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При поддержке РФФИ (8 семинар)

СОВРЕМЕННЫЕ МЕТОДЫ АНАЛИЗА ДИФРАКЦИОННЫХ ДАННЫХ И АКТУАЛЬНЫЕ ПРОБЛЕМЫ РЕНТГЕНОВСКОЙ ОПТИКИ

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22.06. – 02.07.2016 г.

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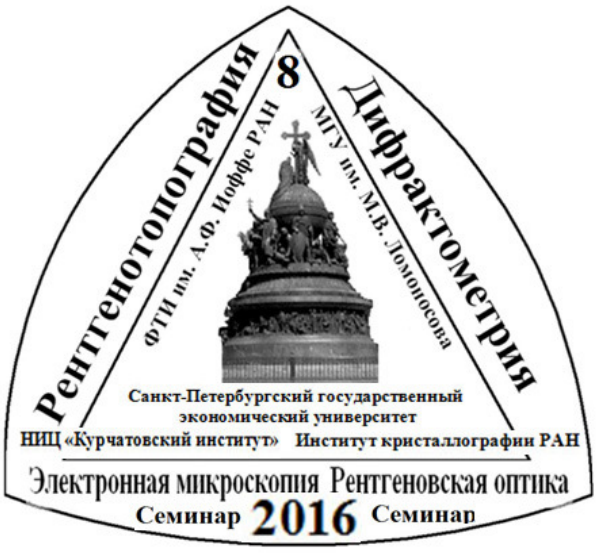

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INFLUENCE OF PORPHYRINS ON DNA DAMAGE INDUCED BY HIGHER ENERGY ELECTRONS

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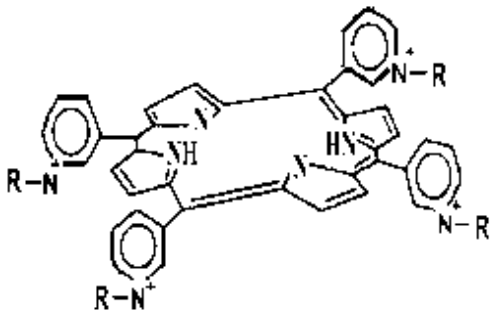
The goal of our work is to study the characteristics of molecular damage induced by ionizing radiation at the DNA level. The passage of ionizing radiation through living organisms initiates physical and chemical processes that create clusters of damaged nucleotides within one or two turns of the DNA. These clusters are widely considered an important initiating event for the induction of other biological endpoints, including cell killing and neoplastic transformation. The reported studies provide new information that will aid efforts to characterize the relative biological effectiveness of high-energy electrons, which are sometimes used in particle therapy for the treatment of cancer.

Introduction

Electron beam therapy isused in the treatment of superficial tumors like cancer of skin regions and diseases of the limbs. The fast electrons directly ionize the DNA molecule, causing damage. These include single-strand breaks and double-strand breaks, DNA–DNA or DNA–protein cross-links [1]. The usage of the porphyrin-based Photodynamic Therapy (PDT) in conjunction with electron beam radiation therapy can be one of the effective treatment methods for cancer [2-4]. Electron beam therapy is performed using a medical linear accelerator. When electrons are required, the x-ray target is retracted out of the beam and the electron beam is collimated with a piece of apparatus known as an applicator or an additional collimating insert, constructed from a low melting point alloy. Electron beams have a finite range, after which dose falls off rapidly. Therefore they spare deeper healthy tissue. The depth of the treatment is selected by the appropriate energy. Unlike photon beams there is no surface sparing effect, so electron therapy is used when the target extends to the patient's skin.

Porphyrins whose structure appears in Figure 1, are well known compounds possess a highly conjugated, and may also contain a central metallic atom such as ferrous iron, magnesium etc. Porphyrins exhibit characteristic optical spectra with a strong π–π^* transition around 400 nm (Soret band) and usually four Q bands in the visible region. Two of the peripheral double bonds in opposite pyrrolic rings are cross-conjugated and are not required to maintain aromaticity. Thus reduction of one or both these cross-conjugated bonds maintains much of the aromaticity (chlorin and bacteriochlorin, respectively). A change in symmetry results in red shifted Q-bands (640 to 800 nm) with high extinction coefficient. As a result, porphyrins have attracted the attention of researchers globally for application as photosensitizing agents in medicine [4].



R= CH_2-CH_2-OH (OE)

R= CH_2-CH=CH_2 (Al)

Figure 1. Scheme of porphyrin

Mechanisms for damage to DNA by electrons (particularly by low-energy electrons) have been plenty investigated [5]. Whereas the studies of the radiation damage at the molecular level in the presence of such PDT agents and anticancer drugs like porphyrins are still actual and necessary.

The goal of our investigations is to examine the DNA damage in the presence of different amount of

porphyrins induced by 3-4 MeV electron radiation depending on radiation doses in vitro.

Material and methods

The most commonly used treatment machine for external beam therapy is the linac, which uses high-frequency electromagnetic waves to accelerate electrons through a waveguide. In our case the AREAL 3–4 MeV electron beam has been used to examine the DNA damage in the presence of porphyrins.

Sample Preparation for High-Energy Electron Irradiation.

The porphyrin-DNA complexes were formed by mixing DNA and porphyrins solutions. In the experiments reported here, the ratios of the number of porphyrins to the number of DNA base pairs were adjusted to be 1:30, 2:5, 1:1, 4:3 and 2:1.

The melting experiments were carried in in 0.1 BPSE buffer (ionic strength μ=0.02). The pH of melting samples was 7.0±0.1.

A stock solution of DNA was prepared and stored in 10^{-3} M NaCl solution, pH 7.0. An extinction coefficient $\varepsilon_{260} = 1.31*10^4$ M^{-1} cm^{-1} was applied to determine the concentration in base pairs of DNA. Porphyrin concentrations and extinction coefficient of porphyrins were determined by spectrophotometric. The porphyrin solutions were prepared before each experiment and were kept in the dark place. The relevant concentrations of DNA-porphyrins complexes equal 0.01; 0.02; 0.04; 0.06; 0.08; 0.1 was used. The meso-tetra-(4N-pyridyl) porphyrins (TOEPyP4, AllPyP4) are used for our experiments.

Results

The samples (calf thymus DNA and TOEPyP4 porphyrins complexes) with different relative concentrations of porphyrins per base pair were irradiated by the electron beam. After samples irradiation, the melting curves (the dependence of denaturated DNA percentage on temperature) of investigated complexes have been obtained. As the melting temperature of DNA is sensitive to double helix stability, it can be used as an indicator of strand breaks of DNA molecules after radiation. The irradiation caused the DNA structural changes (double-strand breaks or local melting), as expected.

At the same radiation dose (1Gy), the porphyrins high relative concentration causes a stronger radiation effect on the DNA structure. The type of porphyrins (TOEPyP4 or TALPyP4) is not influence on radiation effect on DNA/porphyrins complexes. At the higher radiation dose (2 Gy) the presence of porphyrins not influence on melting temperature of DNA. At the different concentration of porphyrins the melting temperature of the complexes is the same, as for the pure DNA. While for not irradiated complexes the melting temperature are increasing upon increasing the concentration.

For more details in vitro investigations of DNA damage for various porphyrins concentrations, DNA sequences and radiation dose levels are planned.

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