Comparison of the dose-effect relationship for UV radiation and ionizing radiation

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ABSTRACT

Ionizing radiation and ultraviolet radiation (UV) are both physical agents with mutagenic and carcinogenic properties. However, there are some basic differences in the fundamental mechanism of their interaction with biological material that may have consequences for risk assessment.
In this paper the dose-effect relationships for gamma radiation and UV at cellular level will be used to demonstrate the different radiobiological effectiveness of both agents. The results will be discussed in the framework of a biophysical model. This model is based on the assumption that DNA double-stranded lesions are crucial for the cytotoxic action. After exposure to ionizing radiation, the lesions are fixed immediately following irradiation, but after UV exposure the lethal lesions are recognized only in the next DNA synthesis phase. The combination of this concept with the mechanism of lesion induction and the possibility of repair, leads to different dose and time relationships for the radiation effects of both agents.
The possible consequences for risk assessment at low dose levels will be discussed.

1. INTRODUCTION

Ionizing radiation and ultraviolet radiation (UV) are both physical agents with mutagenic and carcinogenic properties. Although a comparison of dose-effect relationships for the two agents reveals some similarities, it also reveals basic differences. A comparison of the action of the two radiations from the point of view of biophysical models, which investigate the similarities and the differences, can provide indications about the mathematical form of the dose-effect relationship at low doses and have consequences for risk assessment. In this paper we derive mathematical equations to describe the cytotoxic effect of both types of radiation, compare the theoretical predictions with experimental data, and discuss the implications for risk assessment.

2. THEORETICAL BACKGROUND

We have proposed previously (1) that radiation induced DNA double-strand breaks are the crucial lesions which lead to cell killing. We assume that the number (N) of DNA double-strand breaks induced by a dose (D) of ionizing radiation is given by the equation:

$$N = \alpha D + \beta D^2 \qquad (1)$$

where α is the probability per cell per unit dose that a double-strand break is induced in the passage of one ionizing particle, and β is the probability per cell per unit dose squared that two independently induced single-strand breaks combine to form a double-strand break.

If p is the probability that a double-strand break is lethal, then cell survival (S) is given by:

$$S = \exp\left[-p\left(\alpha D + \beta D^2\right)\right] \qquad (2)$$

The basic hypothesis leads via equation 2, to the prediction of a direct correlation between the number (N) of DNA double-strand breaks induced by ionizing radiation and the logarithm of cell survival (lnS) such that:

$$\ln S = -pN \qquad (3)$$

Results published by Radford (2), Prise, et al. (3) and Dikomey (4) support this direct association.

In contrast to ionizing radiation, which mainly causes strand breakage, UV exposure induces photo-products such as pyrimidene dimers in cellular DNA which lead to a distortion of the DNA strand, but not in the first instance, to breakage. In analogy with our hypothesis for ionizing radiation, we have proposed that damage to both DNA strands should form the crucial lesion induced by UV. Park and Cleaver (5) have proposed that two pyrimidene dimers, one on either side of a replicon terminus, would block the progression of the replication forks forming a long-lived gap which could be a potentially lethal lesion. Extending our model for ionizing radiation and making use of the potentially lethal lesion proposed by Park and Cleaver (5), we can derive an expression for cell survival following UV exposure as follows:

The number of pairs of dimers (N_o) induced by an exposure (X) to UV is given by:

$$N_o = \epsilon X^2 \qquad (4)$$

where ϵ is the probability per cell per unit exposure squared that two

independently induced dimers form a pair (6). Cell survival (S) is given by:

$$S = \exp [-p\epsilon X^2] \qquad (5)$$

A comparison of equations (2) and (5) reveals a basic similarity in the dose-effect relationship for the two types of radiation, equation (5) predicts a pure quadratic dose-effect relationship for UV, while equation (2) predicts a linear-quadratic dose-effect relationship for ionizing radiation. Figures 1 and 2 demonstrate that each equation provides an accurate description of cell survival for each type of radiation as has been demonstrated previously (1, 6).

A consideration of the types of lesion proposed to be crucial reveals the basic differences between the effects of the two radiations. Firstly, the essential difference between the dose-effect relationships rests in the existance of the linear term (αD) for ionizing radiation. All types of ionizing radiation are capable of inducing a DNA double-strand break in one radiation event, and this linear term defines the effectiveness of the ionizing radiation at low doses. Secondly, the paired dimer lesion, crucial for the UV effect, is only recognized at DNA replication. Before replication the dimers are individual single-stranded damage in the DNA, and can be repaired as such. At the S-phase when the dimers block two converging DNA replication paths, the paired-dimer lesion is formed and recognized as a double-stranded lesion. This implies that the S-phase plays a major role in determining the UV induced effect, and this has repercussions for risk assessment.

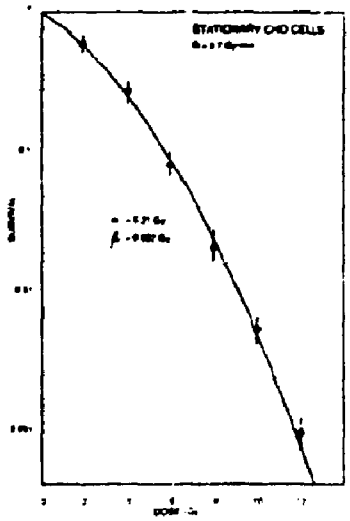

Figure 1. Survival of stationary CHO cells after exposure to ^{60}Co gamma rays. The curve is described by equation 2 with $p\alpha = 0.21$ Gy^{-1} and $p\beta = 0.033$ Gy^{-2}.

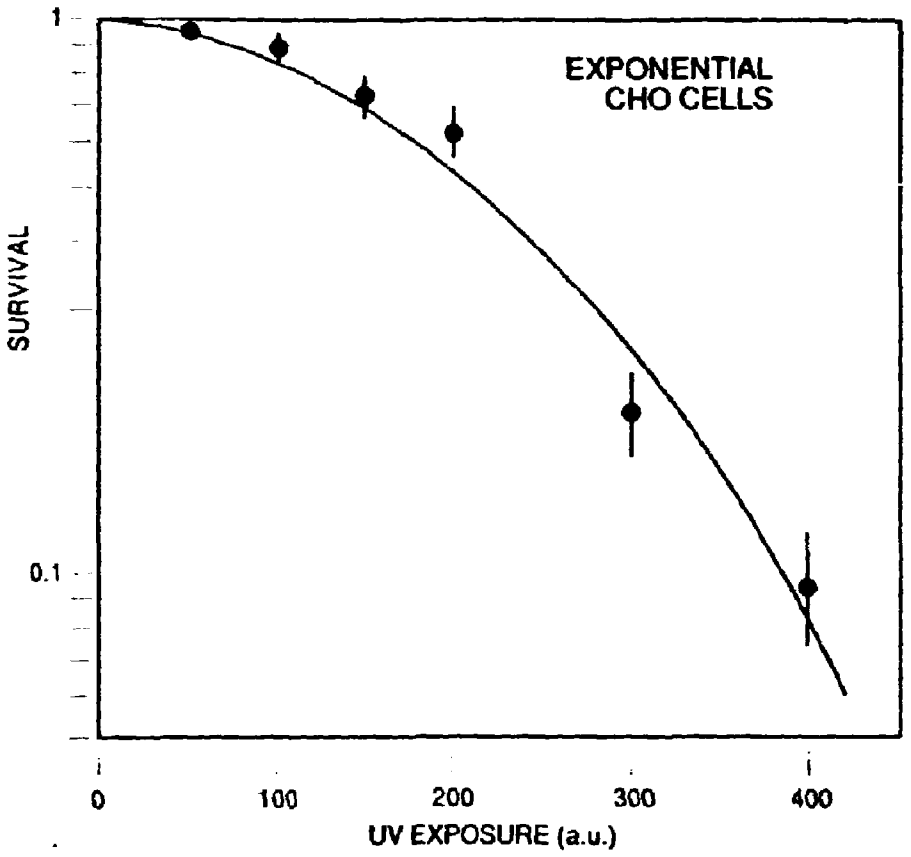

Figure 2. Survival of exponential by growing CHO cells after exposure to 254 nm UV light. The curve is described by equation 5.

2.1. Repair

Two types of repair processes can be considered in the case of ionizing radiation. The repair of sub-lethal damage, identified here as single-strand break repair, which can occur during irradiation or in between fractions. This repair affects only the β coefficient which decreases with decreasing dose rate and increasing irradiation time. As the irradiation time increases, the 'first' single-strand break has more time to repair before the 'second' one occurs to convert it to a double- strand break. The repair of potentially lethal damage, identified here as the repair of double-strand breaks, takes place after irradiation and alters the α and β coefficients to the same extent. It should be noted that the repair of DNA single-strand breaks, i.e. sub-lethal damage, proceeds efficiently and perfectly with a half-life of about 1 h in most mammalian cells. On the other hand, the repair of DNA double-strand breaks, although efficient and almost as fast, can never be guaranteed to be 100% perfect and inevitably

some damage as a result of mis-repair always remains. These two repair processes can be expressed mathematically as:

acute exposure, $S = \exp [-p (\alpha D + \beta D^2)]$, (1)

low dose rate, $S_1 = \exp [-p\alpha D]$. (6)

delayed plating, $S_D = \exp [-g\ p (\alpha D + \beta D^2)]$ (7)

where $g < 1$

Figures 3 and 4 present examples of a dose rate effect and of a delayed plating effect demonstrating the changes in the shape of the cell survival curve in confirmation with the mathematical equations (1), and (7).

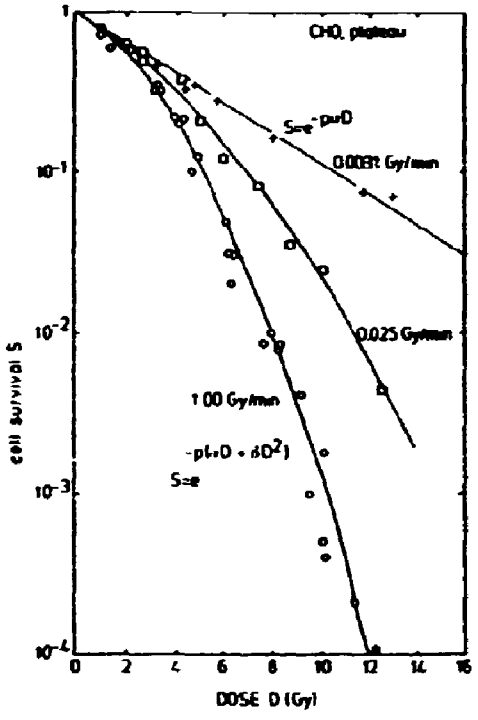

Fig. 3. Survival of stationary CHO cells after exposure to ^{60}Co gamma rays using two dose rates. The curves were described by equation 2 using a constant α value and different β values.
Data from Metting, et. al. (9).

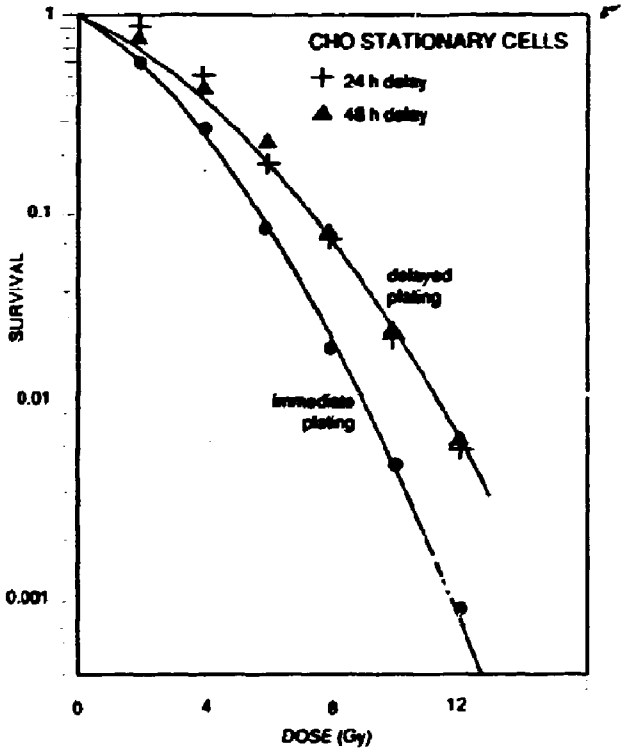

Fig. 4. Survival of stationary CHO cells after exposure to gamma rays with immediate plating and plating delayed for 24 h and 48 h. The curves are descriped by equation 7 with g = 1 (immediate plating) and 0.7 (24 h and 48 h delayed plating).

In the case of UV, the important repair process is that of the repair of the individual pyrimidine dimers, but it is important to note that the time for the repair of these dimers includes not only the time of exposure, but also the time after exposure up to the first S-phase. In repair proficient cells the pyrimidine dimers can be efficiently and perfectly repaired, although somewhat slower than DNA strand breaks. This means that in stationary cells exposed to UV, the repair after exposure should, theoretically be able to remove all the DNA damage. This can be expressed mathematically as:

$$S = \exp [-g\rho\epsilon^2 X] \text{ where } g \text{ goes to } 0 \quad (8)$$

Figure 5 shows UV induced cell killing in stationary cells with increasing delay between exposure and plating. At 72 h delay, the effect is almost negligible. Similar results have been published by Maher, et al. (7) for survival and mutations.

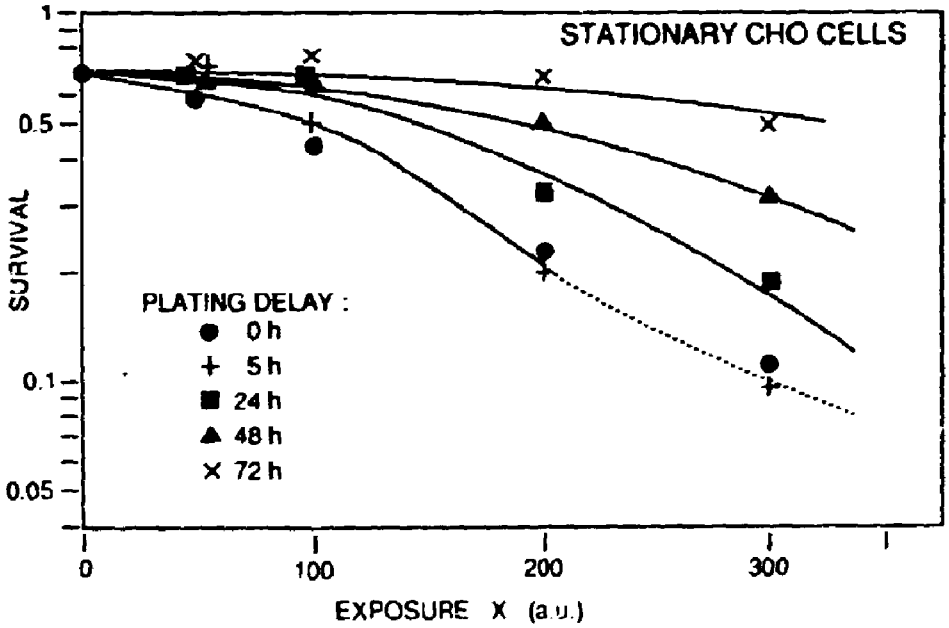

Figure 5a. Survival of stationary CHO cells with plating delayed for 0, 24, 48 and 72 h. The curves are described by equation 8 with g = 1, 0.5, 0.25 and 0.12.

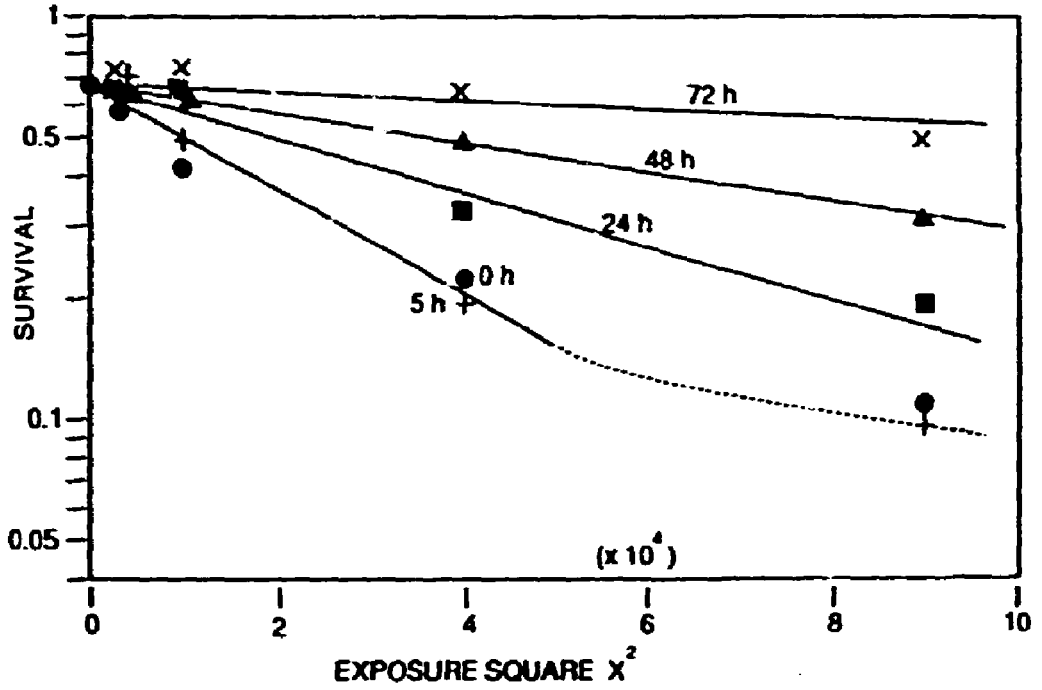

Figure 5b. The same data plotted as a function of exposure squared, showing the pavely quadratic behaviour of the effect with exposure X.

3. DISCUSSION

The theoretical framework which has allowed us to formulate mathematical equations to describe the response of cells to different irradiation conditions, is supported by the congruence between the theoretical predictions and the experimental results. In addition, the mechanistic basis of the model for ionizing radiation is given some credibility by the results of Radford (2), Prise, et al. (3) and Dikomey (4) and the mechanistic basis of the model for UV is in line with the results of Wade and Lohman (8) (see ref. 6). It therefore seems reasonable to use the theoretical framework to consider the consequences of exposure to low levels of both radiations.

In the case of ionizing radiation at low dose and at low dose rates, the mathematical form of the dose relationship becomes linear. The repair of DNA double-strand breaks is not expected to be completely perfect so that the linear component of the dose-effect relationship will never be zero. This model provides a mechanistic basis for the linear extrapolation of the biological effect with dose down to low doses without threshold. Each small increment of dose can be expected to give a proportional increase in risk.

In the case of UV at low exposure levels, the perfect repair of the individual pyrimidine dimers in stationary or slowly dividing cells can be expected to remove all the damage. Thus, in repair proficient stationary cells, low levels of UV exposure need not necessarily incur any risk. However, in non-stationary cells, even though repair will eliminate much of the damage, some paired dimer lesions may still remain to be recognized at S phase. In these cells the risk will increase with the square of the exposure.

4. ACKNOWLEDGEMENT

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