxorubicin binding with irradiated at a frequency of 64.5 GHz with DNA of sarcoma-45 tumor in buffer solution at temperature of 300K. During titration doxorubicin concentration remains constant, equal to $C_0=4.8\cdot10^{-5}$ M (spectrum 1). DNA concentration varies from zero (1) to $10^{-4}$ M/P (6)

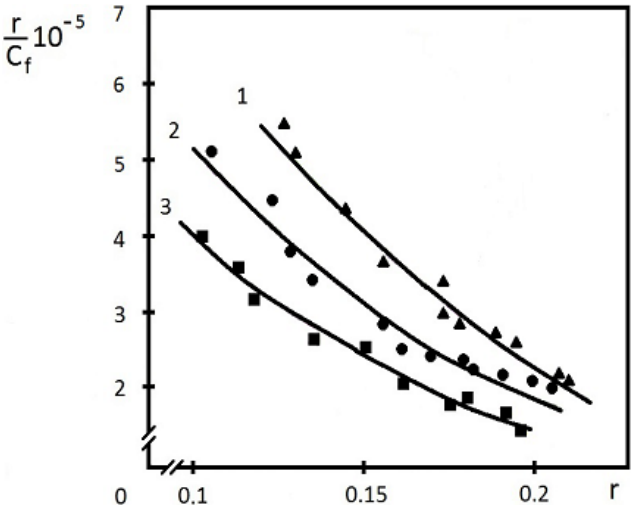


**Figure 2.** The binding isotherms of doxorubicin with non-irradiated tDNA at temperatures: 1-290K, 2-300K, 3-310K

Changes in entropy ΔS and enthalpy ΔH for DX-DNA complex formation can be calculated by the formula (4)

$$\Delta G = \Delta H - T\Delta S \qquad (4)$$

where in view of the expression (3) and by modifying it, it can be represented as follows

$$\ln K = -\Delta H / R \cdot 1/T + \Delta S / R. \qquad (5)$$

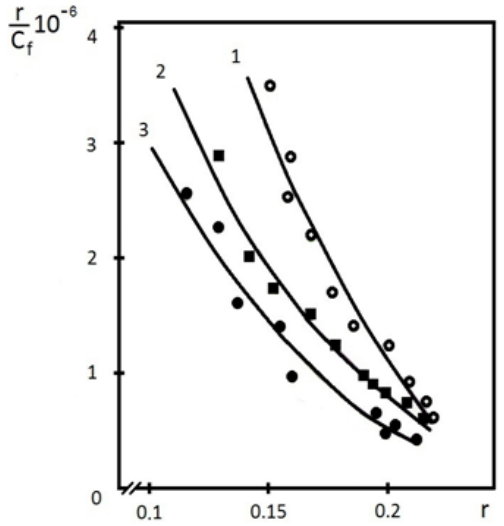


**Figure 3.** The binding isotherms of doxorubicin with irradiated tDNA at frequency of 64.5 GHz at temperatures: 1-290K; 2-300K; 3-310K

According to expression (5), if the dependence of lnK on 1/T is linear, the tangent of the angle of the line with abscissa axis is equal to the value of - ΔH/R, and the ordinate of the intersection point of the straight line with ordinate axis is the value of ΔS/R. From the values of K, determined from experimental data by equation (2), lnK dependence on 1/T (Figure 4) was drawn. From these points by the method of least squares a straight line was drawn and values of ΔS and ΔH have been determined, which are also shown in Table 2. As shown in Table 2, when DNA is irradiated with millimeter waves the binding constant (K) increases: DX forms a stable complex with irradiated DNA. For DNA irradiated with resonant for water structures frequencies of 64.5 GHz and 50.3 GHz coefficient of binding to DX almost an order of magnitude more than for the non-irradiated DNA. When irradiated with non-resonant frequencies (e.g. 48.3 GHz) K increases, but not as much. At the same time from Table 2 it follows that with irradiated and non irradiated tDNA DX forms a more stable complex, and when tDNA is irradiated with 64.5 GHz and 50.3 GHz frequencies DX forms a much stronger complex (for irradiated at 64.5 GHz frequency tDNA-DX complexes at 300K K = $57.4 \cdot 10^{-5}$ $M^{-1}$, and K = $10.1 \cdot 10^{-5}$ $M^{-1}$for irradiated at 48.3 GHz non-resonant frequency). Table 2 also shows the changes in the thermodynamic parameters (ΔG, ΔH and ΔS) when DX is bound to tDNA and hDNA. In the formation of DX-hDNA complexes ΔH =-2.6 kcal/mol, while for DX-tDNA ΔH = -2.9 kcal/mol. Upon irradiation with resonant frequencies for water structures 64.5 GHz and 50.3 GHz, ΔH increases in its absolute value: for DX-hDNA ΔH =-4.4 kcal/mol, while for DX-tDNA ΔH =-4.5 kcal/mol. The change in the ΔS at the formation of DX-DNA complexes is always positive (Table 2) and slightly lower for DX-DNA complexes irradiated at 64.5 GHz and 50.3 GHz frequencies.

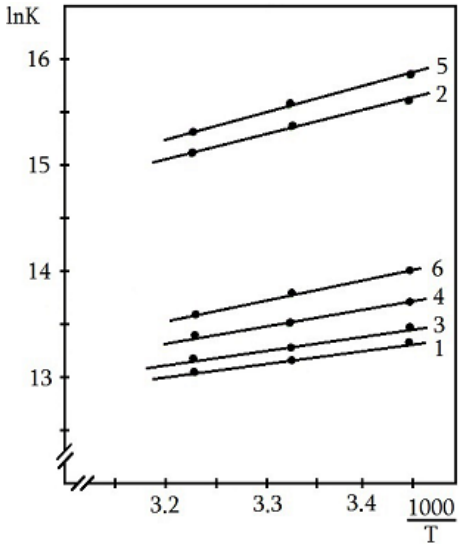


**Figure 4.** lnK dependence on 1/T calculated from absorption isotherms for non-irradiated hDNA-DX (1) and tDNA-DX (4); irradiated with resonant 64.5 GHz frequency hDNA-DX (2) and tDNA-DX (5); irradiated with non-resonant 48.3 GHz frequency hDNA-DX (3) and tDNA-DX (6)

**Table 2. Summary of thermodynamic data for the binding of doxorubicin with non-irradiated and irradiated DNA**

| Type of complex | T, K | $K \cdot 10^{-5}$, $M^{-1}$ | - ΔG, kcal/mol | - ΔH , kcal/mol | ΔS, cal/mol K | n |
|---|---|---|---|---|---|---|
| **hDNA-doxorubicin** | | | | | | |
| Non-irradiated | 290 | 6.0±0.1 | 7.7±0.1 | 2.6 | 17.6 | 4.0 |
| | 300 | 5.2±0.1 | 7.9± 0.1 | | | 4.0 |
| | 310 | 4.5±0.1 | 8.1±0.1 | | | 4.0 |
| Irradiated with 50.3GHz | 290 | 64.5±0.2 | 9.1±0.1 | 4.3 | 16.5 | 4.0 |
| | 300 | 50.3±0.2 | 9.3±0.1 | | | 4.1 |
| | 310 | 39.4±0.2 | 9.4±0.1 | | | 4.0 |
| Irradiated with 64.5GHz | 290 | 62.0±0.2 | 9.1±0.1 | 4.4 | 16.1 | 4.0 |
| | 300 | 48.1±0.2 | 9.2±0.1 | | | 4.1 |
| | 310 | 38.2±0.2 | 9.4±0.1 | | | 4.0 |
| Irradiated with 48.3GHz | 290 | 6.9±0.1 | 7.8±0.1 | 2.7 | 17.6 | 3.9 |
| | 300 | 5.9±0.1 | 8.0±0.1 | | | 4.0 |
| | 310 | 5.1±0.1 | 8.1±0.1 | | | 4.1 |
| **tDNA-doxorubicin** | | | | | | |
| Non-irradiated | 290 | 8.7±0.1 | 7.9±0.1 | 2.9 | 17.3 | 4.1 |
| | 300 | 7.4±0.1 | 8.1±0.1 | | | 4.0 |
| | 310 | 6.3±0.1 | 8.3±0.1 | | | 4.1 |
| Irradiated with 50.3GHz | 290 | 74.9±0.2 | 9.2±0.1 | 4.4 | 16.6 | 4.0 |
| | 300 | 58.3±0.2 | 9.4±0.1 | | | 4.1 |
| | 310 | 46.1 ±0.2 | 9.5 ±0.1 | | | 4.2 |
| Irradiated with 64.5GHz | 290 | 75.0 ±0.2 | 9.2±0.1 | 4.6 | 15.8 | 4.1 |
| | 300 | 57.4±0.2 | 9,3±0.1 | | | 4.0 |
| | 310 | 44.9±0.2 | 9.5±0.1 | | | 4.2 |
| Irradiated with 48.3GHz | 290 | 12.1±0.2 | 8.1±0.1 | 3.1 | 17.2 | 3.9 |
| | 300 | 10.1±0.1 | 8.3±0.1 | | | 4.0 |
| | 310 | 8.5±0.1 | 8.5±0.1 | | | 4.0 |

## 4. Conclusion

Summarizing the experimental data can be said that at *in vitro* irradiation of DNA solutions certain structural changes occur in DNA molecules (due to the partial dehydration of DNA caused by irradiation [17,19]), which are stronger in tDNA, owing to which the irradiated DNA molecules form a more stable complex with DX. Increase in the thermodynamic binding parameters (K, ΔH) in *in vitro* complexation of anticancer drug DX with irradiated DNA indicates to the prospects of development of the millimeter therapy complex with anticancer drug for clinical oncology in the treatment of malignant tumors.

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