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A CALCULATION OF THE PHYSICAL PARAMETERS RESPONSIBLE FOR THE ENHANCEMENT OF RADIATION DAMAGE DUE TO THE INCORPORATION OF Br/I ATOMS INTO THE DNA

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ABSTRACT

It is well known that when analogs of thymidine containing iodine or bromine are incorporated into the DNA of irradiated cells there is a decrease of the D_o. Three mechanisms for this effect have been discussed; (a) Photoactivation of the Br/I atom and the production of Auger electrons, (b) Creation of highly reactive uracil radicals by the interaction of hydrated electrons with BrUdR/IUdR, leading to SSB, (c) Interference with repair or the fixation of the damage by the presence of the Br/I atoms. Experiments to investigate photoactivation of the Br/I atoms will include all three, so that knowledge of the relative size of each contribution is useful. The first process is reasonably well understood and here the second process is examined. It is assumed that the incorporated analogs only produce radicals if they are present in a region of DNA containing energy depositions. An SSB produced by this radical can combine with a nearby SSB produced by electron damage to give a DSB, thus increasing the yield of DSB compared to the yield without the analog present. The increased yields at various levels of Br/I incorporation are compared to experiment for different models of radical action.

INTRODUCTION

It is well known that incorporation of bromine or iodine atoms into DNA via halogenated thymine analogs increases the sensitivity of an irradiated system. Three mechanisms for this enhancement have been discussed in the literature. (i) The Auger effect. Here the photons interacting in the inner shells of the bromine or iodine atoms leads to the release of what has been called an Auger electron cascade. This flux of low energy electrons originating from one atom produces a high-LET-like effect in the DNA and is very efficient per unit dose at producing DNA double strand breakage (1). (ii) An increase in the damage to the DNA per unit dose as a result of the production of highly reactive uracilyl radicals by the action of hydrated electrons on the BrUdR or IUdR, adding to the number of single strand breaks (SSB) (2). The production of SSBs alone will not lead to significant radiation effects since these can readily be repaired by the cell, but in combination with SSB from other sources the more important DSB can be produced. (iii) A reduction of repair or a fixation of the damage (3) by the presence of the Br or I atom. It is likely that all three mechanisms are present in various degrees for a particular experimental procedure.

The enhancement of the radiation damage is not only of interest for radiation biology but is being actively pursued as a means of sensitizing tumor cells which are proliferating in the presence of slowly growing normal cells (4,5,6 for example). A summary of some experimental results is given in Table I and Fig. 1. No distinction is made between iodine and bromine data since they overlap and Miller *et al.* (4) obtained undistinguishable results from incorporation of the two atoms. Strictly the data are not comparable since different criteria for evaluating the increased sensitivity have been used. With non-linear survival curves the choice of level of cell survival greatly influences the calculated enhancement, thus the results of Ling and Ward (7) and Iliakis *et al.* (3 and 8) who use D_o, cannot be directly compared with those of Miller *et al.* (4) or Larson *et al.* (6) who use a 10% level of survival. Nath *et al.* (9) compare the slopes of the survival curves to obtain their enhancement ratios and in addition use a continuously growing cell population under constant low dose rate irradiation as distinct from the acute irradiation used in the other experiments.

Two of the experiments in the table (Maezawa *et al.* (10) and Larson *et al.* (6)) specifically examine the role of the Auger cascade by irradiating the

samples just below and just above the K edge of the target atom, in both cases, bromine. Here if the Auger cascade is important, irradiation just above the K edge of the target atom is expected to produce a lower D_o since these photons can remove the K shell electrons which have a higher photoelectric cross section and which produce a larger cascade originating in the K shell rather than the L shell. However, the increase in sensitization above the edge is less than 10%, suggesting that the contribution from the Auger effect is small. Later, a more detailed examination of the importance of the Auger effect will be presented showing that the results of Larson *et al.* (6) and Maezawa *et al.* (10) are not unexpected.

There is some evidence from the results of Nath *et al.* (9) that the Auger effect can produce significant damage in that ^{241}Am with a mean photon energy just above the iodine K edge yields a significantly greater sensitivity than the irradiation below or far above the edge. Here, since the cells are being damaged through several generations and little is known of the transport of damage through cell division, there may be circumstances in which the Auger effect can not be ignored. Certainly this is a most interesting finding.

For irradiation at photon energies well above the K edges of Br/I, where photoelectric interactions with the target atoms per unit dose are small in number, there is an increase of the radiosensitization which cannot be accounted for by the Auger electron damage. In part this can be due to the second mechanism mentioned above, the additional induction of single strand breaks. Iliakis *et al.* (8) investigated this using repair deficient cells in which repair fixation (the third proposed mechanism) would be small or not exist. Again an increase in sensitivity with incorporation of the thymine analog was observed.

In general, the increased sensitivity, irrespective of how it is measured, is less than three for a replacement of about half of the thymine molecules. Based on 6 pg of DNA in a mammalian cell, this requires an incorporation of about 10^9 molecules of the analog in the DNA of each cell. That such a small enhancement requires such a large incorporation is curious, suggesting that very few of the incorporated molecules participate in the radiation action. One way of explaining this is to require that the incorporated analog be at, or lie close to, the site of damage in the DNA. This is the basis of the calculation presented here.

TABLE I
Sensitization of Cells by the Incorporation of BrUdR or IUdR

Author(s)	Cell type	Radiation	Type of measure	Atom	% incorporation	Sensitization
Iliakis *et al.*(8)	xrs-5	250 kV X rays	D_o	Br	9	1.13
					14	1.17
					25	1.30
Nath *et al.* (9)	V79	$^{226}Ra^a$	α	I	22	1.35
					45	1.89
		$^{241}Am^b$	α	I	22	1.67
					45	3.04
		$^{125}I^c$	α	I	22	1.47
					45	2.48
Ling and Ward (7)	V79	^{137}Cs	D_o	Br	16	1.55
					32	1.88
Iliakis *et al.* (3)	CHO	250 kV X rays	D_o	Br	22	1.18
					50	1.71
Larson *et al.* (6)	V79	13.45 keV	10% surv	Br	32	2.25
		13.49 keV			32	2.31
Maezawa *et al.* (10)	*E. Coli*	12.4 keV	D_o	Br	87	2.32
		13.5 keV			87	2.52
Miller *et al.* (4)	V79	10 MeV	10% surv	I	16	2.0
		100 kVp X rays			16	2.2
Myers *et al.* (14)	T4	^{60}Co 14 keV	D_o	Br	100	2.29
					100	2.12

For further details of these experiments see text.

[a] Mean photon energy 830 keV

[b] Mean photon energy 60 keV

[c] Mean photon energy 28 keV

In this presentation an attempt is made to estimate the increased cell sensitivity by calculating the additional burden of DSB due to an additional SSB production. It will be assumed that the charges associated with ionization and excitation of the DNA in a section of DNA damaged by the electron flux can produce uracilyl radicals or that hydrated electrons generated away from the site of damage can drift into the already damaged region. By either mechanism there is an additional source of SSB at an already damaged site. The SSBs produced by the action of the uracilyl radical will be important only if they occur in conjunction with SSB produced by direct energy deposition in the DNA. It is also required that the ensemble of SSBs be close enough together with some on opposite strands to produce a DSB. In this way a fraction of the SSBs produced in a system irradiated without bromine or iodine incorporation are converted to DSB when irradiated in the presence of incorporated bromine or iodine. Implicit in this approach is the assumption that there is no significant clustering of SSB from uracilyl radicals alone.

A difficulty with the type of analysis which can be performed is that only the production of DSBs can be calculated, whereas a wide range of variables has been used as a measure of increased sensitivity (see Table I).

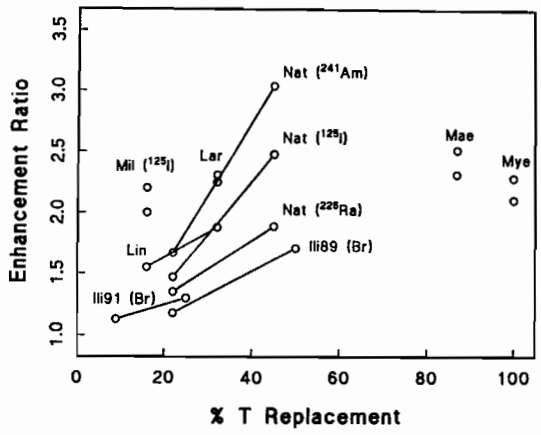

FIG. 1. Experimental results for the sensitization of cells by incorporated thymine analogues containing either bromine or iodine atoms. Key to authors: Ili(91)-Iliakis *et al.* (1991); Ili(89)-Iliakis *et al.* (1989); Lar-Larson *et al.* (1989); Lin-Ling and Ward (1990); Mae-Maezawa *et al.* (1987); Mil-Miller *et al.* (1987); Mye-Myers *et al.* (1977); Nat-Nath *et al.* (1990).

There is some evidence however which suggests that the increased production of DSB correlates with increased sensitivity (Ling and Ward (7), Iliakis *et al.* (8)). This does not necessarily imply that the increase in DSB alone is responsible for the increased effect since interference with repair or fixation of damage could also increase with increasing Br/I load.

METHODS

The Auger Effect in "Cold" Incorporated Atoms

The action of the Auger electrons in producing DNA damage is reasonably well understood and has been described for electrons originating both from radioactive decay (11,12) and from photoelectric interactions in "cold" atoms (13). The method for calculating the production of DSB in incorporated "cold" atoms is first to find the frequency of photoelectric interactions with the atom. This can be done using conventional radiation physics calculations of the photon fluence per Gy to the medium, photoelectric cross sections for the incorporated atom and the number of incorporated atoms per cell. Each photoelectric interaction leads to either the release of a fluorescence photon and/or an Auger cascade originating in the hit shell. Humm and Charlton (12) have evaluated the electron spectra produced by the inner-shell vacancies and, using electron track structure, estimated the number of DSB per interaction. For incorporated cold iodine they obtained 0.66 DSB per photoelectric interaction for photon energies just above the K edge. For incorporated bromine the result was 0.41 and 0.34 DSB per interaction for photon energies just above and just below the bromine K edge, respectively.

The yields of DSB produced by irradiation just above and just below the K edge of bromine which were examined in detail by Humm and Charlton (12) gave an enhancement of 6% for a 100% replacement of thymine by BrUdR. The reason for such a small increase is that while above the edge the bromine photoelectric cross section jumps by a factor of about 6, the yield of DSB produced by the electron flux in the irradiated medium is constant across the edge and considerably larger. Thus, the first mechanism is not important. This is also illustrated by the work of Meyers *et al.* (14) (and Table I) who have shown that with photons from ^{60}Co and 100% replacement of thymine by the bromine analog, the enhancement is about 2.3 even though interactions with

bromine atoms will be rare. Clearly DNA damage by the Auger cascade is not an important mechanism here.

Recently Kobayashi *et al.* (15) have considerably improved the possibility of hitting incorporated cold atoms by irradiating at the absorption edge which is possible using synchrotron irradiation. In this case there is a resonance absorption with a considerably increased cross section and the increase in sensitivity is above the background of effects produced by the normal damage due to the electron flux.

Single Strand Breaks Produced by Uracilyl Radicals

The approach used here was to calculate yields of strand breaks in the DNA using the method described by Charlton and Humm (11) and Humm and Charlton (12). Here the electron track code of Paretzke (16) is used to describe the radiation field for the appropriate source and a volume representing the DNA is superposed at random on it. This technique gives a description of the deposition of energy in the bases and sugar-phosphates of the DNA which can be analyzed for the production of single and double strand breaks using an empirical method based on work of Martin and Haseltine (17). Here if 17.5 eV or more is deposited in the sugar-phosphate moiety of the DNA a single strand break is assigned to that site. Single strand breaks on opposite strands, separated by less than 10 base pairs, are assumed to produce double strand breaks. The method has been reasonably successful in predicting absolute yields of single and double strand breaks for a wide range of radiations (18).

To include the sensitization due to incorporated Br/I atoms producing uracilyl radicals (and subsequent single strand breaks), each base in the portion of the hit section of the DNA is assigned as A, T, C, G by random in equal proportion. The T or the compliment to an A is replaced by the thymine analog carrying the Br/I atom, again by random according to the degree of substitution. In this way the number and positions of Br/I atoms in the hit region can be determined for bifilar incorporation of the analogs. This is illustrated in Table II. In the first example the final sequence of bases is "GATG" but the compliment of A has been replaced by an analog represented by the '+' in the table. In the third example in the sequence "GCCATCT", there is an analog replacing the T complimentary to the A and the first T has been replaced by an analog. These analog sites are the positions at which additional single strand breaks due to uracilyl radical action can occur and

they can combine with already existing breaks due to the ionizing radiation damage to increase the yield of double strand breaks. In particular, damage sites producing only single strand breaks can be converted to sites containing double strand breaks by this method.

Several models of the production of single strand breaks from uracilyl radicals were examined. In the first model it is assumed that an additional single strand break is produced if an energy deposition of any size occurs in a

TABLE II

Energy Depositions in the DNA and Base Sequences

	GCTGTCG+TG		CGA*CGGCAA
75 eV	...x.-....	93 eV	.....132..
	...4.....		..1.3.....
	....		....
	CAAC+ACACCCGCC+*CT*GGACAT		
124 eV	.1-...1..................		
	..........2x.............		
	.......-.-1..........1..		
	*CGAGACCC+CC+*AGACC*GCACC		
190 eV	-2-1.................-2..		
	.151.....................		
	..........-1............		

Key to symbols: Each column of four symbols is one nucleotide pair. The top row represents the base sequence of the segment, the lower three rows are the energy deposited in the sugar-phosphate backbone, the pair of bases and the other sugar-phosphate chain. The energy deposition greater than 17.5 eV in a sugar-phosphate is the condition for a SSB.

-The energy deposition symbols have the following form: no energy '.'; less than 10 eV '-'; less than 17.5 eV '1'; 17.5-20 eV 'x'; 20-30 eV '2'; 30-40 eV '3'; etc.

-The total energy deposited in the DNA is given at the left of each segment.

-The base symbols have their usual meaning and here * means an analog has replaced T and + means a T complimentary to an A is replaced.

-These data are for 50% substitution of thymine.

-Note that without the incorporated atoms these hits in the DNA would normally produce SSB.

base pair containing a Br/I atom. Br/I atoms in neighboring bases are assumed to be unaffected by this energy deposition, that is, there is no movement of charge or energy along the DNA. A second model in which any energy deposition produces SSB at all Br/I sites in the hit region gave very large enhancements (see Fig. 4 later) and showed very clearly that even within the length of DNA containing the energy depositions the probability of SSB production by Br/I action must be small. A third model based on this result was developed in which at least 15 eV (about the size of an ionization) had to be deposited in the DNA and this energy had only a 50% probability of producing one SSB by the action of the uracilyl radical. The activated Br/I atom could lie within ± 4 base pairs of the hit region. In this model even Br/I atoms lying very close to or in a region of damaged DNA did not necessarily participate in SSB production. Analysis will be presented in detail for this model although final results will be shown for all three models.

RESULTS

The calculation was carried out in two stages. Firstly, the relationship between the energy deposited in the DNA (hit size) and the probability that this energy deposition will produce a double strand break was determined. These data were then multiplied by the distribution of hit sizes for a unit dose of a particular radiation and summed to give absolute yields of breaks per Gray. These data give the yields of DSB without the additional effect of the incorporated atom. The calculation was carried out for irradiation by 20 keV electrons and 6 MeV α particles. This method has been fully described by Charlton *et al.* (18) and Charlton (19) and the hit size distribution for these two sources of radiation are given in Table III.

Next, each hit segment of DNA was assigned a sequence of bases and incorporated atoms and the effect of the incorporated analog was examined for each hit segment according to the three models discussed above. Examples of hits calculated from electron track structure and the assigned bases are given in Table II. Note that in the examples given no DSB will be produced by the damage caused by the energy deposited directly by the radiation.

For model 1, the first three examples have no hits in the base pair containing a replaced thymine and no additional breaks will be produced. In the last example (an energy deposition of 190 eV), an SSB will be produced at

TABLE III
Hit Size Distributions per Gy in a Segment of DNA 54 bp Long

Energy interval (eV)	20 keV electrons	6 MeV α particles
0-20	5.770×10^{-6}	2.103×10^{-6}
20-40	2.903×10^{-6}	1.444×10^{-6}
40-60	1.158×10^{-6}	0.970×10^{-6}
60-80	0.552×10^{-6}	0.687×10^{-6}
80-100	0.293×10^{-6}	0.548×10^{-6}
100-150	0.296×10^{-6}	0.804×10^{-6}
150-200	0.078×10^{-6}	0.374×10^{-6}
200-250	0.026×10^{-6}	0.188×10^{-6}
250-300	0.008×10^{-6}	0.084×10^{-6}
300-350		0.053×10^{-6}
350-400		0.020×10^{-6}
>400		0.024×10^{-6}

the second '+' on the lower strand in the figure and this will produce a DSB in the DNA by combining with one of the breaks on the upper strand. For model 2, in which all replaced bases are sources of SSB, examples 1, 3 and 4 will lead to DSB, example 2 will produce two SSB in one strand. In the third model in which any of the replaced bases may act as a source of SSB with a 50% probability, examples 1 and 4 may produce a DSB.

Several thousand hit segments were examined with and without the analogs. The additional SSB produced by the incorporated analogs was found for the three models above and a new yield of DSB determined. The enhancement of the radiation effect is the ratio of the yield of DSB with and without the incorporated Br/I atoms.

Figure 2 shows the probability of producing SSB and DSB as a function of the energy deposited in the DNA without an incorporated analog and for 50% replacement of thymine and calculated for the third model. The calculation without the sensitizer is shown for 20 keV electrons and 6 MeV α particles. These results, which have been reported previously for no

incorporation (18), show that this relationship is independent of type of particle both for SSB and DSB. There is a greater yield of DSB for the same energy deposited when the analog is present and this is greatest for smaller energy depositions where the efficiency of break production is the least. For larger energy depositions there is little change in the yield of DSB. This suggests that high-LET radiations will produce a smaller sensitization than low-LET radiations. This was tested and the results are shown later in Fig. 3.

Combining the data as in Fig. 2, but for different replacements of thymine, with that in Table III gives the relative yield of DSB as a function of the replacement of thymine, and this is taken as the degree of enhancement. The results for model 3 as a function of thymine replacement are shown in Fig. 3. The upper pair of curves are for 20 keV electrons and the higher of the pair includes the increased yield due to the Auger effect. The lower curve shows the calculated results for 6 MeV α particles. The results for model 3 indicate an enhancement of about 2.3 for a 50% replacement of thymine while the same substitution gives about 1.4 for 6 MeV α particles.

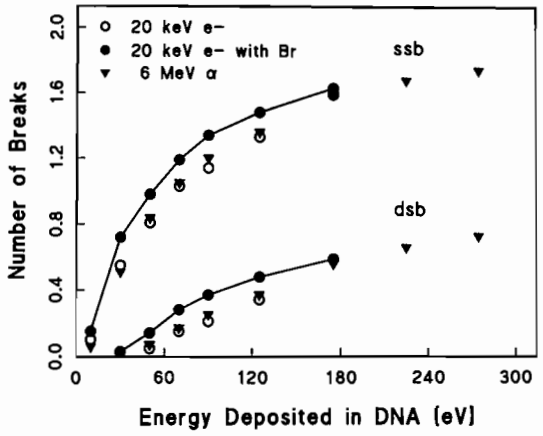

FIG. 2. Calculated yields of SSB and DSB as a function of the energy deposited in the DNA. The yields without sensitization are calculated for 20 keV electrons and 6 MeV α particles. The yields for sensitized DNA are given for 20 keV electrons and 50% incorporation.

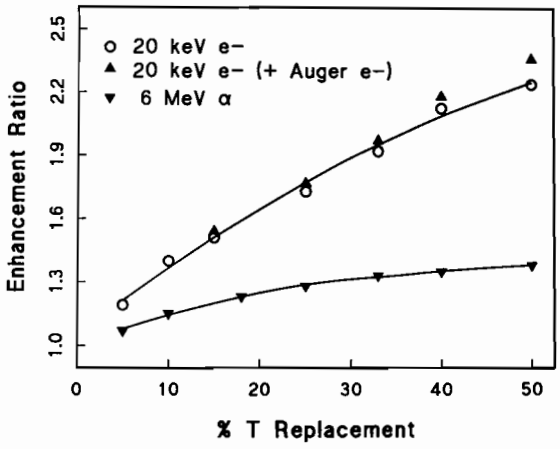

FIG. 3. The increase in yields of DSB as a function of thymine replacement for 20 keV electrons and 6 MeV α particles. These data were calculated for Model 3 in which at least 15 eV must be deposited in a hit region of DNA and only one of the Br/I atoms in this region has a 50% chance of producing an SSB at its location.

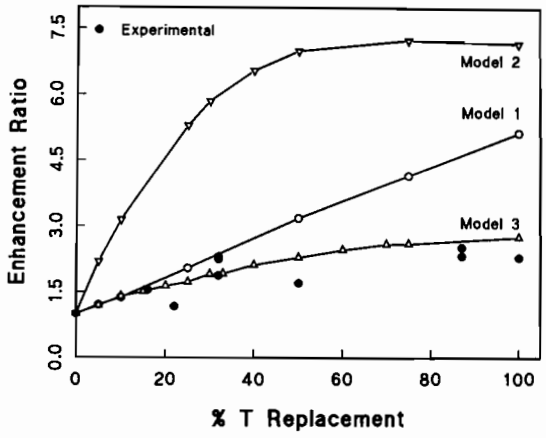

FIG. 4. Comparison of the models of damage with experiment.

In the final diagram (Fig. 4) the calculated results for all three models are compared to the experimental results shown in the first figure. Both models 1 and 3 give reasonable agreement with experiment at the smaller replacements. At higher levels of substitution model 3 is considerably better. In both of these models the number of substituted analogs which participate in producing additional damage is limited to one or less which suggests that even within a damaged region of DNA few of the incorporated Br/I participates in the enhancement. For model 2, where all incorporated Br/I atoms add to the burden of strand breaks, the calculated enhancement of the radiation effect due to the incorporation of thymine analogs is much larger than that measured. This supports the conclusion above that very few of the incorporated atoms play a role in producing enhancement of the radiation damage.

CONCLUSIONS

It has been possible for several years now to describe the initial damage to the DNA from the "direct" interaction of the radiation electron flux with the molecule. This description gives the energy deposited in the base pairs and the sugar-phosphate moieties hit by hit. This initial damage has been used to calculate the generation of single and double strand breaks for radiations of various LET. In this application the description of the initial damage is used to calculate the enhancement of radiation damage due to the action of hydrated electrons on incorporated 'cold' bromine or iodine atoms carried by thymine analogs.

As a measure of this enhancement, the increased yields of DSB have been calculated using techniques which have previously been shown to be in fair agreement with measured values. The method requires that the incorporated atom be present at the site of the DNA damage produced by the usual flux of electrons interacting with the DNA. This is a reasonable initial assumption in that an incorporated atom remote from any other damage producing an isolated single strand break will do little damage to a cell. In the introduction it was pointed out that about 10^9 incorporated atoms were needed to produce an enhancement of less than 3. Since in a mammalian cell there are about 1000 hits of any size in the DNA per Gray for 20 keV electrons (19), the upper limit of the number of the 10^9 incorporated atoms which can contribute to additional damage via SSB production can be estimated. Assuming an average hit length of 10 base pairs and 50% substitution gives

2500 atoms in the hit regions. This initial assumption therefore gives the result that about 2.5×10^{-6} of the incorporated atoms are not utilized in producing additional damage.

Further, in order to get reasonable agreement with experimental results, few of the bromine/iodine atoms lying within an already damaged region produce additional SSB to increase the sensitivity of the cell. These figures give some useful quantitative guidelines as to the maximum sensitivity which can be achieved by this method.

In the following paper in this volume (20) a new test of this model is described in which it becomes apparent that it is not sufficient to model the radiation damage alone but that the biological consequences of the incorporation play an important role.

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