Theoretical Approach to Synergistic Interaction of Ionizing Radiation with Other Factors

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1. Introduction

Living objects including men are never exposed to merely one harmful agent. Many physical, chemical, biological and social factors may simultaneously exert their deleterious influence to man and the environment. Risk assessment is generally performed with the simplest assumption that the factor under consideration acts largely independently of others. However, the combined exposure to two harmful agents could result in a higher effect than would be expected from the addition of the separate exposures to individual agents [1-3]. Hence, there is a possibility that, at least at high exposures, the combined effect of ionizing radiation with other environmental factors can be resulted in a greater overall risk. The problem is not so clear for low intensity and there is no possibility of testing all conceivable combinations of agents. For further insight into the mode of synergistic interaction, discussed are a common feature of synergistic interaction display and a theoretical model to describe, optimize and predict the synergistic effects.

2. Theoretical Model of Synergistic Interaction

The basic assumption is that one sublesion produced, for instance, by ionizing radiation interacts with one sublesion from another environmental agent (for the specificity sake, let it be heat) to produce one additional lethal lesion. It would seem probable to suppose that the number of sublesions was directly proportional to the number of lethal lesions. Let p_1 and p_2 be the number of sublesions that occur for one lethal lesion induced by ionizing radiation and hyperthermia, respectively. Let N_1 and N_2 be the mean numbers of lethal lesions in a cell produced by these agents. A number of additional lesions N_3 arising from the interaction of ionizing radiation and hyperthermia sublesions may be written as

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

Here, $min\{p_1N_1; p_2N_2\}$ is a minimal value from two variable quantities: p_1N_1 and p_2N_2, which are the mean number of sublesions produced by ionizing radiation and hyperthermia, respectively. Thus, the model describes the mean yield of lethal lesions per cell as a function of ionizing radiation (N_1), hyperthermia (N_2), and interaction ($min\{p_1N_1; p_2N_2\}$) lethal lesions. Then the synergistic enhancement ratio k may be expressed as

$$k = (N_1 + N_2 + N_3)/(N_1 + N_2). \qquad (2)$$

Taking into account Eqn. 1, the last expression can be rewritten as

$$k = 1 + min\{p_1; p_2N_2/N_1\} / (1 + N_2/N_1). \qquad (3)$$

It is evident from here that the highest synergistic interaction will be determined by the least value from the two functions: $f_1 = 1 + p_1 / (1 + N_2/N_1)$ and $f_2 = 1 + (p_2N_2/N_1) / (1 + N_2/N_1)$. Fig.1A shows the dependence of both this functions on the ratio of N_2/N_1, calculated for arbitrary chosen p_1 and p_2 ($p_1 = 6$, $p_2 = 4$). The bold line at this Figure depicts the dependence of the synergistic enhancement ratio on the ratio N_2/N_1, i.e. the ratio of the effects produced by each agent used in combination. Since f_1 decreases while f_2 increases with N_2/N_1, the greatest synergistic effect will be obtained when $f_1 = f_2$, i.e.

$$p_1 / (1 + N_2/N_1) = (p_2 N_2/N_1) / (1 + N_2/N_1). \qquad (4)$$

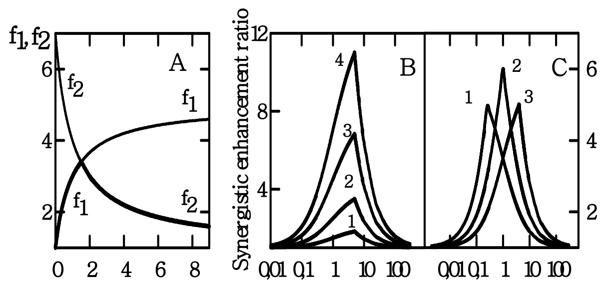

Figure 1. The calculated dependencies of functions f_1 and f_2 on the N_2/N_1 ratio for the following values of the basic parameter: $p_1 = 6$ and $p_2 = 4$ (A) and theoretically expected dependencies of the synergistic enhancement ratio on the N_2/N_1 ratio for the following values of the basic parameter: B - $p_1 = 5$, $p_2 = 1$ (curve 1), $p_1 = 15$, $p_2 = 3$ (curve 2), $p_1 = 35$, $p_2 = 7$ (curve 3), $p_1 = 60$, $p_2 = 12$ (curve 4); C - $p_1 = 5$, $p_2 = 20$ (curve 1), $p_1 = 10$, $p_2 = 10$ (curve 2), $p_1 = 20$, $p_2 = 5$ (curve 3).

From here, the condition of the highest synergistic interaction can be obtained:

$$p_1N_1 = p_2N_2. \qquad (5)$$

It means that the highest synergistic interaction occurred when both agents produce equal numbers of sublesions. Taking into account Eqns. 2 and 4, the value of the greatest synergistic enhancement ratio is given by

$$k_{max} = 1 + [p_1p_2/(p_1 + p_2)]. \quad (6)$$

Some examples of theoretically predicted dependency of the synergistic enhancement ratio on the N_2/N_1 ratio for various values of the basic model parameters p_1 and p_2 are depicted in Figs. 1B and 1C. If the observed biological effect is mainly induced by heat ($p_1N_1 < p_2N_2$) then taking into account Eqn. 3, the parameter p_1 can be expressed as

$$p_1 = (k_1 - 1)(1 + N_2/N_1), \quad (7)$$

where k_1 is the value of synergistic enhancement ratio observed in experiments performed in this condition. On the contrary, if the observed biological effect is mainly induced by ionizing radiation, we have

$$p_2 = (k_2 - 1)(1 + N_1/N_2), \quad (8)$$

where k_2 is the experimental value of the synergistic enhancement ratio observed for the condition $p_2N_2 < p_1N_1$. The corresponding number of lethal lesions can be calculated as

$$N = - lnS, \quad (9)$$

where S is the surviving fraction.

It is easy to demonstrate that the model under consideration can predict two N_2/N_1 ratio, at which equieffective values of the synergistic enhancement ratio (k_i) can be observed.

3. Results and Discussions

The mathematical model has been proposed to explain the experimental data of synergistic interaction of two different agents. The model is based on the supposition that synergism takes place due to the additional lethal lesions arisen from the interaction of non-lethal sublesions induced by both agents. These sublesions are considered noneffective after each agent taken alone. The idea of sublesions is widely used in radiobiology [4,5]. In the model, the synergistic effect is given by $min\{p_1N_1; p_2N_2\}$ (Eqn. 2). This means that one sublesion caused by irradiation interacts with one sublesion produced by heat. This process goes until the sublesions of a less frequent type are used up. To estimate the basic parameters p_1 and p_2 we have used the experimental values of the synergistic enhancement ratio k_1 and k_2 (Eqns. 8 and 9. The model predicts the dependence of synergistic interaction on the ratio N_2/N_1 of lethal lesions produced by every agent applied (Eqn. 4), the greatest value of the synergistic effect (Eqn. 7) as well as the conditions under which it can be achieved (Eqn. 6). The degree of synergistic interaction was found to be dependent on the ratio of lethal damage (N_2/N_1) induced by the two agents applied [6,7]. The synergistic interaction is not observed at any N_2/N_1 ratios.

4. Conclusions

The model indicates that for a lower intensity of physical agents or a lower temperature must be used to provide the greatest synergy. Actually, any decrease in the intensity of physical agents would result in a increase of the duration of thermoradiation action to achieve the same absorbed dose. Therefore, the number of thermal sublesion will also be increased resulting in the disruption of the condition at which the highest synergy should be observed (Eqn. 6). Hence, to preserve an optimal N_2/N_1 ratio with any decrease in the dose rate (or the intensity of other agents) the exposure temperature should be decreased. It can be concluded on this basis that for a long duration of interaction, which is important for problems of radiation protection, low intensities of deleterious environmental factors may, in principle, synergistically interact with each other or with environmental heat.

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