Mathematical Model for Sequential Action of Ionizing Radiation and Other Agents

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1. Introduction

Recently it has been shown that the inhibition of a recovery process after combined treatments cannot be considered as a reason for synergy, but rather the expected and predicted consequence of the production of irreversible damage [1, 2]. On this basis, a simple mathematical model of the synergistic interaction of two agents acting simultaneously has been proposed [3]. Extension of the model to the sequential treatment of ionizing radiation and other agents seems to be of interest for theoretical and practical reasons. Therefore, the aim of this study was to suggest the simplest mathematical model which would be able to account for the currently available experimental information.

2. Mathematical Model

Let N_1 and N_2 be the yield of some hypothetical lethal damages produced by ionizing radiation and hyperthermia, respectively. It is natural to suppose that the additional damage may be produced due to the interaction of some hypothetical sublesions induced by both agents. Let p_1 and p_2 be the mean numbers of the sublesions that arise for each effective damage induced by ionizing radiation and heat, respectively. Then the number of additional lethal damage (N_3) responsible for thermal radiosensitization may be given by

$$N_3 = \min\{p_1N_1; p_2N_2\}. \qquad (1)$$

The whole number of lethal damage (N_Σ) after combined action will be determined by

$$N_\Sigma = N_1 + N_2 + \min\{p_1N_1; p_2N_2\}. \qquad (2)$$

The effectiveness of cell radiosensitivity by hyperthermia was characterized in this study by the value of the thermal enhancement ratio (TER) which was defined as the ratio of a slope of the survival curves obtained after combined action to that after ionizing radiation applied alone. Then we can write

$$TER = \frac{N_1 + N_3}{N_1}. \qquad (3)$$

Combining equations (1) and (3), one can deduce

$$TER = 1 + \min\{p_1N_1; p_2N_2\}/N_1. \qquad (4)$$

If follows from Eq. 4 that if $p_1N_1 > p_2N_2$ we have

$$TER = 1 + p_2N_2/N_1. \qquad (5)$$

Eq. 5 shows that the value of TER should increase with an increase in N_2, i.e. the duration of heat exposure, until the inequality $p_1N_1 > p_2N_2$ holds.

It follows from Eq. 4 that if $p_1N_1 < p_2N_2$, we have

$$TER = 1 + p_1, \qquad (6)$$

i.e. the TER is a constant value from the moment when the inequality $p_1N_1 < p_2N_2$ becomes to be corrected. It is to be expected that the duration of heat exposure, at which the plateau of the curves depicting the dependence of the TER values on the duration of heat exposure begins, should correspond to the following condition

$$p_1N_1 = p_2N_2. \qquad (7)$$

The basic parameters of the model (p_1 and p_2) can be estimated by the following way. If the inequality $p_1N_1 < p_2N_2$ is correct, we have from Eq. (2) that

$$p_1 = (N_\Sigma - N_1 - N_2)/N_1. \qquad (8)$$

On the contrary, if the inequality $p_1N_1 > p_2N_2$ holds, we have from Eq. (2) that

$$p_2 = (N_\Sigma - N_1 - N_2)/N_2. \qquad (9)$$

It is well known that in a general presentation a cell survival (S) is determined by the number of damage by the expression

$$S = \exp(-N). \qquad (10)$$

It enables us to determine the basic model parameters p_1 (Eq. 9) and p_2 (Eq. 10) and then makes an allowance for the prediction of the TER (Eq. 5) until the inequality

$p_1 N_1 > p_2 N_2$ holds, the highest value of the TER (Eq. 6) and the condition (Eq. 7) at which it becomes apparent.

3. Results and Discussions

Fig. 1 shows the typical example of the survival curves for diploid yeast cells irradiated with graded doses of γ rays (2 Gy/min) applied alone (curves 1) or combined with heat exposure (50 ºC). Examination of Fig. 1 reveals some conclusions. The enhancing effect of hyperthermia on radiation cell killing is obvious. Postheating and preheating cells markedly increased cell sensitivity to ionizing radiation. In all cases the interaction is synergistic, i.e. the net effect of ionizing radiation and heat together is greater than the sum of the logarithms of their independent effects. The amount of radiosensitization defined by the TER values tends to increase with increasing of heat exposure: 1.3, 1.6, 2.5, 3.0 and 3.0 for postheating during 0.5, 1.5, 3.0, 6.0 and 9.0 hours. For the inverse order of the treatment, these values were 1.1, 1.5, 1.6, 1.7 and 1.7 for preheating during 0.5, 1.5, 3.0, 6.0 and 9.0 hours. It means that the highest TER value was greater for the sequence γ-rays + heat than for the inverse order. Analogous data have been obtained for different regimens of the sequential action of various heat 50 ºC and 58 ºC at two dose rate of ionizing radiation (2 and 80 Gy/min).

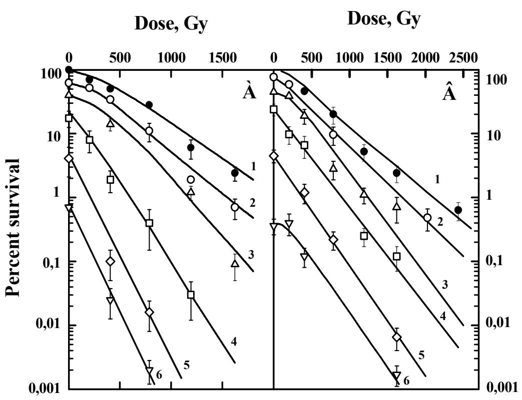

Fig. 1. Survival curves for diploid yeast cells *Saccharomyces cerevisiae*, strain XS800. Panel A, cells were exposed to a sequential treatment with ionizing radiation (^{60}Co γ-irradiation, 2 Gy/min) and hyperthermia (50 ºC); Panel B, cells were exposed to the reverse order of these agents. The duration of heat exposure, hr : 1 – 0, 2 – 0.5, 3 – 1.5, 4 – 3, 5 – 6, 6 – 9.

The theoretical approach presented here was applied to the whole set of experimental results obtained. Table 1 includes the estimated basic model parameters (Eqs. 8, 9) and the greatest TER (Eq. 6) after different conditions of the sequential treatments with ionizing radiation and hyperthermia obtained from experiments and predicted by the model described. A comparison between the theoretically predicted highest values of TER and the experimentally determined values shows good correspondence in all cases.

Table 1. The dependence of the basic model parameters (p_1, p_2) and the greatest TER (I – experiment, II – theory) after different conditions of the sequential action of ionizing radiation (γ) and hyperthermia (H)

ºC	Gy/min	Order	p_1	p_2	I	II
50	2	γ + H	1.9	4.5	3.0	2.9
50	2	H + γ	0.8	2.8	1.7	1.8
50	80	γ + H	1.9	4.5	3.0	2.9
50	80	H + γ	0.8	2.8	1.7	1.8
58	2	γ + H	0.5	0.8	1.5	1.5
58	2	H + γ	0.5	0.8	1.5	1.5
58	80	γ + H	0.8	0.8	1.9	1.8
58	80	H + γ	0.8	1.8	1.9	1.8

4. Conclusion

In spite of the approximations used in the simplified model considered, the experimental results seem to be in reasonable agreement with the model predictions. The results of this study demonstrate a possibility for explanation and prediction of experimental data on the sequential action of heat and ionizing radiation.

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REFERENCES

[1] V.G. Petin and J.K. Kim, Survival and recovery of yeast cells after combined treatments with ionizing radiation and heat, Radiat. Res. Vol. 61, No. 1, pp. 56-63, 2004.
[2] J.K. Kim, V.G. Petin, and M.D. Tkhabisimova, Survival and recovery of yeast cells after simultaneous treatment of UV light radiation and heat, Photochem. Photobiol. Vol. 79, Vo. 4, pp. 349–355, 2004.
[3] V.G. Petin and V.P. Komarov, Mathematical description of synergistic interaction of hyperthermia and ionizing radiation, Mathem. Biosci. Vol. 146, No. 2, pp. 115-130, 1997.