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The Oxygen Enhancement Ratio as a Function of Neutron Energy with Mammalian Cells in Culture*

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* This investigation was supported by Contract EY-76-C-02-3243 from the Department of Energy and Grant Nos. CA 18506 and CA 12536 from the National Cancer Institute, DHEW.

Running Head: Neutron OER's

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ABSTRACT

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Chinese hamster cells (V79) in culture under oxic and hypoxic conditions were irradiated with several neutron beams spanning a wide energy range the oxygen enhancement ratio (OER). Eight essentially monoenergetic neutron beams, ranging from 0.22 to 13.6 MeV and a 0.11 MeV neutron spectrum, were produced at the Radiological Research Accelerator Facility (RRAF) at Brookhaven National Laboratory. Additional experiments were performed at the Naval Research Laboratory, Washington, D.C., where neutrons are produced for radiotherapy by bombarding a beryllium target with 35 MeV deuterons. This beam has a broad energy spectrum with a mean energy of about 15 MeV.

A maximum OER of about 1.9 was observed for 13.6 MeV neutrons. The OER values of the monoenergetic neutrons decreased with neutron energy, plateaued at about 1.45 for the energy range from 0.22 - 2.0 MeV and increased slightly to about 1.55 for lower energy spectrum. In the light of microdosimetric data obtained for the neutron beams at RRAF, the OER appears to depend primarily on the intermediate LET secondaries produced by neutrons in tissue, such as protons, while in contrast high LET secondaries, such as, alpha particles and recoil ions, play a minor role.

The studies using the NRL neutron beam resulted in a lower OER of about 1.67 as compared to the monoenergetic

13.6 MeV beam. This is a consequence of the fact that more of the dose is deposited by intermediate LET secondaries for the NRL neutron beam.

Key words: OER, Neutrons, Microdosimetry, Hamster Cells

INTRODUCTION

Interest in neutrons by the biomedical community is based on the experimental observation that the cell-killing effect of neutrons is less dependent upon the presence or absence of molecular oxygen than is the case for sparsely ionizing radiations, such as gamma or x-rays. The effect of molecular oxygen on radiation damage has been shown to be a function of the linear energy transfer (LET), which is a measure of the radiation quality (1). Since the LET spectrum of the secondary particles produced by neutrons varies with neutron energy, extensive studies have been conducted to measure the effects of neutrons over a wide range of energies. Most of the recent measurements were made at the Radiological Research Accelerator Facility (RARAF) which was a joint enterprise between the Radiological Research Laboratory of Columbia University and the Medical Research center of the Brookhaven National Laboratory (BNL). RARAF consists of a large van de Graaff accelerator capable of accelerating particles up to an energy of 4.2 MeV. By bombarding suitable targets, and using neutrons emitted at an appropriate angle relative to the incident charged particle beam axis, essentially monoenergetic neutrons beams can be generated ranging in energy from 0.22 MeV to 13.6 MeV. In addition, a lower energy neutron beam is available which consists of a wide spectrum of energies (0.0 - 0.11 MeV) with a mean energy of approximately 0.07 MeV.

Several studies have been reported in the literature on the ability of various neutron energies to effect cellular damage with minimal dependence on molecular oxygen. For those experiments in which mammalian cells were used as a test system, a narrow range of neutron energies were explored (2,3). By contrast, for those studies in which tests were performed over a wide range of neutron energies, plant systems were used (4,5,6,7,8,9,10,11,12).

This paper describes experiments in which the oxygen enhancement ratio (OER) was studied over the wide range of neutron energies available at RARAF using mammalian cells in culture. In addition, using the same biological test system, experiments were performed at the Naval Research Laboratory (NRL) at Washington, D.C. The cyclotron on site generates a neutron beam by bombarding a beryllium target with 35 MeV deuterons. The resulting neutron beam, which is currently used for radiotherapy, has a wide spectrum of neutron energies with a maximum of 35 MeV and a mean of 14.3 MeV.

MATERIALS AND METHODS

Culture of the Cells

Chinese hamster cells (V79) were cultured by standard techniques and grown in GIBCO F10 culture medium supplemented with 10% fetal calf serum and penicillin-

streptomycin. Hypoxia was attained by confining a large number of cells in a small volume of medium, so that oxygen depletion resulted from cell metabolism. The method has been widely used and described in detail elsewhere (13).

Briefly, cells from actively growing, partly confluent stock flasks were removed by trypsinization, washed to remove excess trypsin and counted with a Coulter electronic counter. For the hypoxic series of ampules, a concentration of two million cells per ml was used. One milliliter of this cell suspension was pipeted into glass ampules (cylinder of 2 cm in height and 0.6 cm in diameter). The ampules were flushed with a 95% N_2 and 5% CO_2 mixture to remove excess oxygen from the environment before being sealed. They were then tumbled and reciprocated in a $37.5^\circ C$ water bath for one hour to allow the cells to deplete by metabolism any oxygen remaining in the medium. For those cells that were to be irradiated under oxic conditions, a second series of ampules was inoculated with 10^4 cells per ml, gassed with 5% CO_2 in air and heat sealed. A 3mm teflon-coated magnetic stirrer was sealed within each ampule. A ring of magnets of alternating polarity placed on the irradiation apparatus around the ampules effected the spinning of the stirrers. Stirrer speed was maintained at 180 rpm to keep the cells in suspension.

It was thought necessary to irradiate cells in suspension for neutron energies 2 MeV and greater in order to minimize the perturbations to the absorbed dose due to

inadequate secondary particle build-up at the glass walls of the ampules. At neutron energies 1 MeV and below the range of the secondaries is so short that a negligible dosimetry error is introduced. In this case, the cells were not irradiated in suspension but were centrifuged into a pellet at the bottom of smaller glass vials so that the cells could be positioned close to the neutron source. This was necessitated by the relatively low dose-rate and the high dose attenuation through tissue medium at the lower neutron energies. The procedure for obtaining hypoxia was similar to that used for the larger ampules except that the vials were inoculated with a cell suspension of concentrations of 3.3×10^6 cells/ml and 3.3×10^4 cells/ml for the hypoxic and the oxic series, respectively.

For each experiment four or five replicate ampules were used at each of seven absorbed doses for both oxic and hypoxic conditions. Cell irradiations were performed at room temperature. Following irradiation the cells within each ampule were resuspended, after which the ampules were opened and various fractions were inoculated into Falcon flasks containing 6ml of fresh growth medium. Following an 8-day incubation period, the clones were fixed and stained, and counted using a projection technique. By comparison with unirradiated controls, the fraction of cells under hypoxic and oxic conditions surviving various doses of neutrons was calculated.

Methods of Irradiation at RARAF

Nine neutron energies were studied at RARAF. The characteristics of the beams used are summarized in Table I. The glass ampules or vials were positioned in a circle around the target and rotated about the incident charged particle beam axis to compensate for asymmetries in the beam (Figure 1). The vials were rotated 180° about their axis half way through each exposure to compensate for variations of dose through the cell pellets.

Dosimetry was performed using a tissue equivalent $1/4$ inch diameter spherical multiplication chamber, which was placed at the point where the specimens were to be irradiated. Since this chamber measures total dose, separate measurements were made with a Geiger-Mueller dosimeter which is almost solely sensitive to gamma-rays. The calculated dose rates were corrected for gamma-ray contamination, dose buildup and attenuation and inverse square dependence on distance.

Methods of Irradiation at NRL

The neutron beam at the Naval Research Laboratory cyclotron is produced by bombarding a beryllium target with 35 MeV deuterons. The neutrons produced in this way have a broad spectrum of energies with a mean energy of approximately 14.3 MeV (14).

Large glass ampules containing V79 hamster cells in suspension were irradiated in a lucite holder, which was reciprocated by a shaker in order to keep the cells in suspension during irradiation. Dosimetric measurements were taken with a 0.1cc TE ion chamber, placed at the center of the lucite holder. Stability of the 0.1cc chamber is not long termed, so this chamber was intercompared to a more reliable 1.0cc TE ion chamber. The cells were irradiated at a distance of 136.4 cm from the target in order to provide a large enough field without diffraction problems. The dose rate was approximately 50 rads/min.

RESULTS

The results of the experiments in which the oxygen enhancement ratios were determined for monoenergetic neutrons produced at RARAF are summarized in Figure 2. The vertical bars shown in the figure represent one standard deviation determined from gaussian statistics derived from a comparison of the number of surviving clones resulting from replicate vials of cells exposed to the same absorbed dose normalized to the controls. The curves in Figure 2 were fitted to the experimental data by a modified method of least squares, using a computer program. The form of the curves, suggested by the theory of dual radiation action is

$$S(D) = e^{-\alpha D} - \beta D^2 \quad (1)$$

where $S(D)$ is the fraction of cells surviving a dose D (where α and β are constants). For energies less than 5.9 MeV, curve fitting to the oxic points yielded betas that were close to zero. The oxic points for the lower energies were therefore refitted to a survival curve of the form

$$S(D) = e^{-\alpha D} \quad (2)$$

Table II lists the values of the alphas and betas for both oxic and hypoxic curves for each energy. Table II also lists the oxygen enhancement ratio for each neutron energy calculated at the 1% survival level. OER as a function of neutron energy is shown in Figure 3.

Survival data for the study performed at the Naval Research Laboratory Cyclotron, using a neutron energy spectrum generated by 35 MeV deuterons on a beryllium target, is plotted in Figure 4. The data were analyzed by methods similar to those described above for the monoenergetic neutrons; values of alpha and beta obtained are listed in Table II. The oxygen enhancement ratio was determined to be 1.67 at a survival level of 1%. The OER found at NRL is lower than that of either the 13.6 MeV or 5.9 MeV monoenergetic beams, as can be seen in Figure 3.

DISCUSSION

OER as a Function of Neutron Energy

Extensive studies have been reported on the effects of neutrons on a variety of biological systems. Data from several reports in the literature describing the variation of OER with neutron energy are plotted in the upper four panels of Figure 5. Also shown for comparison are the results of the investigations reported here.

Scoring pink somatic mutations in Tradescantia, Dennis and Boot (5) found that the OER rose rapidly between 100 keV to 6 MeV. Two features of their work were not observed in the present study. First, they found a high OER, in excess of 2, at 440 keV which they attributed to oxygen resonance. Second, they found that the OER decreased as the neutron energy rose from 6 MeV to 15 MeV. Besides conflicting with observations made in these investigations, their results have not been confirmed by the more recent measurements of Underbrink and Sparrow (11,12) using the same biological system. The neutron beams used by Underbrink and Sparrow were produced at the Radiological Research Laboratory facility at BNL. There is general agreement between the results of Underbrink and Sparrow and those reported in this paper.

Berry (4), using P388 lymphocytic leukemia cells in vivo, found the OER to be an increasing function of neutron energy in the range from 1 to 25 MeV. The increase in the OER

from 6 MeV upwards is quite similar to that reported here. In contrast, Berry found a very low OER (1.1) at 1 MeV whereas the lowest OER found in these investigations was 1.44. It must be noted that not only were the biological systems totally different, but the 1 MeV neutrons used by Berry and described as 1 MeV were in fact a spectrum of fission neutrons.

The data for the T_1 human kidney cells reported by Broerse et al. (2,3), in which cell-killing was scored, show little change of OER over the limited energy range tested. It should be noted that three of the five neutron energies used (1.0 MeV, 6 MeV and 10 MeV) contained wide energy spectra. Also the hypoxic level attained was questionable because of the porosity of the mylar surface on which the cells were plated. Yet the T_1 cell data do not disagree with the V_{79} data over this limited energy range.

The widest range of energies investigated to date was reported by Hall et al. (6,7,8,9,10) who used Vicia faba seedlings for neutron energies ranging from 0.05 MeV to 15.0 MeV. A reliable and measureable level of hypoxia was attained by vigorously gassing the seedlings in a TE chamber.

A comparison can be made readily between the Vicia data of Hall et al. and the V_{79} data presented here, because both studies utilized the same neutron beams produced at the same facility. Striking similarities can be seen. In both cases, it is evident that the oxygen enhancement ratio is a non-trivial function of neutron energy. There is a clear

indication of an increase of OER with increasing neutron energy. There also appears to be a turning point in the OER curve at about 0.34 MeV. This implies a limitation to the capabilities of neutron radiation to counter hypoxia. Whether the OER increases when the energy of the neutrons fall below 0.22 MeV cannot be ascertained on the basis of the present data. It should be noted that the variance about the mean energy of irradiation increases for decreasing energy to the point where the lowest energy used (.07 MeV) ranges from 0 to 110 keV. Besides the uncertainty in the beam energy, a large proportion of the beam is composed of slow neutrons which are sparsely ionizing. Because of these slow neutrons it is possible that the OER rises, but the extent of the rise cannot be determined.

For the range of neutron energies used, OER values fall between 1.44 and 1.91. This OER range is significantly greater than that observed by Broerse et al. In addition, OER appears to be a smooth function of neutron energy without any discernible singularities as those shown in the Tradescantia data of Dennis and Boot.

A significant conclusion can be drawn from the similarities among the three studies done at the RARAF neutron facility. The relative sensitivity of cells to radiation damage in the presence or absence of molecular oxygen is similar for three very diverse biological systems. This supports the idea that the oxygen effect independent of the biological system.

Microdosimetric Interpretation

Microdosimetry makes possible an interpretation of the mechanisms of biological damage in terms of the deposition of radiant energy. Certain microdosimetric quantities which measure energy deposition, were defined by Rossi (15,16). The quantity specific energy, z , is defined as the energy actually imparted in a microscopic region divided by the mass of that volume. Energy deposition can also be expressed in terms of the lineal energy transfer, y , which is the microdosimetric analogue of the linear energy transfer (LET). The absorbed dose, D , is the expectation value of z . Analogous to this is the dose average event of the lineal energy $\bar{y}_D$, which is defined as the average energy deposited in a specific volume divided by the mean pathlength of the quantum through that volume.

An increasing concentration of radiation in any sensitive regions of a biological system will lead to a concentration at which there is waste. This is called the saturation effect. The number of oversaturated regions will increase as the lineal energy increases. Kellerer and Rossi (17) proposed the quantity, effective lineal energy, y^* , which is the dose average energy modified to take saturation into consideration.

Microdosimetric quantities for the neutron beams produced at RARAF were measured by Rodgers and Gross (18).

The data was reanalyzed and the dose spectra shown in Figure 6 were determined. The fraction of the dose delivered per unit logarithmic interval of lineal energy ($y_d(y)$) is plotted against the logarithm of the lineal energy (y) for a series of neutron energies close to those used for the biological studies reported here. In this presentation, the area under the curve in an interval of lineal energies is proportional to the fraction of the dose delivered in that interval. The data are presented in this form because it is physically more revealing and biologically more significant.

Values of the $\bar{y}_D$ and the y^* were calculated for those values of y that were greater than 5 keV/micron in order to eliminate the low energy background noise. These values are given in Table III for each energy along with the approximate OER. Calculated values of $\bar{y}_D$ and y^* are plotted in Figure 7. There is an obvious correspondence between y^* and the OER's of the Vicia and the V79 investigations. From the BNL dose spectra a correlation can be drawn between the OER and the y_D of the particles with lineal energies less than 150 keV/micron.

Microdosimetric measurements were made at the Crocker Nuclear Laboratory (CNL) at the University of California, Davis for 35 MeV deuterons striking a beryllium target (19). The secondary particle energy spectrum of this beam is shown in Figure 6. As observed by Amols et al., there is a higher contribution to the dose from events with lineal energy above 450 keV/micron for the BNL 15-MeV monoenergetic

beam as compared to their data for the CNL 35-MeV $d^+ \rightarrow Be$ (about 16% higher). This supports the radiobiological observation that the 15-MeV monoenergetic beam is less effective in killing hypoxic cells than the 35-MeV spectrum.

The majority of high LET events is a result of alpha particles and heavy recoil ions, since the maximum proton LET is less than 150 keV/micron. As the energy of the neutron beam increases, the contribution to the dose by events greater than 150 keV/micron will also increase. As a consequence, a beam containing more of these higher energy neutrons will not be as effective in countering hypoxia as a beam that produces a majority of its secondaries within a LET range of 50-150 keV/micron. Experimental data supports this. Hall et al. (20), using V79 hamster cells as a test system, showed that, for a neutron beam spectrum produced by 80 MeV deuterons striking a beryllium target, the OER was about 1.7. A more definitive conclusion on the role of alpha particles, heavy recoil ions and spallation products in countering hypoxia can only be drawn upon the investigations of the effects of higher monoenergetic neutron beams, such as, 25, 50, and 100 MeV, and their secondaries, on biological systems.

ACKNOWLEDGEMENTS

The authors take pleasure in acknowledging much useful advice and support from Dr. Harald H. Rossi. We would also like to thank Dr. Richard Bird for his assistance at Brookhaven National Laboratory. For experiments at the Naval Research Laboratory, we are indebted to Dr. Leon August, Dr. Philip Shapiro and Mr. Richard Theus who were responsible for the dosimetry and for irradiating the specimens. Finally we wish to thank Ms. C. Fillmore and Mrs. C. Miller for their technical assistance.

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TABLE I

MEAN NEUTRON ENERGY (MeV)	% ENERGY SPREAD	NUCLEAR REACTION	INCIDENT PARTICLE ENERGY (MeV)	DISTANCE FROM TARGET (cm)	SCATTERING ANGLE (degrees)	GAMMA CONTAMIN- ATION	AVERAGE DOSE RATE (RAD/HR)
13.6	+2.5 -2.5	$^3\text{H}(^2\text{H}, \text{n})^4\text{He}$	0.60	4.65	120.0	5.8%	2400
5.9	+6.0 -8.0	$^2\text{H}(^2\text{H}, \text{n})^3\text{He}$	3.10	15.55	15.0	4.5%	275
2.0	+9.2 -11.0	$^3\text{H}(^1\text{H}, \text{n})^3\text{He}$	3.40	5.69	45.0	2.7%	310
1.0	+9.5 -9.8	$^3\text{H}(^1\text{H}, \text{n})^3\text{He}$	3.72	2.58	100.0	3.8%	550
0.68	+13 -13	$^3\text{H}(^1\text{H}, \text{n})^3\text{He}$	2.82	2.58	100.0	1.1%	400
0.43	+17 -18	$^3\text{H}(^1\text{H}, \text{n})^3\text{He}$	2.30	2.58	100.0	0.3%	400
0.34	+22 -23	$^3\text{H}(^1\text{H}, \text{n})^3\text{He}$	2.08	2.58	100.0	0.5%	450
0.22	+30 -33	$^3\text{H}(^1\text{H}, \text{n})^3\text{He}$	1.83	2.58	100.0	0.7%	285
0.07 (.11 spectrum)	+60 -100	$^3\text{H}(^1\text{H}, \text{n})^3\text{He}$	4.20	2.58	100.0	2.3%	75

TABLE II

MEAN NEUTRON ENERGY (MEV)	CELL CONDITION	ALPHA (10^{-3} RAD $^{-1}$)	BETA (10^{-6} RAD $^{-2}$)	OER
13.6	HYPOXIC OXIC	2.41 $\pm$.01 3.53 $\pm$.24	0.75 $\pm$.01 4.31 $\pm$.92	1.91 $\pm$.19
5.9	HYPOXIC OXIC	2.49 $\pm$.10 3.94 $\pm$.40	0.63 $\pm$.03 2.39 $\pm$.52	1.74 $\pm$.17
2.0	HYPOXIC OXIC	3.96 $\pm$.31 10.21 $\pm$.24	4.85 $\pm$.51	1.44 $\pm$.16
1.0	HYPOXIC OXIC	5.08 $\pm$.18 10.22 $\pm$.46	2.71 $\pm$.31	1.48 $\pm$.12
0.68	HYPOXIC OXIC	8.00 $\pm$.24 14.95 $\pm$.64	3.93 $\pm$.25	1.52 $\pm$.17
0.43	HYPOXIC OXIC	8.72 $\pm$.33 17.03 $\pm$.84	7.75 $\pm$.42	1.45 $\pm$.17
0.34	HYPOXIC OXIC	7.21 $\pm$.44 15.42 $\pm$.91	7.28 $\pm$.99	1.48 $\pm$.13
0.22	HYPOXIC OXIC	11.07 $\pm$.45 19.19 $\pm$.77	4.39 $\pm$.62	1.52 $\pm$.13
0.07	HYPOXIC OXIC	4.64 $\pm$.26 15.6 $\pm$ 1.2	11.87 $\pm$.61	1.55 $\pm$.15
NRL 15 MeV	HYPOXIC OXIC	2.96 $\pm$.16 5.47 $\pm$.16	0.37 $\pm$.01	1.67 $\pm$.16

TABLE III

MEAN NEUTRON ENERGY (MeV)	$\bar{Y}_D$ (keV/ μ)	Y^* (keV/ μ)	OER
15.0	102.2	30.4	1.91
5.8	61.8	32.9	1.74
2.2	63.6	46.6	1.44
1.0	72.1	55.9	1.48
0.60	80.2	60.5	1.52
0.43	76.3	58.8	1.45
0.34	76.7	58.6	1.48
0.20	71.8	55.1	1.52
0.06	66.7	47.9	1.55

FIGURE LEGEND

Figure 1 - Apparatus used to irradiate Chinese Hamster cells with various energies at the Radiological Research Facility (RARAF) at Brookhaven National Laboratory (BNL).

Figure 2 - Cell survival data of V79 Chinese hamster cells under oxic and hypoxic conditions irradiated using nine monoenergetic neutron beams produced at RARAF.

Figure 3 - Least-square estimates from the alpha-beta survival curve fit of the oxygen enhancement ratio (OER) at the 1% survival level and one standard deviation confidence ranges for various neutron energies produced at RARAF at BNL.

Figure 4 - Cell survival data of V79 Chinese hamster cells under oxic and hypoxic conditions irradiated using the NRL neutron beam.

Figure 5 - OER over a wide range of neutron energies for five different biological test systems.

Figure 6 - Differential dose as a function of the lineal energy for the nine neutron energies used at RARAF at Brookhaven National Laboratory (BNL) and for the 35-MeV $d^+ \rightarrow Be$ neutron beam produced at Crocker National Laboratory (CNL).

Figure 7 - Calculated values of the dose-event of the lineal (Y_D) and the effective lineal energy (Y^*) for various neutron energies.

OXYGEN ENHANCEMENT RATIO

NEUTRON ENERGY (MeV)