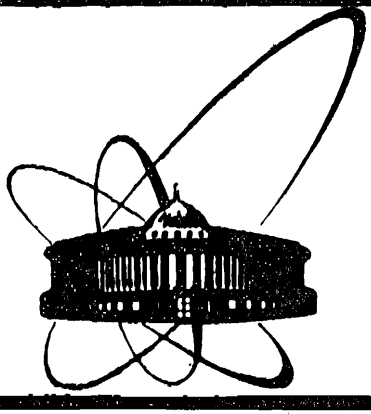

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V.S.Evseev

BIOLOGICAL EFFECTS OF VERY LOW DOSES OF IONISING RADIATION

1987

Ref.[1] has reported upon the discovery of a new radiobiological phenomenon - a physiological reaction of the cell as a whole to very low doses of ionising radiations. This reaction only manifests itself within some time after irradiation and is probably not accompanied with any damages. In that experiment, one measured low-dose suppression of incorporation of tritiated thymidine, or its chemical analogue 5-iodo-2'-deoxyuridine labelled with iodine-125, in DNA of bone marrow cells of a mouse.

The mice were irradiated with cesium-137 gamma-quanta and 14 MeV neutrons, the doses varying from 0.2 cGy and higher. In 4 hours (when the irradiation effect achieved its maximum) the bone marrow cells were separated and incubated in a tracer-containing medium. Then DNA was separated and its activity was measured. The label incorporation intensity rapidly decreases as the dose grows to about 1 cGy, then the dose-response curve becomes significantly flatter. An analysis of the dose-response curve in the region $\lesssim$ 1 cGy allowed the authors of Ref.[1] to draw a conclusion that the target size for the effect under consideration coincides with the cell size. The maximum suppression of the label incorporation in DNA is caused by single recoil proton traversing the cell or by tens of secondary electrons from interaction of cesium-137 gamma-rays in any part of the cell. RBE for 14 MeV neutrons (with respect to cesium-137 gamma-rays) is approximately equal to a unit.

Special experiments[2] allowed finding out that irradiation temporarily inhibits about 1/3 of thymidine kinase activity, and this enzyme plays a key role in using thymidine for synthesis of DNA, as it phosphorylates thymidine to monophosphate. The thymidine kinase activity rapidly drops with doses growing to about 1 cGy and then remains constant up to the dose of 1 Gy.

The authors of Ref.[1,2] suppose that the radiation primary action place is the cell membrane. This idea indirectly confirmed by the results of an experiment on procain effect, this substance actively interacting with the cell membrane. Being injected to mice at least 1 hour before or after irradiation, procain appeared to completely eliminate the irradiation action upon thymidine kinase activity. The authors

of Ref.[1,2] are still ignorant of the mechanism of spreading the process over the whole cell.

Quite recently the existence of the phenomenon under consideration has been independently confirmed at another object. Ref.[3] deals with inactivation of mouse oocytes with low doses of ionising radiations. The analysis of survival curves has shown that the target size coincides with the volume of the cell and not of the cell nucleus. Moreover, administration of tritium-labelled compounds in the nucleus or protoplasm of the oocyte has clearly shown that the effect is by no means due to hitting the cell nucleus. The authors of the paper also think that primary action of radiation occurs in the cell membrane.

This paper provides a qualitative microdosimetric analysis of the new phenomenon. The analysis is aimed at identifying the type of the primary action of radiation with the cell and finding its place in the cell.

Putting aside a discussion of possible mechanism of radiation primary actions and mechanisms of the process spreading over the cell, we consider in detail the problem of the primary action application place. Actually, a detailed microdosimetric analysis shows that experimental data obtained in Ref.[1,2] under an assumption of the primary event taking place in the surface spherical layer of the cell (sphere of diameter 20 μm) and of the energy deposition being equal to the most probable value (ΔE_{min} = 60 eV) in every energy loss event are only compatible at the thickness of the layer 1 = ≈ 5-6 nm. Analysis of initial parts of all dose-response curves given in Ref.[1,2,4-6] shows that the dose-response curves for neutrons and gamma rays have a "one-hit" character and that the extrapolation number is close to a unit within several tens of per cent.

However, along with the hypothesis of Ref.[1,2] which we shall call hypothesis (a), the most general energy considerations allow at least two more assumptions on the primary event application place and on some characteristics of the related energy absorbtion process, and these assumptions do not contradict the main facts mentioned earlier. One may admit that the primary event depends on: (b) the spatial density of energy deposition ρ in any part of the cell, or (c) the total energy deposition ∈ in the volume of the cell.

Hypothesis (a) can be formulated in two ways within the framework of ideas typical of hypotheses (b) and (c): either as a dependence of the primary event probability on ρ in the surface spherical layer, or as dependence on ∈ in this layer.

Evidently, the latter version of hypothesis (a) does not practically differ from hypothesis (c), therefore one should confine oneself to the first formulation of hypothesis (a).

Explanation of the effect under consideration within the framework of hypothesis (b) is reduced to the fact that for both the neutrons and gamma-rays a large energy deposition in quite a small microvolume occurs in some part of the cell with 100% probability at a dose approximately 1 cGy. This is the same "one-hit" mechanism as on hypothesis (a), and the explanation of the observed effect also requires an understanding of how the process is spread over the whole cell from the primary event place.

Hypothesis (c) assumed that the physiological reaction of the cell to radiation is of additive character in the sense that any microvolume of the cell makes its contribution to the observed effect which thus becomes a sum of effects in each microvolume. In this case one cannot speak about a special mechanism of a spread of the process over the cell, for primary events occur in its whole volume.

A method to find out which of the three hypothesis is true is, we think, to measure relative values of RBE for neutrons of different energies. The method is suited for any type of cells. Consider a simplified situation, where peculiarities of each of the three hypotheses are most clearly manifested, namely, the dependence of RBE on the proton energy E_p; let assume that neutrons of energy E_n produce monochromatic pro-

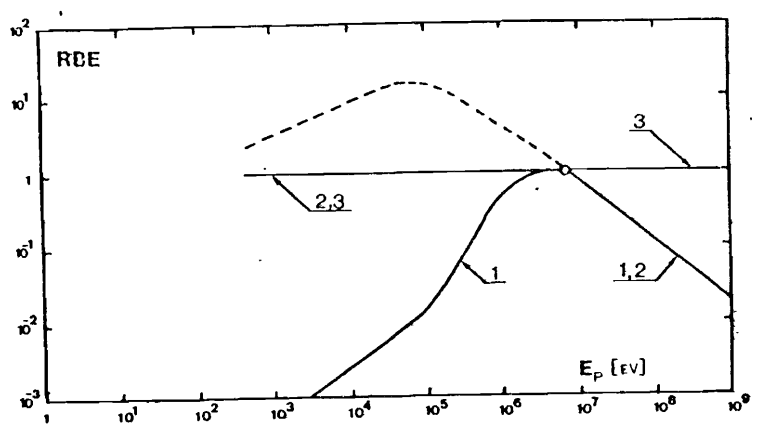

Fig. 1. Dependence of RBE on proton energy E_p.

tons of energy $E_p = 1/2\ E_n$. In this case dependences of RBE on E_p for each hypothesis are such that they retain their character after integration over the spectrum of recoil proton ranges for a given E_n.

The point of reference with RBE = 1 (a circle in the Figure) will be the data for E_p = 7 MeV at the dose of about 1 cGy when each proton traversing the cell produces 100% effect.

If hypothesis (a) is true, i.e. if 100% effect is obtained when a proton crosses the surface layer of thickness l = 5 nm two times, the probability of the necessary energy deposition will decrease with an increasing E_p (curve 1 in the Figure) in according with a decrease of ionisation loss dE_p/dx. The dashed curve in the Figure shows the part of dependence of dE_p/dx on E_p with a typical maximum at $E_p \simeq 10^5$ eV. On the reference point at E_p = 7 MeV the proton range $R_p >> d$, where d is the diameter of the cell. If R_p reduces comparable with d within hypothesis (a), not every proton produced anywhere in the cell will cross the surface layer; efficiency of this proton and, consequently, the value of RBE will decrease. The shape of curve 1 is determined by d = 20 μm and l = 5 nm.

If hypothesis (b) is true, and $E_p > 7$ MeV, the situation depends on the volume density of energy deposition ρ needed for 100% effect. If it is so large that it can be realised only once within the cell diameter, the proton efficiency should decrease proportionally to dE_p/dx with growing E_p (as in the case hypothesis (a)). This is what curve 2 in the Figure shows.

If the necessary value of ρ is achieved when the proton with E_p = 7 MeV traverses the cell several times, then for $E_p > 7$ MeV RBE will remain constant up to that value of E_p when dE_p/dx becomes so small that the necessary value of ρ is again achieved only once within the cell diameter, and RBE must decrease in accordance with the decrease of dE_p/dx as E_p continues increasing.

For $E_p < 7$ MeV RBE must remain constant, the probability of achieving the necessary value of ρ equals I at all values of dE_p/dx exceeding those at E_p = 7 MeV.

If hypothesis (c) is true, RBE must not depend on E_p in the first approximation (curve 3 in the Figure).

There is little to say about primary action mechanisms typical of each hypothesis considered. It is assumed in Ref./7/ that in the case of hypothesis (a) local heating in a separate spur can move the complex of lipides of the cell membrane out of an instable state, and, starting in one point, this process can be rapidly spread over the whole cell membrane and even

embrace the plasmatic membrane net with which the cell membrane is connected. It is clear that a similar scheme can be applied to hypothesis (b), the difference being that the primary event occurs in the membrane of endoplasmatic reticulum. It is chemical compounds produced by radiation that can be regarded within hypothesis (c) as the agent causing transition of the cell into a new physiological state.

A significant difference in approaches to the consideration of mechanisms for hypotheses (a) and (b) and for hypothesis (c) is that in the former case the primary event is a single phenomenon and in the latter it is multiple. Possible interaction between products of multiple events requires a time or dose factor to be introduced in the consideration. Despite the fact that the macrodose rate for neutrons and gamma-rays in experiments/1,2/ is the same, the approach to the dose rate must be different when events within one cell are considered. Indeed, when the proton passes through the cell, the whole energy is released within 10^{-12} sec; in the case of gamma-irradiation it occurs during 10 sec, i.e. microdose rates differ quite significantly. Therefore it is very important to consider interaction between products within the framework of hypothesis (c). If, for example, "burn-up" of radicals in proton and electron tracks is taken into consideration, dependence 3 in the Figure can have its minimum in the region of dE_p/dx maximum.

Dependences 1, 2, 3 shown in the Figure noticeably differ from those one often comes across when studying other irradiation effects accompanied with DNA damages. In these cases dependence of RBE on E_n often looks like dependence of dE_p/dx on E_p (e.g. see/8/).

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Евсеев В.С. E19-87-465

Биологические эффекты сверхнизких доз ионизирующих излучений

Дается качественный микродозиметрический анализ нового радиобиологического явления /физиологической реакции клетки как целого на сверхнизкие дозы ионизирующих излучений/, направленный на выявление типа первичного взаимодействия излучения с клеткой и места его приложения в клетке.

Работа выполнена в Лаборатории ядерных проблем ОИЯИ.

Сообщение Объединенного института ядерных исследований. Дубна 1987

Evseev V.S. E19-87-465

Biological Effects of Very Low Doses of Ionising Radiation

The paper deals with a qualitative microdosimetric analysis of a new radiobiological phenomenon (physiological reaction of the cell as a whole to very low doses of ionising radiations). The analysis is aimed at identifying the type of the primary interaction of radiation with the cell and finding its place in the cell.

The investigation has been performed at the Laboratory of Nuclear Problems, JINR.

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