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Biophysical and Radiobiological Studies of Neutron Beams from Nuclear Reactors (A Brief Review from Data of MRRC RAMS, Russia)

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Abstract

A brief review is presented, including the position data on the general topics of scientific studies of reactor neutrons. These studies has been conducted to adapt research reactors to biomedical purposes such as radiobiological research program, the treatments of cancer patients with external teletherapy, BNCT, the combined and/or mixed radiotherapy, and the experimental modeling of biodistribution of newly synthesized compound and it efficiency.

1. Introduction

Long-term studies have been performed by the Medical Radiological Research Center (MRRC) in collaboration with the other Institutes in Obninsk, Russia. The studies have clearly shown that neutron beams emerging from the core of a nuclear reactor can be considered to be reliable and economic sources of neutrons for radiation teletherapy together with those obtainable from cyclotrons and accelerators. Reactor neutrons are superior in their space-temporal and energy stability, parallel spreading, width of energy producing neutron spectrum, and flux values. They permit to form action radiation fields with a variety of desirable parameters for radiobiological studies and clinical applications [2,4]. These neutrons have higher LET and RBE than all other types of radiation used therapeutically. The 50% of the absorbed dose are located at the depth 5-6 cm in a tissue. Modification of preexisting channels for medical purposes is far cheaper, than continued constructions and usage of new cyclotrons or accelerators. Application of BR-10 reactor neutrons to teletherapy of gamma-neutron therapy has been successfully carried out for more than 290 patients so far.

2. Results and Discussions

Biophysical parameters of biomedical reactor neutron beams

The scientific interests have been focused on the study of neutrons in a wide range of energies on molecular, genetic, cellular, tissue and organism level. In Obninsk, the investigations are performed on radiobiological, biophysical and dosimetric parameters of neutron beams from nuclear reactor BR-10 (channel B-3 – fast neutrons, channel T-4 – thermal neutrons) and WWRc reactor (horizontal channel 1 - mixed gamma-neutron beam). The energy spectrum of biomedical neutron beams from reactor BR-10 shown on Fig.1.

The flux of thermal neutrons from channel T-4 at the BR-10 reactor are measured as ~ $2{,}9 \times 10^8$ n/cm^2 s. The depth-dose distribution of thermal neutrons in the tissue-equivalent phantom is shown in Fig.2.

As compared to the specrometric and the dosimetric accounts of the energy spectrum of mixed beams from WWRc –reactor, followings are the data at outlet beams (3650 mm from active zone):

- flux of thermal neutrons ~ 3.8×10^9 n/cm^{2}sec;
- flux of epithermal neutrons ~ 1.0×10^9 n/cm^{2}sec;
- flux of fast neutrons ~ 3.0×10^9 n/cm^{2}sec;
- dose rate of gamma-rays ~ 350 cGy/min

Now, on the channel HC-4 of WWRc reactor (E=0.0147 eV, flux thermal neutrons ~1.0×10^6 n/cm^{2}sec), the neutron lens for focusing of thermal neutrons in phantom depth are being tried.

MRRC has some neutron beams with a wide energy spectrum [1], which allows the basic researches and biomedical and medical studies for neutron therapy.

The main biological effects of neutrons from different sources

It is known that the biological effects are essentially based on cell lethality [6]. The response of the cells, as well as the response of tissues, can be interpreted through cell survival curves, which express the variation of cell survival fraction as a function of absorbed dose.

The researches on the inactivation of neutron actions on E.coli (B/r and Bs-1) have shown their large efficiency in comparison with gamma-radiation. For B/r, RBE of neutrons with energy 0.85 and 0.35 MeV is equal to 2.1 and 4.0. For Bs-1, RBE of neutrons is equal to 1.1-1.15 and is identical to both specified importance energy. These results, however, will not be coordinated with the data from E. coli cells irradiated with fast heavy ions, according to which their radiosensitivity remains practically constant with increase of LET down to 50 KeV/microns but if LET value goes higher, RBE decreased. As a spectrum LET has known for neutrons [1], it is possible to calculate radiosensitivity to them of E.coli cells. Results have shown, that RBE of neutrons with energy 0.35 and 0.85 MeV should be equal to 0.9 (for B/r) and 0.6 (for Bs-1), which are

significantly less RBE's. Apparently, the high efficiency of neutrons is caused by slow heavy nuclei of feedback (P, N, O, C), having approximately the same LET as fast heavy charged particles, but smaller speed. For the check of this assumption the special experiments on cells irradiated with neutrons in conditions of presence and absence of proton balance were carried out. The results showed that RBE of slow protons and heavy nuclei of feedback on cell survival of bacteria B/r is equal to 3.5- 6.6. It was possible to determine RBE of cell inactivation in bacteria B/r. It varied from 20 to 60, depending on the energy of ions and the condition of irradiation. The scoring of complete number of the displaced atoms with an irradiation phantom by neutrons showed that RBE of neutrons and elastic nuclear collisions correlated with the number of the displaced atoms. Therefore, though the dose of nuclei of feedback in the absorbed dose makes only 8-9 % for neutrons with energy from 0.85 to 6 MeV, their contribution to biological effect corresponds to 30 to 55 %.

The shape of the cell survival curves varies according to the beam quality and the irradiation modalities (single or fractionated irradiation). It varies also according to the type of cells and the physiological status of the population. Potential advantage of neutrons is essentially based on the improvement of differential effects. In reality, neutrons have many radiobiological properties that can be turned to clinical application. However, the major problem remains in the choice of indications and irradiation modalities.

Radiobiological advantages of reactor neutrons:

- Biological efficiency of neutrons depends on neutron dose and energy. Neutrons with energy of 0.35 MeV have the highest efficiency (there is an energy spectrum of nuclear reactor neutrons).
- The average value of OER of reactor neutrons for different biological objects is equal to 1.7.
- For some cells (human lymphocytes, mouse thymocytes) there is a resistant fraction in which no final damage is detected even after very high neutron doses while no such effect is observed for gamma-radiation.
- Additional mechanism of cell damage stipulated by resilient nuclear bumping collisions lies in inactivating effect of neutrons. The relative biological efficiency of neutrons varies in the range of 20 to 60 depending on the energy of ions derived from neutrons.
- At all levels of biological organization a number of radiation effects that become strikingly apparent for gamma-radiation (oxygen effect, fractionation effect, relationship between sensitivity and phase of cell cycle and cellular type, etc.) are poorly or not detected at all for reactor neutrons. Other effects (for example, delay in division) mostly appear under the action of neutrons.

Radiolabeled ^{131}I-B12H11SCN and its radiobiological properties.

The objective of this work is the evaluation of novel boron compounds with useful medical applications and in particular the fitness of these for neutron capture therapy (NCT). New compounds are

being evaluated for toxicity, and tumor to healthy tissue boron concentration ratios and using this to determine an optimal biological regime for selected compounds. Boron compounds are of increasing interest in biology and medicine. Most work has concerned their application to cancer therapy via ^{10}BNCT. Additional interest has focussed on compounds with antiarthritic, hypolipidemic, and neurotropic and anticonvulsive activity. The factor limiting the development of tumor chemoradiation therapy such as BNCT, is the lack of good tumor-seeking, especially tumor cell-seeking drugs. Potentially the most promising boron compounds for NCT which could help boron to penetrate into the tumor cells are thio-derivatives of higher boron hydrides, boronated porphyrins and phthalocyanines, amino-acids and precursors of nucleic acids, amongst others.

Previous work reveals that new compound for BNCT - $Na_2[B_{12}H_{11}SCN]$ (BSCN) is accumulated in several experimental malignant tumors to a greater extent even than $Na_2[B_{12}H_{11}SH]$ (BSH), which has been most studied for BNCT, and is one of two compounds (BSH and 4-dihydroxyborylphenylalanine {BPA}) authorized for clinical trials of this therapy. The development of biological and analytical methods for BSCN was shown up well by murine tumor studies. In order to shed light on the biodistribution of $[B_{12}H_{11}SCN]^{2-}$ (BSCN) in tumor-bearing animals *in vivo* as a precursor to clinical ^{10}B neutron capture therapy,

It has been carried out iodination of BSCN with a radioactive iodine - I-131 (by method of V.A. Brattsev) in order to approach an agent which can be used for the scintigraphic studies of the compound determinations in tumor and normal tissues *in vivo* and *in vitro*. Studies of biodistribution of the radiolabeled ^{131}I-BSCN in the form of the radioiodination reaction mixture (contains 3% of radioiodide-anion impurity) and precipitated (Bu4N)2B12H10(131)I(SCN), dissolved in DMSO-water, have been carried out on intact rats by means of the radioactivity measurements of their blood, muscle and thyroid in 3 and 24 hours after intraperitoneal injection. The results obtained show that ^{131}I-BSCN has rather long retention in blood and very low level of thyroid uptake, that unequivocally indicates on the high "biological" stability of both B-I bond in the compound studied and closo-B12 icosahedral structure in general. In another set of experiments more detailed examination of ^{131}I-BSCN biodistribution in organs, tissues, and tumors (sarcoma M-1) in rats after different ways of BSCN administration have been performed (Table 1).

Modeling of BNCT and neutron capture potentiation (“boost”)

Lsst time we had possibility to plan working on the “clear” BNCT (using of thermal and epithermal neutrons from WWc-reactor) and the “boost” or the neutron capture potentiation (using the mixed neutron beams: WWRC reactor – thermal, epithermal and fast neutron, and gamma-radiation; and BR-10 reactor: fast neutron and thermal neutron). However, now thermal neutrons fraction is very low in the energy spectrum of “fast” B-3 channel of BR-10, which is in the medical complex for treatment of oncological patients with external neutron therapy. And we let BNCT go into two ways. The first is the construction works on medical

room of WWRc; and the second is thermalization of fast neutrons (BR-10) on a necessary depth of tumors. The physicians and engineers in Obnisnk are creating the special filters and they get the result that at tumor deep around 4-5 cm it will be 30% dose with capture reaction (thermal neutrons + 30 ppm of ^{10}B) from total absorption dose. In experimental studies was used two neutron beams of BR-10 (T-4, thermal and B-3, fast neutron beams) for modeling the similar situation.

The studies have been performed on tumor-bearing rats with sarcoma M-1. The degrees of radiation damage of skin and antitumor efficiency after irradiation have been estimated, using standard criteria. Dose rate of fast neutron was ~ 0.165 Gy/min. The flux of thermal neutron was 2.9×10^8 n/cm^2 in reactor hall after the shielding. The total dose in tumor was estimated as 40 Gy. The researches performed earlier at the thermal channel T-4 and previous data on the use of a fast neutron beam B-3 of reactor allowed to calculate basic dosimetric parameters of combined experimental neutron therapy [3]. Before irradiation tumors were injected of 30 μg/g (30 ppm) enriched ^{10}B in 0.1 ml of physiological solution. For this contents of ^{10}B was based on the calculation of the dose-rate at the experimental tumor. The contribution of thermal neutrons in the absorbed dose with protons from the reaction 14N (n, p) 14C, whose computerized dose-rate achieved 0.4 cGy/min, and α-radiation input, 2.5 cGy/min. The RBE for α-particles was accepted equal to 4.1, and for proton, 2. Exposition time of animals on the channel T-4 for tumor irradiation in dose 10 Gy-eq. was 40 min. The irradiation schemes were as follows: fission-spectrum neutrons (“fast neutrons”); “fast neutrons” + thermal neutrons + 30 μg/g of ^{10}B in tumor; “fast neutrons” + thermal neutrons (without ^{10}B). The equivalent doses were calculated with RBE values of 4.1 for α-particles and 2 for protons taken from literature. The results of irradiation are shown in Table 2.

The parameter St was calculated with integration of the area under the curve of tumor progression (in coordinates: relative volume of tumor – days after irradiation). The efficiency of action is higher, the less St-parameter. The α_1 (regression) is the inclination of tumor growth curve from least squares liner regression at the tumor regression stage (3-15 days after irradiation) and α_2 (recurrences) is the curve of recurrences development (16-30 days after irradiation), accordingly. The comparison between computerized RBEs of "boosted" irradiation and the experimental data has revealed amplification effect of 1.3-1.7 times with the combined irradiation, whereas the computerized dose-rate was based on the equal effects in these cases. Both points - the higher RBE for α-particles, and the prospect of enhancement of neutron therapy, are owing to concomitant BNC-potentiation.

3. Conclusions

A brief review is presented on up-date problems of neutron radiobiology, related to neutron therapy development using the reactor neutrons. The main attention is paid to the effects of combined and mixed gamma and wide energy neutron irradiation, peculiarities of reactor neutrons biological action and new

approaches in neutron capture therapy. On the basis of own and literature data the results of cellular and whole-body studies as well as the applicability of biophysical modeling for description and interpretation of experimental data are mentioned. Our previous theoretical and experimental studies permit to consider nuclear reactor neutron beams as reliable sources of thermal and epithermal neutrons for BNCT and fast neutrons with wide energy spectrum for enhancement of neutron teletherapy. Now we have planning of the development of *in vivo* and *in vitro* methods for boron determination in organs and tissues, radiobiological and pharmacological studies of an acknowledged compound for BNCT – BSH and its derivation – BSCN. The specially designed new, perspective small, safety reactors [5] will be used for BNCT, external neutron therapy and for radionuclide productions. Regulative normative basis should be developed for the use of nuclear reactor neutron beams for neutron and NCT of tumors in accordance with international standards.

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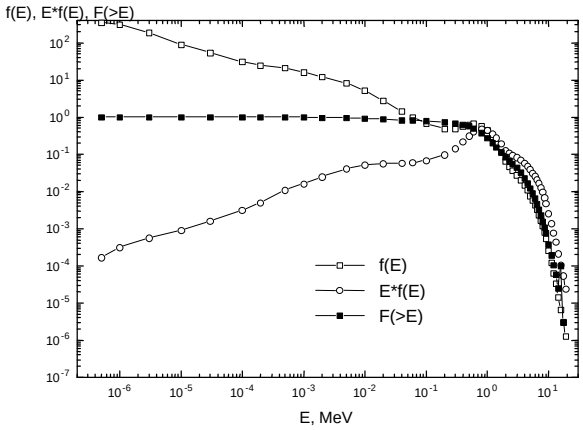

f(E) [1/(sm^2·s MeV)] and F(>E) [1/(sm^2·s)] - DIFFERENTIAL and INTEGRATED DENSITY of NEUTRON FLUX .The AVERAGE ENERGY of FAST NEUTRONS is ~0,85 MeV.

Fig.1. Energetical spectrum of neutron beam from BR-10 reactor, channel B-3

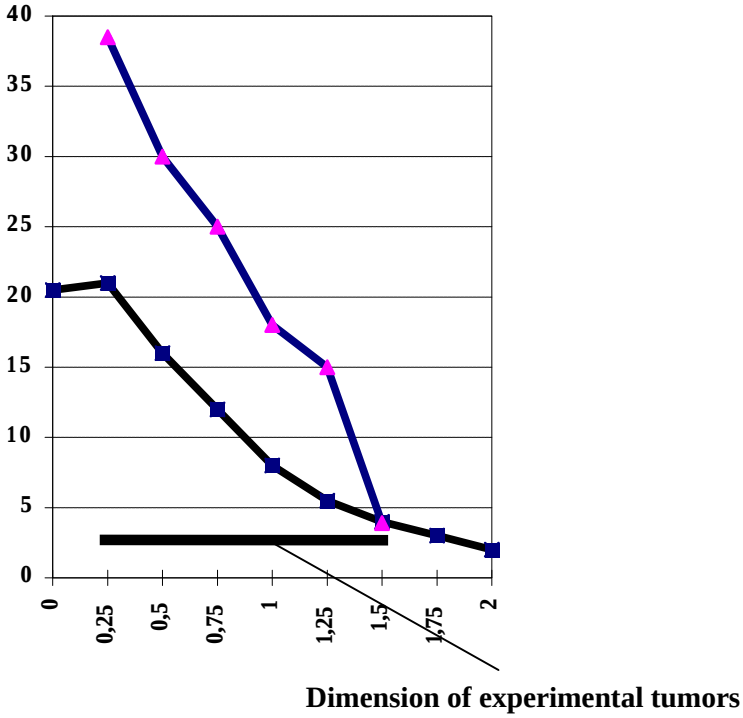

Fig.2. Dose-rate depth distribution in the phantom (y – Dose-rate, cGy/min; x –Depth in phantom, cm).

△ - Thermal neutrons + α-particles (30 ppm of ^{10}B); □ - Thermal neutrons.

Table 1. **Distribution of labeled ^{131}I-BSCN in tumor-bearing rats with sarcoma M-1**

(% from injected radioactivity per organ and per ***1 g of organ or tissues***)

Modality of injection	**Muscle**	**Skin**	**Brain**	**Tumor**	**Blood**
1.Intravenous injection in indicators amounts (12 hr after injection)	1.1±0.1 ***0.12±0.01***	0.71±0.13 ***0.28±0.05***	0.01±0.01 ***0.03±0.001***	0.10±0.01 ***0.40±0.03***	1.18±0.04 ***0.86±0.04***
2. Intraperitoneal injection in therapeutic dose (12 hr after injection)	0.92±0.19 ***0.11±0.01***	0.54±0.17 ***0.23±0.03***	0.01±0.01 ***0.03±0.001***	0.07±0.01 ***0.35±0.03***	0.75±0.11 ***0.59±0.03***
3.Control with Na^{131}I (12 hr after p.p. injection)	0.16±0.01 ***0.02±0.01***	0.46±0.24 ***0.19±0.11***	0.01±0.001 ***0.02±0.001***	0.02±0.01 ***0.05±0.01***	0.09±0.03 ***0.61±0.01***
4. Intratumoral injection (12 hr after injection)	0.78±0.13 ***0.08±0.01***			0.30±0.19 ***1.04±0.55***	- ***0.17±0.03***

Table 2. **The efficiency of neutron and combined neutron and neutron-capture action at tumor rats**

Modality Of irradiation	**Dose**	**Antitumor efficiency**			**Skin reactions, relative to the modality N1(%)**
		St (Square under curve)	**tga_1 (regression)**	**tga_2 (recurrences)**	
1. “Fast neutrons”	40 Gy-Eq	20.05	-0.074	+ 0.102	100
2. “Fast neutrons”(f.n.) + thermal neutrons (th.n.) +30 μg/g ^{10}B	30 Gy-Eq (f.n.) +10 Gy-Eq (th.n.)	12.43	- 0.091	+ 0.017	69,9 71,1
3. “Fast neutrons” + thermal neutrons (without boron)	30 Gy-Eq (f.n.) +10 Gy-Eq (th.n.)	20.01	- 0.080	+ 0.060	

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