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Comments on the mechanisms of action of radiation protective agents: basis components and their polyvalence

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Abstract

Purpose: These comments suggest a division of radiation protective agents on the grounds of their mechanism of action that increase the radio resistance of an organism.

Conclusion: Given below is the division of radiation protective agents on the basis of their mechanism of action into 3 groups: 1) Radiation protective agents, with the implementation of radiation protective action taking place at the cellular level in the course of rapidly proceeding radiation-chemical reactions. At the same time, when the ionizing radiation energy is absorbed, these agents partially neutralize the "oxygen effect" as a radiobiological phenomenon, especially in the radiolysis of DNA; 2) Radiation protective agents that exert their effect at the system level by accelerating the post-radiation recovery of radiosensitive tissues through activation of a number of pro-inflammatory signaling pathways and an increase in the secretion of hematopoietic growth factors, including their use as mitigators in the early period after irradiation prior to the clinical development of acute radiation syndrome (ARS). 3) Radiomodulators including drugs and nutritional supplements that can elevate the resistance of the organism to adverse environmental factors, including exposure to ionization by means of modulating the gene expression through a hormetic effect of small doses of stressors and a "substrate" maintenance of adaptive changes, resulting in an increased antioxidant protection of the organism. Radiation protective agents having polyvalence in implementation of their action may simultaneously induce radioprotective effect by various routes with a prevalence of basis mechanisms of the action.

Keywords: Radioprotector; Radiomitigator; Radiomodulator; Mechanism of action

Introduction

Clinical radiotherapy of tumors demands a knowledge of the potential effectiveness of radiation protective agents to reduce radiation damage to healthy tissues, as well as knowledge of their impact on the radiosensitivity of tumor tissues. A theoretical understanding of the mechanisms of the radiation protective action of the agents may contribute to this knowledge.

The key aspects of radiation protective agents are the practical need to use them in specific scenarios of radiation exposure and the corresponding tactical and technical requirements for medical preparations. These aspects are related to the indications for use (depending on the nature and severity of a radiation injury), possible routes of administration, acceptable side effects in certain situations, pharmacodynamic characteristic, as well as the possibility of expected scheme of repeated administration.

A recent monograph (Arora et al. 2008) and a review (Weiss and Landauer 2009) provide a contemporary view of the pharmacological measures against the harmful effects of ionizing radiation, as well as comprehensive information about radiation protective agents — their classification, the history of discovery, pharmacological and radiation protective properties, data on tolerability, and their current use. Based on the current knowledge of the mechanism of action of radiation protective agents, in particular gene regulation induced by the increased radiation resistance of the organism, this commentary mainly focuses on some of the common features typical for their mechanism of action. For most of these agents applied in practical medicine it is possible to distinguish three main pathways for the

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implementation of the mechanism of action, each of which has their own specificity in predetermining the pharmacodynamic properties and possible methods in their practical application (Vasin 1999, 2012).

Review

Radioprotectors (chemical protection by Zenon Bacq) that exert their effect on physicochemical and biochemical levels in cells during exposure to ionizing radiation through partial neutralization of radiosensitizing oxygen effect

The mechanism of protective action of the radioprotectors from the family of aminothiols

Radioprotectors realize radiation protective action at the cellular level in the course of rapidly proceeding radiation-chemical reactions. At the same time, when the ionizing radiation energy is absorbed, these agents partially neutralize the "oxygen effect" as a radio-biological phenomenon, especially in the radiolysis of DNA (Hutchinson 1961). The essence of the "oxygen effect" which finds its manifestation at different levels of the biological organization in the world of plants and animals lies in the increased radiation damage of DNA, membranes, proteins, carbohydrates in the presence of oxygen and transition valence ions (Fe^{+2}, Cu^+, Zn^{+2}). Reactive oxygen species are formed as a result of radiation-chemical reactions: superoxide anion radical ($O_2^-\bullet$), hydroperoxide radical ($HO_2\bullet$), atomic oxygen, oxygen in the long-lived excited form, singlet oxygen ($O_2{'}$).

According to the oxygen fixation hypothesis, radicals in DNA induced by indirect action via aqueous radicals may be fixed by reaction with oxygen or chemically repaired by H-atom donation from antioxidants such as sulphydryl compounds (Hall and Giaccia 2012).

The mechanism of the action of radioprotectors is achieved either by a pharmacological reduction of the oxygen content in the cell or by a direct participation of thiol groups of sulfur radioprotectors in competitive reactions with oxygen for the DNA radical.

The main role in the realization of radioprotective properties of the known most active sulfur-containing radioprotectors at the level of radiation-chemical reactions is assigned to their ability to interact directly with the radiolysis products of macromolecules, thus causing their reparation (reaction of type II in Figure 1), rather than to the competitive relationships with macromolecules for the radiolysis products of water.

These radioprotectors exerting their effects by this mechanism include sulphur-containing radiation protective drugs that are β-mercaptoethylamines, aminoalkyl thiosulphates, aminoalkyl dithiophosphates, aminoalkyl isothiouronium, and thiazolidine and thiazoline derivatives.

The protective effect of sulfur-containing radioprotectors is associated with a free SH-group in the composition of their molecule. The possibility to transfer the hydrogen atom from the SH-group of the protector to the radical of the macromolecules provides its chemical reparation: $M\bullet + HS{-}R \rightarrow MH + R{-}S\bullet$ (Alexander and Charlesby 1954).

Chemical reparation of the radical of deoxyribose in DNA by a hydroxyl radical under dehydrogenation of the molecule is of crucial importance for the reduction of the frequency of chromosomal aberrations in the cells under the influence of radioprotectors:

deoxyribose $(\text{-H})\bullet + RSH = $ deoxyribose $+ RS\bullet$ (Fahey 1988; Held 1988).

The rate constants for the transfer of a hydrogen atom from cysteamine to the radical of a macromolecule are close to $10^6 - 4\bullet10^8$ $M^{-1}\bullet c^{-1}$ (Ormerod and Riesz 1967).
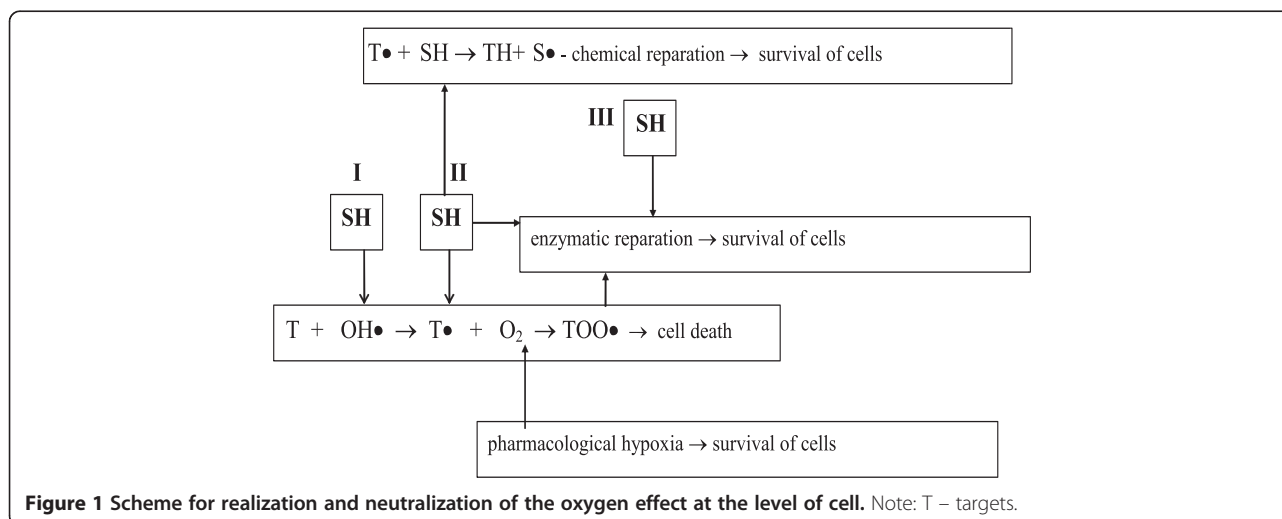

Figure 1 Scheme for realization and neutralization of the oxygen effect at the level of cell. Note: T – targets.

The known sulfur-containing radioprotectors in the reactions of interaction with the radicals of macromolecules and DNA reach the radiation protective effect at the concentrations ~ 2 - 3 times lower than it is possible under the influence of endogenous thiols.

This phenomenon is mainly associated with the positive charge of aminothiols due to the presence in a molecule of the amino group, which should be located no further than 2 - 3 carbon atoms from the free thiol group of the radioprotector to provide the optimum effect of the particular chemical structure. Due to the positive charge of their molecule and by means of electrostatic attraction aminothiols can closely interact with the DNA molecule bearing a negative charge (Zheng et al. 1988, 1992; Spotheim-Maurizot et al. 1991).

However, the interaction of aminothiols with the DNA molecule can have a more specific character than a simple adsorption on a macromolecule. Jellum (1965) was the first to show the possibility of forming a chemical complex between cysteamine and DNA through a diamine link. Due to a high positive charge of the disulfide WR-1065 ($Z = +4$) on the surface of DNA the amount of the radioprotector fixed through a diamine bond is 3 times higher than by means of its electrostatic adsorption (Newton et al. 1996).

Neutralization of the negative charge of DNA during the formation of a new complex of disulfide WR-1065 with DNA leads to the contraction of the DNA molecule along the axis with the formation of a liquid crystal spring-like structure with the narrowing of the channels between the DNA helices (Savoye et al. 1997). The latter mechanism can be effective for the reduction of the radiation damage to DNA due to the decrease in the number of the sensitive places to be attacked by the hydroxyl radical at a density of fixation of more than one molecule of the protector per 4 nucleotides of DNA (Savoye et al. 1997).

Since the radioprotector action is competitive with the ionizing radiation effect, its radioprotective efficacy may be detected by a dose reduction factor (DRF), which is defined as the ratio of radiation 50% lethal dose (LD50) for the drug-treated, irradiated animals to the LD50 for irradiated control animals. This exponent is the most informative for comparative quantitative evaluation of potential of radiation protective agents.

The realization of radioprotective action of sulphur containing radioprotectors through physicochemical reaction with products of radiolysis predetermines a direct correlation between the level of expression of radiation protective efficacy of aminothiols in terms of DRF and the administered dose of the preparation and its concentration in the radiation-sensitive tissues (Patt et al. 1953; Doherty 1960; Koch 1967; Hasegawa and Landahl 1970; Vasin et al. 1970) (Figure 2).

The efficacy of radioprotectors is limited threshold that cannot exceed the radio-sensitising action of oxygen dissolved in tissues, which increases radiation damage of the cells by 2- to 3-fold in the term of DMF. Similar high protective effect with DRF being equal 3 was observed at radioprotective composition of cysteamine, AET, glutathione and serotonin in the experiment on mice (Maisin et al. 1968).

The highest activity of radioprotectors takes place in the hematopoietic tissue and salivary glands (DRF = 1.5 – 2.0), to a lesser extent in the skin (DRF up to 1.5), intestines (DRF up to 1.3) and testis (DRF = 1.1 – 1.2) (Travis 1984).

The radioprotective effects of aminothiols is first of all associated with the reduced radiation damage to stem cells of bone marrow, intestine and skin (Duplan and Fuhrer 1966; Smith et al. 1966; Vasin et al. 1977). Comparative studies in vitro showed protecive effect amifostine in the term of DRF for the cells forming colonies of myeloid, megakaryocyte and erythroid lineages, as well as bone marrow fibroblasts was close to 2 (Ramdas et al. 2003).

Radioprotectors are of great practical interest because of their ability to rapidly (within minutes) increase the resistance of the cells to radiation exposure as well as their ability to protect against high levels of radiation, including exposures at super-lethal doses (up to 10-15 Gy), both of which are absent in other types of radiation protective agents. The time needed to implement the radiation protective action of this group of compounds is within 1 to 2 minutes after administration beginning from a moment of an incorporation of aminothiol molecules in cells. The short duration of maximum action of the radioprotectors is associated with a sufficiently high rate of metabolism in the body and is generally limited to one hour (Vasin et al. 1970) (Figure 3). The time of an elimination of aminothiols from a radiosensitive tissues and decrease of their optimal radioprotective action is identical (Vasin et al. 1971).

However, small protective effect of aminothiols prolongs over several hours after their administration that can be induced by biochemical effects of aminothiols. As shown in Figure 3, the appearance of protective effect of aminothiols in six hours after their administration is possibly induced through an activation of Mn-SOD by the radioprotector (Murley et al. 2006, 2007). Pharmacological properties of aminothiols can determinate complex of poly-functional actions that is significant for the radiation protection, including the influence to mitochondria respiration following acute hypoxia, gene Mn-SOD expression, activity of the Tip60 acetylransferase, etc.

The decrease of DNA damage by aminothiols is basic factor in their protective action. Aminothiols can inhibit DNA synthesis and cell division (Vaughan et al. 1989; Chigareva et al. 1990). Cystamine molecules can block an activity of some thiol-dependent enzymes: caspase-3
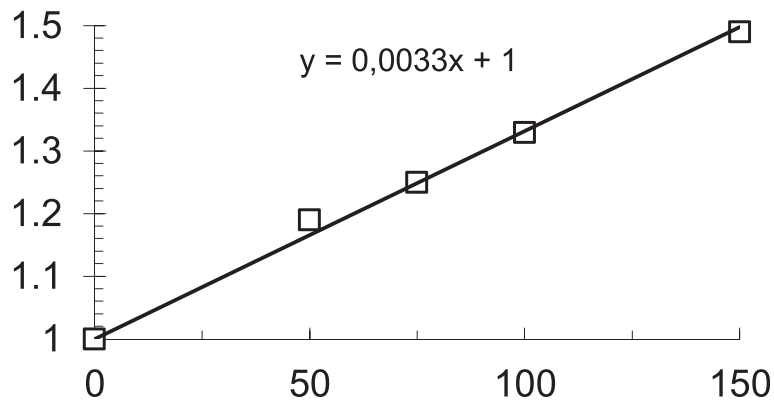
Figure 2 Dose-response relationship of radiation protective effect of cystamine in the experiment on mice (Vasin et al. 1970). Abscissa: the dose of cystamine, mg/kg. Ordinate: radiation protective effectiveness of cystamine, DRF.

(Lesort et al. 2003), transglutaminase (Jeitner et al. 2005) that tie together enzyme molecules. It is likely that the conformational structure of DNA undergoes some changes under the influence of aminothiols associated with the condensation and stabilization of chromatin, thus enhancing the interplay between the transcriptional factors (nuclear factor - kappaB, protein-1 activator and tumor supressor p53) and DNA, which leads to the subsequent activation of a number of genes. One of the constituents of this reaction is the activation of the p53 tumor suppressor under the action of aminothiols. This reaction develops given the interaction of extracellular thiols with the cell membrane. The transfer of the stress signal to p53 is carried out through the c-Jun N-terminal kinase (Pluquet et al. 2003). In addition, aminothiols due to their ability to block topoisomerase II, as well as under activation of p53 through the inhibitor of cycline-dependent kinases p21waf-1 prevent the passage of cells through the cell cycle in the G1 phase. Mitotic block over six-eight hours provide more opportunities for the reparation of the DNA from "hidden" potential radiation damage (Murley and Grdina 1995; North et al. 2000). The activation of nuclear factor – kappaB by amifostine also inhibits apoptosis of hematopoietic progenitor cells (Romano et al. 1999). These
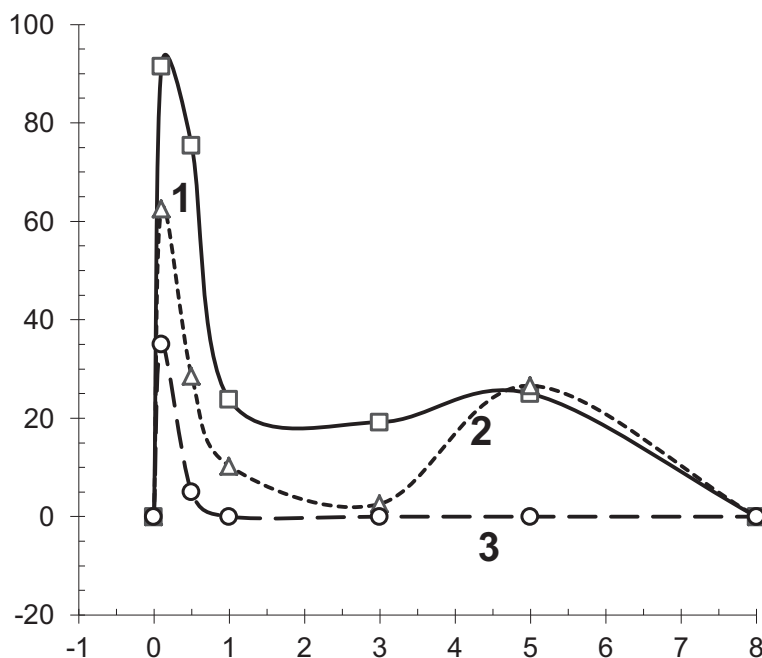

Figure 3 Radioprotective effect of cystamine administrated IP at various periods before irradiation in the experiment on mice (Vasin et al. 1970). Abscissa: the periods of cystamine administration before irradiation, hours. Ordinate: radioprotective effect of cystamine at $LD_{95/30}$ of gamma-irradiation, %. 1–150 mg/kg, 2–100 mg/kg, 3–75 mg/kg.

processes can be cause of radiation mitigative effects of aminothiols at their administration after irradiation that more extensively develop in the condition of non-uniform irradiation or partial shielding of the body (Maisin et al. 1953a, b; Shashkov et al. 1971; Vasin 2012). That is possibly connected with the stimulatory effect of aminothiols on the hematopoietic stroma elements (Romashko et al. 1990).

Radioprotective properties of aminothiols is associated with their ability to raise the level of reduced equivalents in the cells and, in the first, endogenous thiols: glutathione and cysteine - from 2-3 up to 10 times (Wardman et al. 1992). The elevated level of endogenous thiols under the influence of aminothiols causes the development in the cell of the "redox stress" or "biochemical shock" (according to the terminology of Z. Bacq), which, in particular, manifests itself as the swelling of mitochondria in the cells (Lehninger and Schneider 1959; Neubert and Lehninger 1962). The swelling of mitochondria is directly regulated by the state of the thiol-disulfide equilibrium in the respiration chain. Under conditions of the mitochondrial swelling, the number of SH-groups increases.

The changes in the structure of mitochondria in the form of swelling are directly reflected in the operation of the phosphorylation respiratory chain, namely, in the degree of relationship between the processes of electron transport and oxidative phosphorylation, which is measured by the P/O ratio. The maximum values of the P/O ratio are observed when the integrity of mitochondria is the highest. When mitochondria swell, the distance between the outer and inner membrane decreases and the flow of electrons through the membranes accompanied by the release of energy in the form of heat due to the intensification of the processes of free oxidation increases.

The reduced level of the P/O relationship represents itself one of the ways of regulating the respiratory chain. A mild and moderate uncoupling of oxidative phosphorylation is a necessary condition for the acceleration of oxidation when there is a physiological requirement for increased energy. Extensive uncoupling of oxidative phosphorylation with sharp oxygen consumption in cells induces to the development of acute cellular hypoxia that is key factor for an implementation of high radioprotective effect. This fact was confirmed by the administration of uncoupler of oxidative phosphorylation 2,4-dinitriphenol when it was detected 100% protective effect (Praslicka et al. 1962; Vacek and Rotkovska 1964).

Aminothiols have an effect on respiration and phosphorylation in cells, which is accompanied by mitochondrial swelling and intensification of free oxidation processes (Lelievre 1965; Firket and Lelievre 1966; Skrede 1966; Vladimirov and Libikova 1970). Amifostine added to the medium of mammalian cell culture rises rapidly oxygen consumption and the temperature of the tissue culture in vitro (Purdie et al. 1983). Cystamine also increases cellular respiration of hepatocytes (Iarmonenko 1961) and erythrocytes in vitro (Kuznetsov and Tank 1964). The administration of cystamine in humans at a dose of 0.6 g was found to increase the oxygen consumption by 9% and body temperature by $0.2 - 0.3°C$ for $1 - 2$ hours (in 72.3% of the cases) (Kuznetsov and Tank 1966). Succinate dehydrogenase activity rise by cystamine in vitro in lymphocytes is indicator the development of acute cellular hypoxia (Vasin et al. 1999).

Cellular hypoxia under the influence of aminothiols in combination with the growth of the level of thiol groups in the cell due to radioprotector molecules and endogenous sources is an important components in the mechanism of radioprotective effect of sulfur-containing radioprotectors. The quota of acute hypoxia in protective effect of amifostine can consist 20–30% (Yuhas et al. 1973; Allalunis-Turner et al. 1989, Allalunis-Turner 1990).

It seemed likely "biochemical shock" induced aminothiols over five-six hours can potentiate radioprotective effect at repeated their administration with the interval of some hours. As shown in Figure 4, repeated IP injection of cystamine in the dose 150 mg/kg over hours five increase twice an efficacy of radioprotectors in the term of DRF. In case of decrease of the dose of cystamine, the time of the potentiation shortens up to two-three hours.

However, long time everyday administration of aminothiols in high doses causes decrease of their protective efficacy through the cumulation of their cytostatic or cytotoxic effects inhibited early post-radiation reparation of radiosensitive tissues (Travis et al. 1988; Coia and Brown 1989; Vasin et al. 1991, Vasin et al. 2004b).

Amifostine currently finds its application in clinical practice as a radioprotectant and chemoprotector during the radio-chemotherapy of patients with head and neck tumors, lung cancer and breast cancer, allowing the reduction of the radiotoxicity and toxicity of cytotoxic preparations (Trog et al. 1999; Feng et al. 2012; Koukourakis et al. 2013).

According to my calculation of clinic data by Trog et al. (1999) on the reduction of the symptoms of post-radiation mucositis during the radiotherapy treatment of head and neck cancer patients, DMF for amifostine is equal to 1.37 (Vasin 2014a).

The role of pharmacological hypoxia in radiosensitive tissues in the mechanism of the action of radioprotectors from the family of vasoactive biogenic amine and their derivatives

Endogenous vasoactive neuromediators such as adrenaline, noradrenaline, dopamine, serotonin, histamine, acetylcholine, prostaglandins, and purine nucleotides induce their radioprotective action through cell receptor
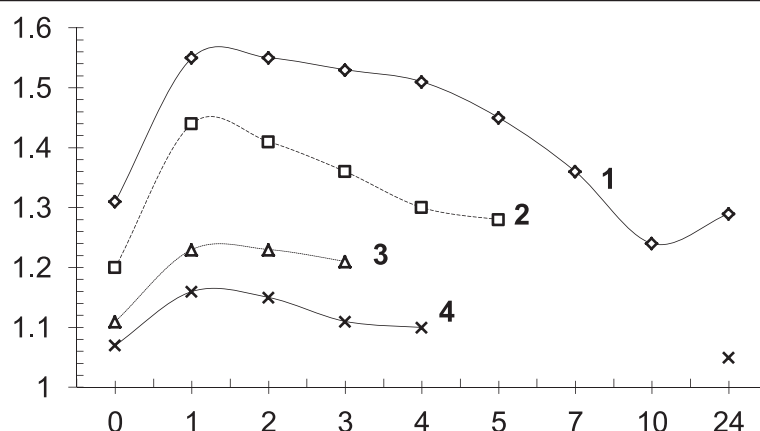
Figure 4 Potentiation of radiation protective effect of cystamine administered IP to mice twice before exposure to radiation at various interval between two injection (Vasin and Antipov 1972). Abscissa: the time interval between administration of two doses of cystamine, hours; value 0 stands for a single administration of the drug. Ordinate: radiation protective effectiveness of cystamine, DRF: 1 - 150 mg/kg, 2 - 100 mg/kg, 3 - 75 mg/kg, 4 - 50 mg/kg. Note: cystamine was administered intraperitoneally, with the second dose injected 5-10 minutes prior to γ-irradiation.

mechanism by developing of acute circulatory and/or cellular hypoxia in radiosensitive tissues.

The first information about the ability of biogenic amines having a pronounced radiation protective effect to reduce the oxygen content in the hematopoietic tissues allowed van der Meer and van Bekkum (1959, 1961) and Konstantinova and Graevskii (1960) to propose a hypothesis about the role of pharmacological hypoxia as the main mechanism of the radiation protective action of these compounds. This idea was also supported by the experimental data on the reduction of radiation protective properties of biogenic amines after the application of pharmacological antagonists which block their effects on blood vessels, as well as under the influence of hyperoxia partially eliminating the disturbances in the oxygen delivery to tissues in the case of hemo-circulatory disorders under the action of biogenic amines (Van den Brenk and Moore 1959; van den Brenk and Haas 1961; van den Brenk and Jamieson 1962).

The role of pharmacologically induced disturbances of the local blood flow in hemopoietic tissues in the implementation of radiation protective action for many derivatives of serotonin at different doses and methods of application was confirmed later (Zherebchenko and Suvorov 1963; Hasegawa and Landahl 1967; Iarmonenko et al. 1970; Prewitt and Musacchia 1975; Vasin et al. 1984, 1987). Similar correlation for sympathomimetics was not always quite explicit (Kulinskii and Zolochevskaia 1973). Nevertheless, application of pharmacological antagonists eliminated the radioprotective effect epinephrine, norepinephrine, phenylephrine, and indralin (Kulinskii et al. 1986; Vasin et al. 1996, 2001). The same effect was observed with animal radiation exposure in an atmosphere of increased oxygen pressure (van den Brenk and Haas

1961; van den Brenk and Jamieson 1962; Vasin et al. 1979, 1996, Vasin et al. 1997a).

The real opportunities for the modification of the radiosensitivity of the organism in the case of pharmacologically induced disorders of the oxygen delivery to tissues can be compared with the radiation protective effect of the hypoxic hypoxia under the conditions of the drop of oxygen tension in the blood as low as twice or three times. The increase of radioresistance of animals breathed by gaseous hypoxic mixture (GHM) during irradiation was first of all obtained by Dowdy et al. (1950).

Figure 5 shows radioprotective effect of normobaric hypoxic hypoxia with respiration of GHM with the deficient oxygen content from 15% to 5% in the experiment on mice and rats. Reduction of the oxygen delivery to tissues can lead to the shifts in the radioresistance of the organism close to the theoretically possible for the oxygen effect.

Oxygen tension level in cells with the acute reduction of the oxygen delivery to tissues is mainly determined by the intensity of the tissue respiration, which, for example, in dogs and rats is 5 and 2 times as low as that in mice that, in all probability, is a cause for the reduction of the radiation protective action of GHM in these animal species (Vasin 1986, Vasin et al. 1997a).

As shown in Figure 5, the effect of GHM in the experiment on rats is lower than that in mice (Vasin 1986). In the experiments on large animals (dogs) the radiation protective action of GHM was even less pronounced and did not exceed 50-60%, which is not higher than 1.2-1.3 in terms of DRF (Strelkov et al. 1974; Titov et al. 1977; Vasin et al. 1997a).

Reduction of the radiation protective properties of mexamine, an active derivative of serotonin, in the
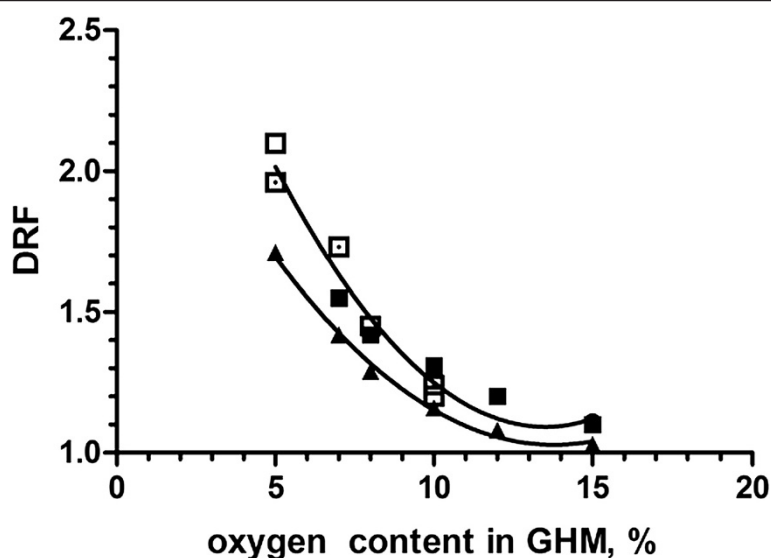
Figure 5 Radioprotective efficacy of acute hypoxic hypoxia at respiration by gaseous hypoxic mixture with various content of oxygen during irradiation of mice and rats. Abscissa: oxygen content in gaseous hypoxic mixture, %; Ordinate: radioprotective efficacy of GHM, DRF, Note: squares – mice, triangle – rats, black squares and triangle – (Vasin 1986), white squares – (Hasegawa and Landahl 1967), white square with point – (Iarmonenko et al. 1980).

experiments on rats and dogs, as compared with the effect on mice is associated, as in the case of application of hypoxic mixtures, with the influence of a lower initial level of the tissue respiration (Vasin 1986; Vasin et al. 1997a).

A high radioprotective efficiency of indralin in the large animals (dogs, monkeys) (Vasin et al. 1997b, 2014a) is largely predetermined, in addition to the vasoconstrictive effect, by its ability as a α_1-adrenomimetic to stimulate the oxygen consumption in hematopoietic tissues (Vasin et al. 2013) thus inducing acute cellular hypoxia (Vasin et al. 1997a, 1999).

Besides, biogenic amines inducing radioprotective effect at their administration before irradiation have radiation mitigating properties when they are applied after exposure to radiation. Rixon and Baird (1968) showed first of all mitigatory effect of serotonin at repeated its administration after irradiation. Later, mitigating properties were observed when mexamine (5-methoxitryptamine) (Shashkov et al. 1971), adrenaline (Smirnova et al. 1984a) or α_1-adrenomimetic indralin were injected at once after irradiation (Vasin et al. 2008b, 2014b). The mitigatory effect of indralin achieved steep rise in the condition of partial shielding of body (Vasin et al. 2008a). Radiation mitigatory effect of serotonin was detected in vitro (Smirnova et al. 1984b).

As noted, the sympathetic nervous system is actively involved in the regulation of the mobilization and migration of haematopoietic cells (Katayama et al. 2006). This characteristic feature accounts for the fact that norepinephrine (Maestroni et al. 1997) and α_1-adrenomimetic indralin (Vasin et al. 2006, Vasin 2012) reduce the hemotoxicity of

carboplatin. Catecholamines also enhance the stress-associated increase in the secretion of pro-inflammatory cytokines interleukin (IL)-1 and IL-6, which contribute to the mobilization of myeloid hematopoiesis (Johnson et al. 2005). The mechanism of hematopoiesis stimulation is probably associated with an activation of tissue transglutaminase and new G-protein-coupling α_1-adrenergic receptors (Feng et al. 1999; Zhang et al. 1999; Park et al. 2001) that are able to activate nuclear factor (NF)-kappa B (Chen and Minneman 2005; Kumar and Mehta 2012). This is associated with a subsequent increase in gene expression of pro-inflammatory cytokines, including IL-1, tumour growth factor, IL-6, and IL-12, which promote cell proliferation of myeloid hematopoiesis (Zhao et al. 2012).

This study found that the mitigating effects of indralin, when it is administered after exposure to supralethal dose of radiation and when it is administered together with shielding of the abdominal region of rats, can not be explained by hypoxic mechanisms of α_1-adrenomimetic activity. Radioprotectors cannot neutralize the "oxygen effect" when they are admin-istered after radiation exposure. The mitigable effect of radioprotectors applied after irradiation on the haematopoietic tissue is implemented through their interference with the processes of accelerated proliferation and migration of stem cells and progenitor cells of the myeloid group from the haematopoietic tissues that are protected by partial shielding.

Experimental principles for the use of hypoxia in radiation therapy have been presented (Jarmonenko et al. 1975). There are first clinic investigations of radioprotective effect of radioprotector mexamine (Voĭtkevich and Palyga

1974) and GHM (Strelkov et al. 1985; Goldobenko et al. 1995). Mexamine as a mitigator is used to reduce chemotoxicity of chemotherapy (Lissoni et al. 2003, 2012; Lissoni 2007). Indralin (B-190) is used as a radioprotective agent for medical protection of personnel during emergency situations at nuclear power plants (Ilyin et al. 1994, 2012, 2013).

Radiomitigators (oestrogens, androgens, cytokines, and immunological adjuvants etc) that exert their effect on system levels by promoting the acceleration of the post-radiation restoration of radiosensitive tissues through an activation of pro-inflammatory signalling pathways and a stimulation of HSPC and MSC mobilization

Second group of radioprotective agents using in medicine exert their effect on system levels by promoting the acceleration of the post-radiation restoration of radiosensitive tissues, and is not directly connected with the primary radiation-chemical and biochemical processes in cells that occur during the absorption of the energy from ionizing radiation. For this reason, these agents are effective not only at administration before irradiation, but also during the early period after, acting as mitigators. Their DRF is not restricted by an "oxygen effect", but is limited by the physiologic actions of systems of the body, through which their pharmacological properties are mediated. For example according to available data (Lukashin and Sofronov 1996), the greatest radiation protective effect of the agent from the given group heparin takes place in the radiosensitive strains of CBA mice (DRF = 1.2), while it is almost completely absent in radioresistant animals C57Bl/6.

In some cases these agents have protective effects that are similar to the action of "classic" radioprotectors. However, their dependence on the functions of complex systems is reduced, so that most of the radiation protection takes place in radiation injuries of hematopoietic tissues, although it is seen in other tissues (e.g., intestines, skin) with acute radiation syndrome (ARS) (Smith et al. 1958, Ainsworth and Mitchell 1968, Monette et al. 1972, Wu and Miyamoto 1990, Roberts et al. 1993).

Given agents can exert their effects through activation of the reticuloendothelial system. They increase phagocytic function of mononuclear cells in the blood and tissues, stimulate the migration of hematopoietic cells and antibody formation, and increase resistance to exogenous infections (Lukashin and Morozova 1981; Klestova et al. 1984). Their radiation protective effects are related to their ability to accelerate the processes of post-radiation regeneration of the hematopoietic system and, above all, to restore myelopoiesis (Neta et al. 1986, Neta and Oppenheim 1988).

The common feature of these radiation protective agents is that the development of an elevated radioresistance due to these agents requires a certain period of time, usually hours or days. The optimum radiation protective effect exerted by long-acting radioprotectors is observed when they are used within a period of several hours to 3 to 4 days before exposure to radiation at doses not exceeding the levels that can result in bone marrow toxicity of ARS. These agents maintain their effectiveness for up to 2 weeks. A long-term action is not reflected in their tolerability because it is not closely related to their pharmacokinetics. These agents are not effective after exposure to radiation at super-lethal doses, distinguishing them from "classic" radioprotectors (Neta et al. 1995)

The radiation protective agents exerting their effects through second pathway described above include: (I) hormones or steroid structure and synthetic analogs, such as estrogens and androgens; (II) immunologic adjuvants and high-molecular structures of microbe, plant, and animal sources (vaccines, endotoxins, polysaccharides, glucans, polynucleotides); (III) cytokines such as inflammatory interleukins (IL-1beta, IL-8, IL-12, and IL-18), tumor necrosis factors (TNF), hemopoietic growth factors (G-CSF, GM-CSF, M-CSF, IL-3), soluble cytokines — interferons, and (IV) immune regulatory peptides.

The common feature for their action is the activation of the transcription factor NF-kB separately as well as together with AP-1 и STAT-3. This leads to the expression of genes responsible for cell proliferation, reduction of apoptosis of stem cells, and an increase in their survival rate after radiation damage. Immune defense is also improved, through an increased production of pro-inflammatory cytokines and hematopoietic growth factors (Shannon et al. 1997; Aggarwal et al. 2004; Chung et al. 2006b; Park et al. 2001). NF-kB, a "rapid-acting" primary transcription factor, is in a non-active state in the cytosol and is activated through IL-1beta, TNF, and lipopolysaccharide (LPS) receptors, bacterial and viral antigens, and by reactive oxygen species (ROS) and ionizing radiation (Qin et al. 2005; Gilmore 2006; Hayden and Ghosh 2011; Gerondakis et al. 2012). The agents of this group act as radiomitigators, and when administrated early after irradiation (up until clinic signs of ARS are apparent) their ability for myelopoiesis stimulation is preserved. This effect is of interest for use of these agents for emergency and early treatment of ARS (Neta 1988; MacVittie et al. 2005; Drouet et al. 2008). From this group of preparations, GM-CSF, G-CSF, IL-1, IL-3, and IL-2 are used in clinical practice as mitigators and therapeutic agents to minimize radio- and chemotoxicity (Robak et al. 1993; Baranov et al. 1994; Hartmann et al. 1997; Gershanovich et al. 2001, Westermann et al. 2001).

NF-kB activation is also possible through G-protein-coupled receptor (GPCR) mediators (biogenic amines, nucleosides, prostanoids, and angiotensin) and hormone nuclear receptors (Papayannopoulou et al. 2003, Katayama et al. 2006). These compounds also have the ability as mitigators to exert a favorable effect on the post-radiation recovery of hematopoiesis (Lebedev et al. 1994, Haznedaroglu and Oztürk 2003, Watanabe et al. 2006, Vasin et al. 2008a, Gudkov et al. 2009).

Radiomodulators (natural antioxidants, anti-inflammatory agents, inhibitors of angiotensin converting enzymes etc) that increase the resistance of the body to irradiation and other unfavourable environmental factors by adaptively shifting the effectiveness of the antioxidative protection of the organism

The mechanism of the radioprotective action of third group of agents is worthy of a detailed analysis in view of their great biological importance. The third group of radiation protective agents includes drugs and nutritional supplements that can elevate the resistance of the organism to adverse environmental factors, including exposure to ionization by means of modulating the gene expression through a hormetic effect of small doses of stressors and a "substrate" maintenance of adaptive changes, resulting in an increased antioxidant protection of the organism. Recently, they belonged to "biological protection" agents or stimulators of radioresistance (Saksonov 1975, Vasin 1999, Nair et al. 2001). Now, the third group of agents has a reason to refer to radiomodulators as original class of radioprotective agents. By definition, radiomodulators have both radiation protective features (relative to normal healthy tissues) and radiosensitizing properties towards cancer cells (Arora et al. 2008). Unfortunately, radiomodulators are not a member of present-day classification of radiation protective agents (Stone et al. 2004).

Radiomodulators have anti-inflammatory, anti-bacterial, anti-oxidant, and anti-mutagenic properties (Table 1) (Fang et al. 2002; Hong et al. 2006; Izzi et al. 2012). Similar properties are manifested in natural antioxidants. These agents, acting through the same mechanism may have a beneficial effect when administered before, during, and immediately after exposure to radiation; they also have a therapeutic effect in the development of clinical symptoms of radiation injury (Landauer et al. 2003; Landauer 2008; Arora et al. 2008).

These agents can enhance resistance of the body to environmental factors that are adverse for human health, including ionizing radiation, with reducing the risk of carcinogenic effects and decreasing the biological age (Goel and Aggarwal 2010; Epperly et al. 2011; Lee et al. 2013). The best practical value of this medications

consists, above all, in the fact that they can be considered as the agents for prophylaxis against the development of oxidative stress with long-term (months, years), low-rate-dose ionizing irradiation (Turner et al. 2002, Prasad 2005). These agents were previously and are currently being developed for use during long-term, low-rate-dose exposures to radiation, under conditions of long space missions (Chertkov and Petrov 1993; Rabin et al. 2005; Ushakov and Vasin 2011). Since these substances have low toxicity and do not have side effects at the administered doses, they can be used repeatedly, life-long if necessary, with alterations in the cycles of metabolic correction and substrate therapy depending on the appearance of symptoms of chronic oxidative stress.

The theoretical basis for the research into the mechanism of increasing the nonspecific resistance of the organism under the influence of pharmacological agents is from a classic study by *Selye* (1985) and from additional research in this area, including studies investigating into the formation of different adaptive stages, depending on the strength and duration of the impact of adverse environmental factors (Garkavi et al. 1980; Lindsay 2005; Speciale et al. 2011).

The fundamentally important characteristic feature of the pharmacological agents that enhance the nonspecific resistance of the organism is the fact that their optimal effect can be formed due to the slowly proceeding structural signs manifesting themselves as the alteration and complication of the adaptive phases of "activation" and "training" supported by the definite rhythm of repeated exposures to low doses of an adaptogen (Garkavi et al. 1980).

Acting as low-dose stressors through a hormetic mechanism and a "substrate" support of adaptive shifts radiomodulators results in an increase in the antioxidant defense of the body and the rearrangement of its functioning in the new environment with the modulation of gene expression of antioxidant response elements by activation of NRF2/KEAPI and SIRTUIN/FOXO pathways and a decrease in the transcription factor NF-kB (Renard et al. 1997; Chen et al. 2005; Paur et al. 2010). According to their action, these agents are to some extent opposite to drugs of noted above second group—classical mitigators (e.g., vaccines, LPS, pro-inflammatory cytokines) which have pro-inflammatory properties and whose mechanism is based on the activation of the transcription factor NF-kB.

The repeated administration of vitamin complexes results in the increase of the total nonspecific resistance, including some degree of enhancement of the radiation resistance of the organism. This is associated with the maintenance of a specific tonus of the pituitary-adrenal system. For example, ascorbic acid (which is essential for the functioning of the adrenal glands where its concentration is sustained at a high level and exceeds that in other tissues) is a cofactor for

Table 1 The mechanisms and optimal conditions for radioprotective action of flavonoids (Vasin 2014b)

Pharmacological action	The mechanisms of anti-radiation action	The optimal condition of protective action
Antioxidan	Enzyme and non-enzyme anti-radical effect, activation of Nrf2/Keapl and Sirtuin/FoxO pathway	Low-dose-rate irradiation, repeated prophylactic dose of drugs and nutrient supplement
Pro-oxidant	Activation the NF-κB pathway, increase of pro-inflammatory cytokines → stimulant effect of myelopoiesis	High-dose-rate and lethal irradiation, ovendose of drugs, delayed protective effect
Estrogenic	Immunostimulant action, G-CSF increase → stimulant effect of myelopoiesis	High-, low-dose-rate, and lethal, non-lethal irradiation, therapeutic dose of drugs, delayed protective effect
Anti-carcinogenic	Inhibition the NF-κB pathway, and the mutation or hyper- expression of the Nrf2-Keap1 signaling pathway in tumor genesis, and angiogenesis	Low-dose-rate irradiation, repeated prophylactic dose of drugs and nutrient supplement
Anti-inflammatory	Inhibition the NF-κB pathway, pro-inflammatory cytokine decrease → mitigation of acute radiation syndrome, long-term radiation oxidative stress and post-radiation fibrosis of tissues	High-, low-dose-rate, lethal and non-lethal irradiation, therapeutic dose of drugs, delayed protective effect

the synthesis of adrenaline and glucocorticoids (Bornstein et al. 2003, Patak et al. 2004). The basis of the pathogenetic mechanism for their action lies in the stimulation of the neuro-immuno-endocrine system with the activation of individual axes of regulation (pituitary-adrenal, hypothalamic-thymic, and pituitary-thyroid), whose predominance depends on the nature, dose, and pattern of administration of a pharmaceutical agents. A direct substrate regulation of the antioxidant system and biosynthetic processes, which are important for the post-radiation reparation of the tissues of the body, is also possible when natural antioxidants are used as nutritional supplements—vitamins, nucleotides, oligopeptides, amino acids, and other compounds. However, in this case system reactions affecting the neuro-immuno-endocrine regulation in the organism are inevitable.

Dietary antioxidants such as vitamins A, C, and E, polyphenols, anthocyanins, flavonoids, isothiocyanates, and other natural antioxidants are considered as impacting redox reactions (Meyers et al. 2008). Those with high oxidant potential can directly interact with radiation-induced radicals; this has been recently considered as a basic mechanism of their radioprotective action. However, natural antioxidants, in all probability, participate in the gene regulation of the antioxidant system of the organism (Landauer 2008). Their indirect involvement as antioxidants can be achieved by means of inhibition of the redox-sensitive transcription factors (NF-kB, activator protein-1) and pro-oxidant enzymes (iNOS, cyclooxygenase, xanthine oxidase) through the induction of antioxidant enzymes (gluthation-5-transferase, superoxide dismutase), and phase II of cellular respiration (Frei and Higdon 2003). Experiments in vitro revealed that genistein and quercetin are able to significantly increase the gene promoter activity of glutathione peroxide and superoxide dismutase in the absence of the effect on the activity of catalase (Ullmann et al. 2008). Genistein also increased the expression of metallothionein genes (Chung et al. 2006a) and suppressed post-radiation pro-inflammatory cytokine induction (Grace et al. 2007,

Singh et al. 2009, Ha et al. 2013). Quercetin inhibits the synthesis of iNOS through the inhibition of NF-kB and STAT1 (Meyers et al. 2008) and suppresses the growth of xenograft A2780S ovarian tumors by causing cancer cell apoptosis and inhibition of angiogenesis in vivo (Gao et al. 2012). Epigallocatechin-3-gallate protects cells from ionizing radiation via heme oxygenase-1 overexpression that suppresses ROS generation (Zhu et al. 2014).

Drugs with NF-κB pathway suppressive and anti-inflammatory actions, such as angiotensin-converting enzyme and prostaglandin biosynthesis inhibitors, genistein and melatonin, can mitigate post-radiation fibrosis of kidney, lungs, and skin (Table 1) (Sklobovskaia et al. 1984; Molteni et al. 2001; Vasin et al. 2004a; Day et al. 2008; Sieber et al. 2011; Medhora et al. 2012; Kma et al. 2012) and post-radiation myelosuppression of ARS (Davis et al. 2007, 2008; Day et al. 2013; Vasin et al. 2014c).

Anti-inflammatory effect of ginestein suppresses post-radiation increase of Il-1-beta, Il-6 and COX-2 in hematopoietic tissues that is regard as key mechanism of radioprotective action the isoflanone (Ha et al. 2013). Indeed, inhibition of COX-2 by meloxicam, administered shortly after irradiation increases survival of lethally irradiated mice (Hofer et al. 2011). Natural delta-tocotrienol significantly enhanced survival in total-body irradiated mice, through Erk activation-associated mTOR survival pathways via inhibition of radiation-induced production of pro-inflammatory factors interleukin-1β and Il-6 and suppressed expression of protein tyrosine kinase 6, a stress-induced kinase that promotes apoptosis in mouse intestinal cells (Li et al. 2013) (Table 1).

The favorable action of natural antioxidants in the presence of the chronic oxidative stress is the reduction in the intensity and time needed to implement the remote impact of radiation damage to particular tissues and systems, primarily associated with their important role in the functioning of the vascular system.

This prevents the development of atherosclerosis, disorders of the microcirculation in tissues and their fibrosis,

and the manifestation of chronic inflammatory processes in the patients with the immune system disorders; in other words, premorbid states leading to, as noted above, cardiovascular and endocrine diseases and the progression of carcinogenesis (Zhao and Robbins 2009).

It is also known that the bioflavonoids epigallakatehin-3-gallate, luteolin, quercetin, kaempferol, apegenin, and taxifolin are able to block the fatty acid synthase, which is the basis for the anti-carcinogenic action of these compounds (Brusselmans et al. 2005).

The tissues of the body contain ascorbic acid at a certain concentration; cell membranes contain tocopherols. There is a recirculation of the oxidized and reduced forms of these natural antioxidants, which supports the antioxidant protection of cell membranes. It involves bioflavonoids, which are the most powerful antioxidants, and the antioxidant system of cells as a whole (Table 1). Quercetin is able to accumulate in mitochondria and bind to the DNA molecule (Janjua et al. 2009).

These are the reasons why the administration of natural antioxidants have a pathogenetic justification for exposures to chronic (months, years) low-rate-dose ionizing radiat (Okunieff et al. 2008). The reduction of the consequences of the exposure to the long-term radiation can be achieved by providing an adequately balanced diet rich in vitamins, fibers, and nutritious animal proteins.

The realization of the action of natural antioxidants takes a certain period of time, so the effect is enhanced following the repeated administration of vitamins (Orsolić et al. 2007; Benković et al. 2009). A peculiar feature of pharmacodynamics of the preparations comprising the "biological shield" is that the modifications in the radiation resistance of the organism under their impact do not happen immediately, but gradually over repeated administration, more often within 2 weeks, and can be maintained at the elevated level during the entire course of treatment and prevention. When the preventive measures are well tolerated, they can be repeated without any loss of their effectiveness (Table 1).

Antioxidants (quercetin, vitamins A and C, beta-carotene, selenium, melatonin, and glutathione) can be used in clinical practice for the decrease of the toxicity of radio-chemotherapy for cancer patients (Lamson and Brignall 2000, Vasin et al. 2004a, 2004b).

Conclusion

For most of these agents, it is possible to distinguish three main pathways for the implementation of the mechanism of action, each of which have their own specificity in predetermining the pharmacodynamic properties and possible methods in their practical application: 1) radiation protective agents, with the implementation of radiation protective action taking place at the cellular level in the course of rapidly proceeding radiation-chemical reactions. At the same time, when the ionizing radiation energy is absorbed, these agents partially neutralize the "oxygen effect" as a radiobiological phenomenon, especially in the radiolysis of DNA; 2) radiation protective agents that exert their effect at the system level by accelerating the post-radiation recovery of radiosensitive tissues through activation of a number of pro-inflammatory signaling pathways and an increase in the secretion of hematopoietic growth factors, including their use as mitigators in the early period after irradiation prior to the clinical development of acute radiation syndrome (ARS). 3) radiomodulators including drugs and nutritional supplements that can elevate the resistance of the organism to adverse environmental factors, including exposure to ionization by means of modulating the gene expression through a hormetic effect of small doses of stressors and a "substrate" maintenance of adaptive changes, resulting in an increased antioxidant protection of the organism. Anti-inflammatory properties of radiomodulators can be key basis of realization of their radioprotective action.

The possibility that radiation protective agents may implement their action by various routes and through different mechanisms mentioned above cannot be excluded. For example, indralin, a radioprotector with urgent action can act as a mitigator (Ilyin et al. 1994; Vasin et al. 2008a, b, 2014b), while the radioprotector amifostine is capable of stimulating the antioxidant system of the body through the activation of Mn-SOD (Grdina et al. 2009), and the radiomodulator α-tocopherol succinate, at very high doses, possibly acting as a pro-oxidant, induces G-CSF mobilization (Singh et al. 2010).

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