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Radioadaptation and radioresistance during deep space travels[☆]

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ABSTRACT

The radiation adaptive response phenomenon, also called radioadaptation, is a potential way for modern radiation protection during deep space travels. This can help to improve astronauts' health after chronic irradiation by relative low dose-rates of ionizing radiation. Adaptive response enhances DNA repair availability due to the stimulation by a stressor. However, this effect is not always observed and is generally narrowed to radioresistant individuals. The presented paper discusses the relation between adaptive response appearance and radiosensitivity (or radioresistance), as well as their possibilities for practical application using the recent simple biophysical model. Additionally, the exemplary case of novel light active radiation shields was also mentioned within this context.

1. Radiation shields

One of the biggest problems during manned space missions is high level of ionizing radiation [1]. High energy protons, electrons and gamma rays are just examples of a large family of radiation types. The natural solution for that problem seems to be an appropriate radiation shield. However, massive and large shields made from e.g. lead or concrete are popular on Earth but are not possible in space. The mass of a typical shield makes it hard to transport to orbit, therefore there are some potential solutions for that, like the cylindrical water or fuel tank around the ship, electrostatic or magnetic field deflecting charged particles or, the very recent idea, light active radiation shield against gamma and X-rays based on the negatively charged surface to improve its absorption parameters.

This last item needs more detailed explanation. Very recently the experimental investigation of that shield was carried out in the National Centre for Nuclear Research (NCBJ), Poland, where the electrically charged graphene slab was irradiated by X-ray to prove that additional electrons in absorbing material can improve the absorption coefficient [2]. Medium- and high-energy photon radiation when passing through matter can interact with atoms in four main ways: the photoelectric effect, the Compton effect, electron-positron pair production in a nuclear field and analogical pair production in an electron field (triplet reaction). All of these, aside from pair production in a nuclear field, need electrons to interact - the more electrons, the more significant the cross section is for photon interaction with matter. This is the physical basis of the mentioned effect which was theoretically described in recent research articles [3,4]. As mentioned, it was experimentally confirmed two years ago that additional charge can increase the total cross section of photon interaction with matter, and the relative reduction of radiation intensity by (0.42 ± 0.15)% per 10^{-5} C / cm^2 on the single slab proved that it is possible to construct thin and lightweight radiation shields [2].

There is, however, an additional solution for high radiation, irrespective of any shields or radiation type. This solution is connected with biological adaptation to ionizing radiation, namely the human radioresistance and radioadaptation.

2. Radiation adaptive response

The radiation adaptive response (or radioadaptation) is a biophysical phenomenon which may appear in organisms irradiated by low doses of ionizing radiation. This effect stimulates natural mechanisms responsible for antioxidants, apoptosis, immune system, and DNA repair processes, reducing the risk of neoplastic (cancer) transformation of irradiated cell(s) in the organism [5–13]. The strength of the adaptive response is related to many different factors, like type of cells, cell's phase, organism's age, gender and individual predispositions. This is an example of the complex response of organism to ionizing radiation.

In the most common approach, the probability function of the adaptive response appearance can be described by the hunchbacked curve [14,15]:

$$p_{AR} = \alpha_0 D^2 t^2 e^{-\alpha_1 D - \alpha_2 t} \tag{1}$$

where D is a radiation single dose by which the organism was irradiated t time ago. Additionally, $\{\alpha\}$ are free parameters related to the individual response which can be calculated experimentally, for example α_0=22.9 Gy^{-2}h^{-3}, α_1=79.4 Gy^{-1}, and α_2=0.0832 h^{-1} for human lymphocytes *in-vitro* [15]. It is worth to note that the dose, D, is a physical absorbed dose of all types of radiation, for example low-dose-rated gamma-rays,

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[☆] Tribute to Professor Ludwik Dobrzyński (1941-2022).

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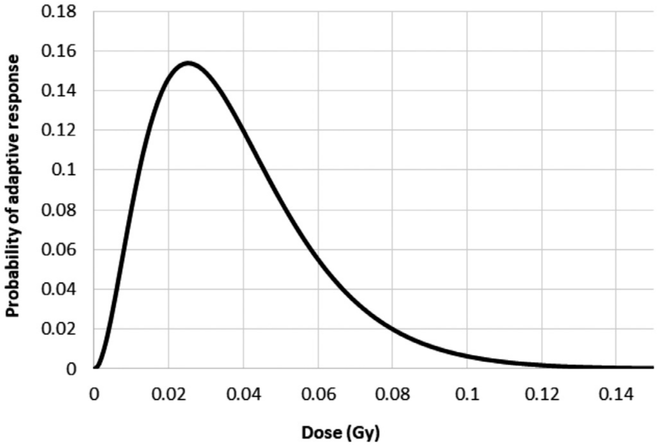

Fig. 1. The probability function of radiation adaptive response appearance (Eq. (1) with parameters of α_0=22.9 Gy^{-2}h^{-3}, α_1=79.4 Gy^{-1}, and α_2=0.0832 h^{-1}) activated for human lymphocytes, for t = 24 hours after irradiation in-vitro by the single dose pulse (given in horizontal axis) [15].

high energy ions, or the high flux of secondary low-energy neutrons and protons. To implement their biological effectiveness, the appropriate factors and equivalent doses (given in Sieverts) need to be applied due to the ICRP standards [16], and all $\{\alpha\}$ parameters can be re-scaled afterwards.

There are many ways in which the adaptive response can be presented. The easiest way for experimenters is when the adaptive response is associated with a small priming radiation dose that reduces a significant portion of the detrimental effects of a higher challenging dose; this is called the priming dose effect (or the Raper-Yonezawa effect) [15].

The other way how the radiation adaptive response can appear, is a constant low dose-rate irradiation. This situation can be found e.g. in high background radiation areas [17,18] or during manned space travels. Therefore this case needs more explanation here.

Eq. (1) is related to the single dose pulse where the organism's response (adaptive response signal) is spread over time as hunchbacked curve: it quickly grows up to its maximum value and slowly asymptotically goes to zero after that. Of course the priming dose, which activates the adaptive response signal, needs to be taken from a very narrow dose range because only these dose values give the highest chance for radioadaptation (see Fig. 1). However, to apply it into the constant dose-rate ($\dot{D}$) conditions one need to sum all individual signals given by Eq. (1) – this sum has a sigmoidal shape of [19,20]:

$$\int_{t=0}^{T} p_{AR}\left(\dot{D}, t\right) dt = 2\beta \frac{\alpha_0^{'}}{\alpha_2^3} \dot{D}^2 e^{-\alpha_1^{'} \dot{D}} \times \left(1 - e^{-\alpha_2 T}\left[\frac{1}{2}\left(\alpha_2 T\right)^2 + \alpha_2 T + 1\right]\right) \quad (2)$$

where $\beta \approx 0.0225$ is a scaling constant to keep the same maximum value as in Eq. (1) and Fig. 1 (for human lymphocytes). Moreover, constant dose-rate conditions differs to single dose pulse ($D[Gy] \rightarrow \dot{D}[Gy/h]$, see Fig. 2a), therefore α_0'=$\alpha_0\theta^2$ and α_1'=$\alpha_1\theta$ where θ≈145 h is a saturation time of Eq. (2) (assumed that for θ the value of Eq. (2) for two consecutive hours differs less than 0.1%). To simplify, one can assume just a new constant $\alpha_3 \equiv 2\beta\alpha_0'\alpha_2^{-3}$.

The Eq. (2) saturates with time to a constant value of $P_C = \alpha_3 \dot{D}^2 e^{-\alpha_1' \dot{D}}$ [15,19], which is presented in Fig. 2 in three exemplary scenarios (Fig. 2b, 2c and 2d) regarding the maximum value of adaptive response probability for exact dose-rate (Fig. 2a). Of course the strong adaptive response signal makes DNA repair processes more effective. Therefore one can define the repair effectiveness (R) of postradiation DNA damages as $R = 1 - N(T)/N_0$, where N_0 corresponds to the initial number of DNA postradiation lesions and $N(T)$ means the number of lesions reduced by repair processes, which were induced by adaptive response signal(s) [15]. Thus, the repair effectiveness, R, for a long time (T) can be described by:

$$R = 1 - e^{-P_C} = 1 - \exp\left(-\alpha_3 \dot{D}^2 e^{-\alpha_1' \dot{D}}\right) \quad (3)$$

where $\dot{D}$=const is a dose-rate. The exemplary values of the R function for human lymphocytes are presented in Fig. 2. Please note, however, that the optimal values of dose-rate cannot be too small (too weak radioadaptation) and too high (where detrimental effects of radiation prevail). This is a natural conclusion from the radiation adaptive response action [12,21,22].

3. Radiosensitivity and radiosusceptibility

The radiation adaptive response (or radioadaptation) seems to be an excellent phenomenon which can be used e.g. in the radiation protection enhancement during deep space travels. This is true, however, the radioadaptation is not always observed and depends on many conditions [9]. This makes it difficult to predict and implement in practice - but important conclusion can be deduced from many recent scientific findings: the effectiveness of adaptive response is strictly correlated with individual radiosensitivity [13,15,23–25]. This is an important element of a wider aspect of individual response to ionizing radiation [26–28] and was originally observed many years ago as an *induced radioresistance* [29–32].

There are, in fact, three terms describing radiosensitivity [25,33,34]:

- the radiosensitivity itself, which describes deterministic effects like cells killing,
- the radiosusceptibility, which describes stochastic effects like cancer transformation, and
- the radiodegeneration, which describes metabolic effects like accelerated aging.

Health aspects of manned space missions are very complex, therefore the broad and general single term "radiosensitivity" will be used - within this paper - to simultaneously describe all of the effects mentioned above. This simplified approach allows to define the opposite term, namely radioresistance, which describes the overall response of the organism where the radiosensitivity, rasiosusceptibility and radiodegeneration are weak.

The radiosensitivity, which is a population trait, can be described by a specific statistical curve similar to log-normal distribution, which has both experimental [35–38] and theoretical [13,39] basis. Especially, its central part can be approximated by the typical Gaussian distribution which generally shows that most of population is *radionormal* but some groups represent *radiosensitivity* or *radioresistance*, see Fig. 3. There are also rare cases of a so called *hyper-radiosensitivity* [40], which absolutely need to be excluded from the future space travels.

There are no clear criteria to determine thresholds between mentioned groups (Fig. 3), therefore their selection is usually rather arbitrary. One can use, for example, some standardized criteria, like RTOG (*Radiation Therapy Oncology Group Criteria*) [41], CTCAE (*Common Terminology Criteria for Adverse Events*) [42] or other ones grounded more in radiobiology for low doses (see the discussion below). Additionally, one has to note that the radioresistance (left tail in Fig. 3) is naturally limited by the maximum repair capabilities, however, the hyper-radiosensitivity is a rare phenomenon (presented mostly in oncological or genetic pediatric diseases) which is represented as dotted line in Fig. 3 (right long continuum tail).

There are two major questions connected with the problem of the proper biophysical description of the radiosensitivity:

- Question no. 1: what is the relation between radiation adaptive response appearance and individual radiosensitivity / radioresistance?
- Question no. 2: is it possible to provide some medical test(s) to determine which candidate to astronaut is radiosensitive or not?

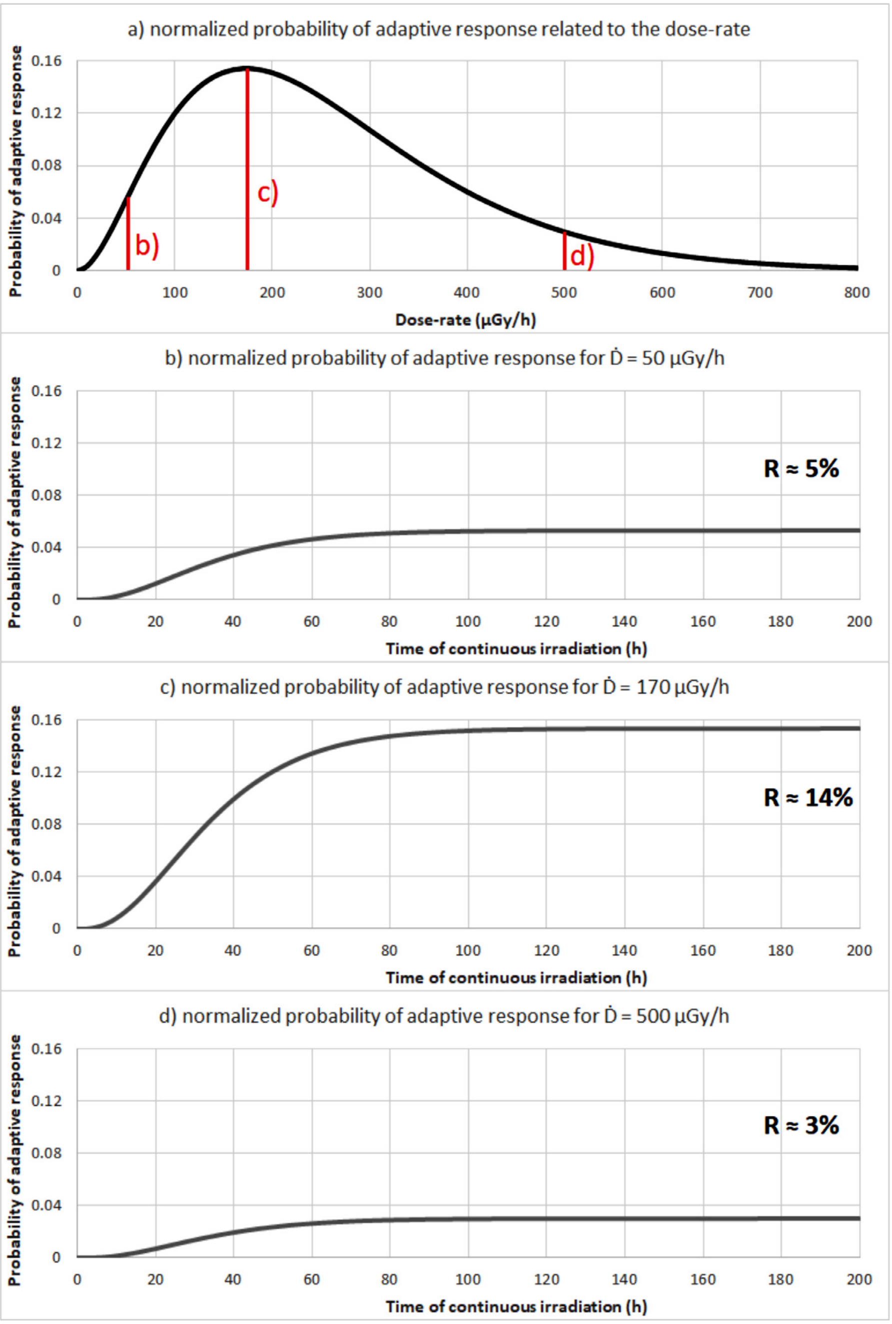

Fig. 2. The radiation adaptive response phenomenon for continuous irradiation by constant dose-rate (Ḋ). Plot a) represents the distribution of maximum values of probability of adaptive response appearance for exact dose-rate value. Plots b), c) and d) represent three exemplary scenarios, where the probability of adaptive response saturates for $\theta \approx 145$ h after the beginning of irradiation, for exact values of dose-rates represented by vertical lines in plot a). All repair effectiveness (R) values were calculated by Eq. (3) (for long time, $T > \theta$).

Let us try to answer to both of those questions below.

Question no. 1: The general simplified relationship is: the higher radioresistance (or the lower radiosensitivity), the stronger adaptive response. This finding was confirmed experimentally [15,23–25] as well as supported by theoretical calculations [13]. This means that the proper selection of radioresistant astronauts would create safer radiation conditions for them. This task is not trivial, see Question 2, but one additional relationship can be determined: as mentioned earlier the distribution of radiosensitivity among population is given by quasi-Gaussian function, therefore the radioresistant population is located on the shorter tail side of the distribution function (Fig. 3). Unfortunately, it is not possible to determine the exact value of probability of adaptive response related to the level of individual radioresistance because there are no such data available. More than that, as there is a great variety in the radioresistance and its origins (inherent, acquired, temporary, permanent, etc.) the relationship between radiosensitivity / radioresistance and the adaptive response is more complex than the simplified approach discussed here.

Question no. 2: The problem of the proper selection of radioresistant or radiosensitive individuals based on some medical test is not new, especially to check the cancer predisposition [26–28,37,38,43]. However, as the human body is a complex system, it is hard to determine single coefficient which may distinguish radiosensitive from radioresistant individuals. Therefore multi-criteria method seems to be more appro-

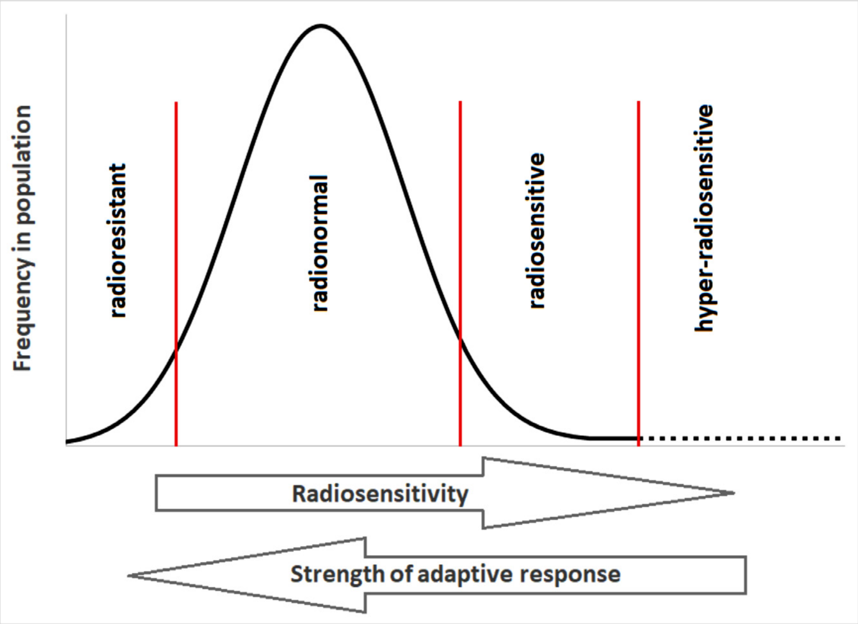

Fig. 3. The non-normalized probability distribution of the radiosensitivity among human population - based on [13,35–39]. Four arbitrary ranges were presented (from left to right): radioresistant, radionormal, radiosensitive and hyper-radiosensitive individuals (see the main text for further explanation).

priate [28] where all factors would create the multi-dimensional phase space. This idea can be based, among others, on existing experiments which tried to localize exact values of single variables correlated with individual radiosensitivity, like:

- chromatid breaks and gaps in peripheral blood lymphocytes after 1 Gy irradiation with caffeine [37,38],
- chromatid breaks and micronuclei in peripheral blood lymphocytes after irradiation by different dose values [43],
- general counting of chromosomal aberrations in irradiated peripheral blood lymphocytes [36],
- unstable chromosomal aberrations and micronuclei in irradiated peripheral blood lymphocytes [44],
- cytokinesis-block micronucleus assay in irradiated peripheral blood lymphocytes [45],
- double-strand breaks, repair kinetics and the induction of chromatid aberrations after irradiation of peripheral blood lymphocytes [46],
- γ-H2AX and pATM foci frequencies reduction related to the post-radiation DSB repair dynamics [47],
- differences between shapes of survival curves of irradiated cells, correlated with the markers of DSB repair dynamics [39],
- adaptive response quantification based on the priming dose (Yonezawa) irradiation scheme – mutation frequency in lymphocytes irradiated by low and high doses [15,48,49].

This last case strictly connects radiosensitivity and adaptive response, so it is of crucial importance here. The idea of that method is precisely described by prof. J. Mortazavi and Collaborators who "have proposed that before any long-term space mission, the adaptive response of all potential crew members should be measured by routine cytogenetic tests and after in vitro exposure of blood lymphocytes to an adapting low dose and later to a challenging high dose and evaluation of the magnitude of the observed adaptive response, only those with high adaptive response should be chosen. Then, during the mission, chronic exposure to elevated levels of space radiation can considerably decrease radiation susceptibility and better protect astronauts against the unpredictable exposure to sudden and dramatic increase in flux due to solar particle events" [48,49]. This idea was mathematically enhanced and quantified few years later in the Raper-Yonezawa experimental scheme [15].

Some other cytogenetical methods were also tested for pilots and astronauts [50], however, this approach still needs further development, both radiobiological and numerical, for proper data analysis. Now, all those tests mentioned above allow at least to identify hyper-radiosensitive individuals to potentially exclude them from the group of astronauts. But anyway, the analysis of DNA changes in blood samples seems to be the most optimal method for radiosensitivity determination at this moment.

4. Conclusions

The discussion about individual biological predispositions of astronauts in the case of high level of cosmic radiation is still going on [1,51]. Some interesting solutions based on the adaptive response phenomenon was widely discussed by prof. J. Mortazavi and Collaborators [49,52,53]. Generally, the radiation adaptive response (or radioadaptation) effect can be useful in a wide spectrum of radiation protection actions during manned deep space missions. Based on its biophysics it is possible to calculate simplified probability functions of its appearance in constant dose-rate or in the priming dose (Yonezawa) scheme [15]. The latter is also a good example of experimental examination of individual radiosensitivity / radioresistance which is an important factor correlating with the adaptive response [13]. This makes both effects: radioadaptation and radioresistance - two sides of the same coin.

Credit author statement

I declare that I am the only author of the manuscript – the idea of it is my own only.

Declaration of Competing Interest

I kindly declare that I have no conflict of interest.

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