DOSE-EFFECT RELATIONSHIP THEORY BASED ON METABOLIC KINETICS OF NATURAL ENDOGENOUS RADIOPROTECTORS *

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Abstract. The paper presents the mathematical proofs for the creation of a linear-quadratic function describing the dose-effect relationship (neglecting the cell killing exponential term), of the type:

$$E \text{ (effect)} = a\,D \text{ (dose)} + b\,D^2 \text{ (dose)},$$

where a, b — are coefficients relevant to the object of irradiation (tissue, cell, subcellular structure, etc.), without assumptions based on the "two events" concept. The final conclusions are as follows:

1. Only "one event" interaction model would be responsible for the creation of the linear-quadratic function, but the metabolic kinetics of the NER may play an essential role in the creation of this from of function,
2. The "two events" interaction model does not seem to be necessary for the explanation of the linear-quadratic function of the dose-effect relationship.

INTRODUCTION

The relationship between the ionizing radiation dose to a given object (tissue, cell, subcellular structure etc.) and possible effects to be observed in the object is the most important question in radiobiology. This problem has an entry called the dose-effect relationship. Sometimes, it is called the problem of the course of the "dose-effect relationship" curve.

Many experiments have already been conducted, many objects have been considered and studied and, obviously, a lot of data exist. The results can be grouped into at least two classes, namely, curves of linear shape and linear-quadratic or quadratic ones. Obviously, the character of curves could suggest the model of a mechanism of induction of the certain effect in the object. So the linear shape is attributed to the so--called "one event" model, whereas the quadratic or linear-quadratic

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dependence is attributed to the "two events" model. The question of how many "event" mechanisms really exist remains open. Moreover, some other questions stil remain without a definite answer, namely:

— why the slope of the dose-effect relationship curve, (in the case of the linear-quadratic curve or even in the linear one) depends proportionally on the dose rate (1,2); and,

— why the mentioned curve sometimes reveals the so-called 'plateau' or 'inflection point' between the range of low and high doses (3,4); and,

— why the dependence of the slope of curve sometimes is reversely proportional to dose rate (5).

The resolution of questions have frequently been the subject of discussion, speculation and the objective of many experiments. The aim of this paper is to draw the attention of researchers to the fact that many of the above mentioned questions may be explained in a different way. Namely, by considering a possible dose effect relationship in the light of metabolik-metics of radioprotectors naturally existing in living objects, i.e. natural endogenous radioprotectors (NER).

THEORETICAL CONSIDERATIONS

It is a well known fact that some chemical substances play the role of the NER in the living object. Enzymes called superoxide dismutase (SOD) and catalase can serve here as an example. The chemical nature and mechanisms of action of the NER can be different. Some of them, such as SOD, can act as radical scavengers, others, such as catalase, can act as neutralizers of toxic products of water radiolise. In any case, their presence and protective role for the object or for the whole organism has been proved in animal experiments (6,7).

Therefore, firstly let us assume that, at a certain level of concentration, a living object contains substances playing the role of the NER. If that is so, let us assume next that the irradiation of an object or the whole organism has a significant impact on the physiological content of the NER. This assumption has been proved experimentally (8). It has been experimentally observed that the endogenous content of SOD in rats drops rapidly soon after irradiation.

These two assumptions mentioned above constitute the starting point for further theoretical considerations. So, let us assume the simplest model of dose-effect induction in the considered object, namely, linear proportionality of the type:

$$E \text{ (Effect)} \sim D \text{ (Dose)} \quad (1)$$

This proportionality can be expressed as a function, namely,

$$E\ (\text{Effect}) = D\ (\text{Dose}) \times F\ (\text{Proportionality factor}) \qquad (2)$$

Such linear proportionality corresponds to the "one event" model of induction of possible effect in an object. In the mathematical sense, the factor F stands for the slope of the dose-effect linear curve, but in a real sense it means the sensitivity of the considered object to ionizing radiation. Generally, one can expect that sensitivity will depend on the content of the NER in an object. The validity of such an assumption has been proved experimentally with animals. That is, it has been found that the survival by animals (rats) of a fifty percent lethal dose (LD_{50}) was correlated with the whole body content of the NER (6). Moreover, the frequency of chromosomal aberrations in the lymphocytes after the irradiation correlated reverse proportion with the content of NER (7). Let us accordingly state that:

$$F = 1/P, \qquad (3)$$

where P is the initial level of the NER considered object, before irradiation has taken place. Thus, the formula describing the dose-effects relationship can be rewritten:

$$E = C\,\frac{D\ (\text{Dose})}{P\ (\text{Level of the NER in object})}, \qquad (4)$$

where C is the mathematical constant, normalizing dimensions of both sides of the equation. The meaning of the equation (4) should now be considered more carefully. The linear dependence between the dose and effect means that the "one event" direct mechanism of interaction would exist for the creation of effect. However, in the light of the previous considerations and described experimental facts (8), P is a function of dose D, i.e. $P = P(D)$, and, finally, E is also a function of P. So let us consider this function.

First Approximation. The "linearity" in eg. (1) corresponds consequently to the assumption that the diminution of NER should be governed by the so-called, "first-order" reaction. In mathematical form it can be expressed as:

$$\frac{dP}{dD} \sim P \quad (5), \qquad \text{or} \quad \frac{dP}{dD} = -k_R D, \quad (6)$$

where k_R means the 'first order' reaction constant of diminution due to the irradiation, expressed as [dose^{-1}]. If the initial content of the NER in an object is $P = P_o$ then it is easy to find that:

$$P = P_o \exp(-k_R D) \qquad (7)$$

Now, using the eq. (7) and inserting it into the eq. (4) one can state that:

$$E = \frac{C\,D}{P_o} \exp(k_R D) = \frac{C\,D}{P_o}\left(1 + k_R D + \frac{k_R^2 D^2}{2!} + \ldots\ldots + \frac{k_R^n D^n}{n!}\right) \quad (8)$$

Neglecting terms with k_R in powers being higher than 1, (since $k_R \ll 1$), one can obtain:

$$E = \frac{C}{P_o} D + \frac{C}{P_o} k_R D^2 \quad (9)$$

It is easy to recognize that E is the linear-quadratic function of the dose, type $E = a D + b D^2$, where $a = C/P_o$, and $b = k_R C/P_o$. It is very characteristic that the slope coefficient in the linear term of the formula depends only on the initial level, whereas in the linear-quadratic it depends on the k_R as well.

Some examples of dose-effect curves with the assumed k_R are presented in Fig. 1. It may be asked why such numerical values have been used in these examples. The author used some available data (8) which were useful for this purpose. A dose has been found which caused a 50% decrease of NER content in some organs. This dose is

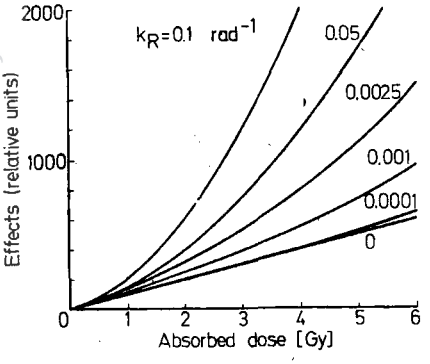
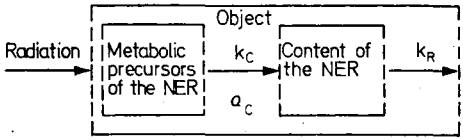


Fig. 1. The dose-response relationship theoretically derived for different values of constant k_R in the model expressed by the First Approximation.

approximately 750 rads. Thus it is easy to calculate that k_R should correspond to the numerical value which is about 0,001 rad^{-1}.

The presented approximation corresponds to the case in which the pool of the NER was not renewed during and after irradiation. This assumption seems not to be quite realistic since, presumably, certain processes of the metabolic supply do exist.

Second Approximation. The new case corresponds to Scheme 1. Biophysiological interpretation of this model is the following:



Scheme 1.

— certain metabolic precursors of the NER do exist,

— the dose-dependent compensation process exists,, and is triggered by the irradiation of precursors, proportionally to the dose.

The meaning of k_R remains the same as in the previous approximation, but k_C [rad^{-1}] represents the constant of the dose dependent compensation process. The Q_C means the quantity of the NER which is produced by the precursor due to the irradiation of the object and precursor as well. The following relation for the expression of k_C would be defined: $k_C = Q_C/P_o$.

The balance equation for the system after irradiation would be expressed by eg. (10):

$$\frac{dP}{dD} = -k_R P + Q_C; \qquad P(0) = P_o \tag{10}$$

The content of the NER in the object after irradiation is expressed by eg. (11):

$$P = P_o \left[\exp(-k_R D) + \frac{k_C}{k_R}(1 - \exp(-k_R D))\right] \tag{11}$$

So, inserting (11) into (4), the following formula for E can be found:

$$E = \frac{C}{P_o}\left(\frac{1}{1 + k_C D} D + \frac{k_R}{1 + k_C D} D^2\right) \tag{12}$$

Again, E is the linear-quadratic function of D, type $E = a D + b D^2$. The difference between this and the previous form of the function is in the different form of denominators of a and b. However, this new form has bio-physiological sense, namely, the product $k_C D$ represents the fraction of the NER which appears in the object due to the compensating reaction of the precursor. The product $k_C D$ means the compensation process decreasing the value of coefficient a and b as compared to the previous case given in the First Approximation.

The relevant graphs of dose-effect curves drawn for this case are presented in Fig. 2. It can be seen from the graphs that the process of compensation influences remarkably the course of the dose-effect relationship curve. When the compensation constat k_C is approximately equal to the constant k_R, then the curve goes closely to the linear, since

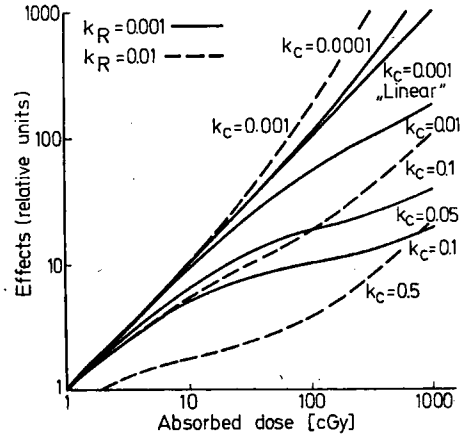


Fig. 2. The dose-response relationship theoretically derived for different values of constant k_R and k_C in the model expressed by the Second Approximation. The "linear" course corresponds to the case $k_R = k_C$.

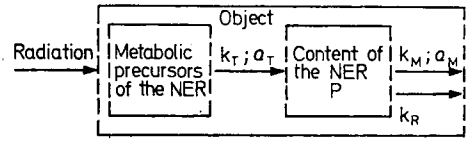
the diminution of the NER in an object is compensated entirely. When the compensation constant is higher, the curve becomes flattened and reveals a tendency to inflection. Thus the inflection of the curve definitely requires the assumption of the presence of any compensation process, which would be more intensive than the diminution of the NER due to irradiation. However, an important question appears, namely, what could be the bio-physiological interpretation and justification for this phenomenon. The interpretation exists. Namely, any metabolic process is governed by competitive substances called 'inhibitors' and 'activators'. Let us suppose that the inhibitor is more sensitive to the radiation than his competitor, i.e. the 'activator'. Possible functional damage of the inhibitor due to irradiation would then cause relatively more intense work by the activator. Nevertheless, the Second Approximation does not fulfil two important conditions, namely:

— the dose-effect relationship curve does not depend on the dose rate 'a priori', and,

— the post irradiation increase of the NER due to the compensation process does not reveal saturation.

These two imperfections of the model are eliminated in the following more advanced approximations.

Third Approximation. This is presented by Scheme 2, where the physiological metabolic turnover of the NER is considered and where Q_T and Q_M mean quantities of the NER which are, respectively, produced and metabolized in an object during exposure time, expressed as units of quantity of the NER per unit of time. If Q_T and Q_M were divided by P_o (the initial level of the NER in the object prior to irradiation) then rations: Q_T/P_o and Q_m/P_o would be defined as k_T and k_M, respect-



Scheme 2.

ively, with dimensions [time^{-1}]. So, in the equilibrium, i.e. prior to irradiation, one can write that $Q_T = Q_M$, $k_T = k_M$, $P = P_o$. This approximation represents the model in which the time of exposure plays a significant role. The reason lies in the fact that metabolic processes are time-dependent ones, whereas the 'compensation' and 'post radiation diminution' have been processes classified as dose-dependent only. Therefore, the balance equation for the system after irradiation must be expressed by a time-dependent equation (13), namely:

$$\frac{dP}{dD} = -Q_M + Q_T - k_R RP;\ Q_M(D) = \text{const.},\ Q_T(D) = \text{const.}, \qquad (13)$$

where $R = D/t$ means the dose rate, whereas t means the time of duration of continuous irradiation.

Simple mathematical transformations lead to the formula describing P as the function of D, i.e. the function of R and t.

$$P = P_o[\exp(-(k_R R + k_M)t) + \frac{k_T}{k_R R + k_M} \cdot (1 - \exp(-(k_R R + k_M)t) \qquad (14)$$

As previously, using the eq. (4) one can find:

$$E = \frac{C}{P_o}\left(\frac{1}{1 + k_T t} D + \frac{k_R + k_M/R}{1 + k_T t} D2\right)$$

Again, in this case, the dose-effect relationship has the linear-quadratic shape. The relevant graphs are presented in Fig. 3. Two variants are presented there. Variant (A) corresponds to $k_R = 0.001$ [rad^{-1}] selected previously, variant (B) corresponds to a case when the diminution constant k_R would be higher. Nevertheless, both figures (A and B) show that for this approximation, the inflection of curves does not appear, but all curves differ as compared to the line representing the linear dose--effect dependence. Obviously the degree of distortion depends on the proportion between constants k_R and k_M. However, on the first occasion the clear dependence between slope and the dose rate appears and has proportional trend, i.e. the larger slope corresponds to the higher dose rate.

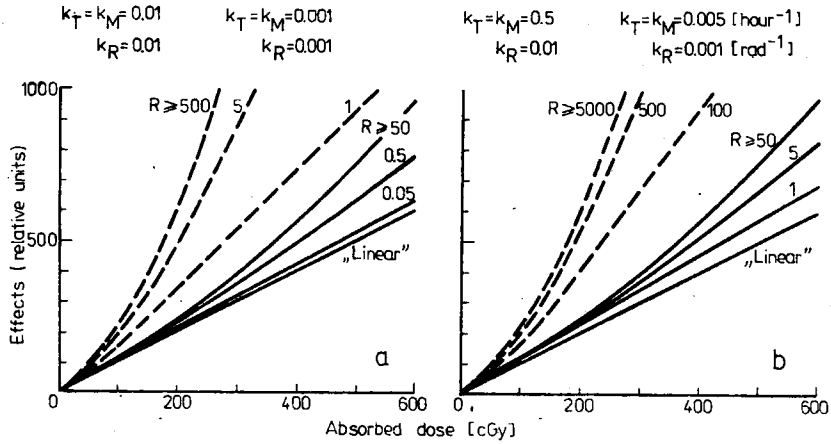
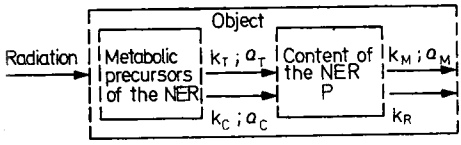


Fig. 3. The dose-response relationship theoretically derived for the model expressed by the Third Approximation. Variant B corresponds to the case of 'quick' metabolic turnover; A corresponds to the case of 'slower' metabolic turnover. The constants k_R expressed in units [rad^{-1}]; constants $k_M = k_T$ in units [hour^{-1}]; R in units [cGy/hour].

Complexed Approximation. This covers all features of approximations previously described, that is, the consumption of the NER for the post radiation effects neutralization, possible compensation of the NER due to any distortion of precursor action, and metabolic processes. Scheme 3 presents the appropriate model



Scheme 3.

However, in the present approach, the interpretation of the compensation process should be reconsudered. The idea of this process remains the same as previously, i.e. $Q_C = Q_C$ (D) but the character of this function is changed. In the Second Approximation this function has been quoted simply as the 'first order' dose-dependent process leading to the paradox that the P = P (D) has revealed monotonic, unlimited increase with the dose D. Such a phenomenon has not been observed in nature, since any compensation has to reveal the saturation in the high dose. The simplest way of introducing this compensation is to assume that the saturation appearance would be characterized again by the 'first order'

reaction. If so, the compensation constant should obviously have a time--independent but a dose-dependent form as follows:

$$k_C(D) = k_C \exp(-k_S D) \tag{16}$$

where the constant k_S describes the saturation process.

Finally, the balance equation for the model has the form:

$$\frac{dP}{dt} = -k_R R P - Q_M + Q_T + Q_C =$$
$$= -(k_R R + k_M) P + k_T P_o + k_C P_o \exp(-k_S D); \tag{17}$$

where $P(0) = P_o$.

In the same way as previously one can obtain:

$$P = P_o \left[\exp(-(k_R R + k_M)t) + \frac{k_T + R k_C \exp(-k_S D)}{k_M + k_R R} \cdot \right.$$
$$\left. \cdot (1 - \exp(-(k_R R + k_M)t)) \right] \tag{18}$$

and

$$E = \frac{C}{P_o}\left[\frac{1}{1 + k_T t + k_C D \exp(-k_S D)} D + \right.$$
$$\left. + \frac{k_R + k_M/R}{1 + k_T t + k_C D \exp(-k_S D)} D^2\right], \tag{19}$$

where, as previously, $t = D/R$ means the duration time of exposure, with the dose D and with the constant dose rate R. Relevant graphs are presented in Fig. 4. Curves are drawn for different values and different configurations of constants and certain regularities can be observed.

Firstly, the curves are inflected. The degree of inflection depends on the intensity of the compensation process represented by the constant k_C. Secondly, the presented approximation can justify the inceredible phenomenon, described in literature, that the slope of the dose-effect curve, is sometimes reversely proportional to the value of the dose rate. Thirdly, the saturation mechanism described by the constant k_S and introduced to the compensation process seems to work correctly, since an analysis of the formula (18) shows that the function $P = P(D,R)$ reveals the saturation and decrease. Thus the inherent paradox of the Second Approximation is eliminated.

In conclusion, the model expressed by the Complexed Approximation seems to justify inflections of the dose-effect curves and slopes which are sometimes reversely proportional to the dose rate. Other general regularities observed for all considered cases are discussed below.

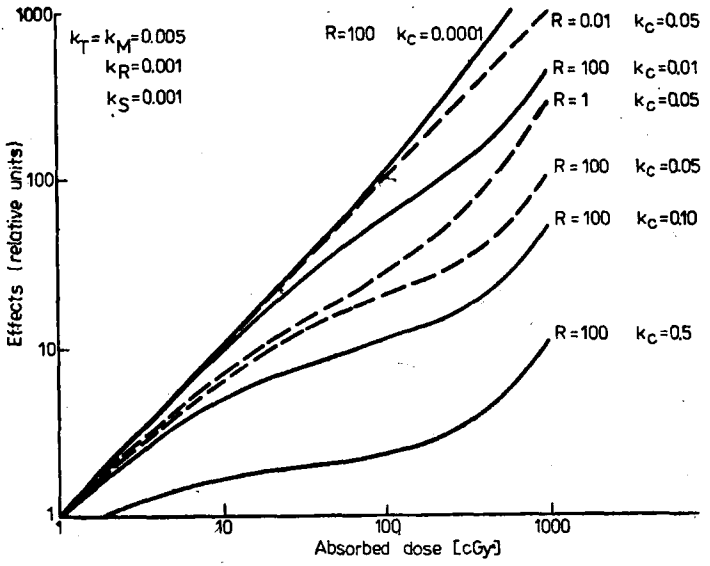


Fig. 4. The dose-response relationship theoretically derived for the model expressed, as the Complexed Approximation. The constants $k_R = k_C$ and k_C expressed in units [rad $^{-1}$]; constants $k_M = k_T$ in units [hour $^{-1}$]; R in units [cGy/hour].

CONCLUSION

The most important conclusion is that, in the light of the above considerations, the quadratic or the linear-quadratic character of the dose-effect relationship does not require the "two event" model of induction of the effect. Such a shape can be created by simple mechanisms based on "first order" kinetic reactions of the metabolic turnover of the NER.

This approach to the dose-effect problem would explain other experimentally observed phenomena, namely, the appearance of the so-called 'plateau' or 'inflection points' and the reverse proportionality to the dose rate, which has been described in several papers (3.4,5).

The presented approximations do not fully describe the reality, i.e. the metabolic turnover actually existing in a living object. However, even these few considered cases (approximations) could be used for the creation of certain general conclusions concerning coefficients of the function $E = a D + b D^2$.

In all cases coefficients 'a' have a form which can be easily generalized as:

$$a = \frac{C}{P_o} \cdot \frac{1}{1 + \Sigma q_i} \qquad (20)$$

where q_i represents all quantities of the NER which 'come' into the considered object during the exposure period and which are expressed as a fraction of the initial content of the NER. Moreover, the denominator, i.e. $P_o(1 + \Sigma q_i)$, represents the net income of the NER to the object during that period plus the content existing initially, prior to the exposure.

The form of coefficients 'b' can be similarly generalized, i.e.

$$b = \frac{C}{P_o} \cdot \frac{\sum_i k_i}{1 + \sum_i q_i} \tag{21}$$

where k_i represents all constants of processes 'dreasing' of content of the NER in the object during the exposure period (sometimes they are divided by R for unification of dimensions).

Ratio b/a also has a certain biophysical sense, namely:

$$b/a = \sum_i k_i \tag{22}$$

Thus, the ratio b/a represents the sum of all decreasing constants in the metabolic model.

Coefficient 'a' does not contain constants of any processes; the coefficient 'b' contains them. Therefore, in the case in which the metabolic turnover is very slow ($k_M \to 0$) the quadratic term is governed by the constant k_R. If the constant $k_R \to 0$ the quadratic term disappears and the dose-effect relationship becomes linear. So, the appearance (or disappearance) of the quadratic term depends on the presence (or absence) of endogenous radioprotectors in an object. This means that if the object contains a substance actively playing the role of the NER, then one can expect that for such an object the dose-response relationship will have the linear-quadratic course. Otherwise, if it does not contain such substances or if their scavenging abilities would be inhibited entrirely, then the "a priori" linear shape can be expected. In the light of the above, one can try to offer a hypothesis explaining why the dose-effect curve for a high LET radiation has, in many cases, a linear course, whereas for low LET radiation, in analogical objects, the course is the linear-quadratic or quadratic. The hypothetical reason is the "oxygen effect", appearing in the case of the interaction of the high LET radiation with matter. Such an effect can neutralize the scavenging effectiveness of the NER, and then the constant $k_R = 0$. The mathematical expression of this hypothesis is that for the considered object, the k_R (for the low LET radiation) > 0, whereas k_R (for the high LET radiation) $= 0$.

The question of the validity of the presented theory obviously arises. Specially programmed experiments would answer this question. Nevertheless, the aim of this paper was to draw the attention of researchers and radiobiologists to the fact that the biochemical and metabolic approach to the problem should be considered.

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