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RADIOPROTECTIVE AGENTS IN MEDICINE

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The diminished probability of strategic nuclear confrontation alleviates some of the global concerns about large numbers of radiation casualties in the event of a nuclear war. As a result of the protection of the environment, the management of smaller numbers of radiation casualties assumes a more predictable and more specific role confined to accidents in nuclear energy projects, industry, technology and science. Recent experience of the consequences of accidents in nuclear power plants, in the field of radiotherapy and in the disposal of radioactive waste and spent fuel, present the medical and scientific communities with formidable problems if such events are to lead to minimal adverse effects on the biosphere. Whereas it is not possible to predict a nuclear or radiation accident, radioprotection is hardly an issue of health science alone, but rather an issue of the strictest quality assurance in all aspects of the utilization of nuclear energy and ionizing radiation. Thus, the medical community concerned with radioprotection will have to confine its emphasis on the management of radiation-induced alterations of the human organism from acute radiation syndromes to the stochastic concepts of chronic alterations of radiosensitive organic systems. Current multidisciplinary research in the field of radioprotection involves all aspects of basic and clinical research ranging from the subatomic mechanisms of free radical formation, macromolecular and intracellular radiation-induced alterations, biochemical and physiological homeostatic mechanisms and organ level manifestations to the clinical management of radiation casualties in a controlled hospital environment. Radioprotective agents, although widely studied in the past four decades and including several thousand agents, have not reached the level of providing the field of medicine with an agent that conforms to all criteria of an optimal radioprotectant, including effectiveness, toxicity, availability, specificity and tolerance.

This article discusses the current state of radioprotection in medical therapy, and emphasizes a need for continued research in the area of medical management of radiation casualties from the viewpoint of a realistic probability of nuclear incidents or accidents in the nuclear energy-dependent world at the end of the millennium.

Key terms: aminothiols, antioxidants, chemical-molecular mechanisms, immunomodulators, ionizing radiation, macromolecules, membrane lipids, proteins

HISTORICAL BACKGROUND

The early experimental data of over 43 years ago, reporting radioprotective properties of some chemical agents in lethally irradiated mice, initiated world-wide experimental and clinical investigative efforts to identify and evaluate various agents that facilitate survival and recovery in irradiated organisms. Of over 5000 compounds tested, only a few remained with promising benefits in the management of radiation casualties. The main objective of a universal agent or a group of agents that could reduce pathologic alterations of irradiated living organisms has not, as yet, been met. The current state of nuclear fuel, either from the stockpiles of the military arsenal or nuclear power plants where the potential for large scale accidents is a realistic possibility, warrants further search for a viable radioprotective agent. With the diminishing threat of global nuclear confrontation on a strategic scale, the focus of attention has been shifted to plans involving a tactical nuclear arsenal of industrial accidents.

Over four decades ago, the Atomic Energy Commission initiated a program of research efforts to develop a substance that would possess the following characteristic properties: 1) reduce the harmful effects of radiation by a factor of two; 2) be easily administered by a radiation victim's self-application; 3) provide long-term protection; 4) be tolerated with minimal side-effects; 5) provide protection with minimal interference with the completion of a mission in either civilian or military scenarios; 6) not incompatible with other drugs; 7) have a long shelf half-life and 8) not cause drug dependency. Although the aim of the research had been focused on prophylactic radioprotective agents, the scope of the work soon included issues related to radiation therapy in clinical management of cancer patients, in conjunction with tumor-cell specific radiosensitizing agents.

Although several such drugs have progressed to the stage of clinical testing in the last decade, none has yet been found to be useful for routine clinical use, or for use in military medicine. The criteria for an effective radioprotectant have not been met in either field requirements, or in a radioprotector-radiosensitizer combination, that would provide an opportunity to reduce the doses of ionizing radiation in tumor therapy.

MECHANISMS OF INJURY FROM IONIZING RADIATION

Pathological alteration of living tissue by ionizing radiation results from energy transfer to macromolecules, particularly DNA, proteins and membrane lipids (1). The damage may be direct through ionization or excitation from the radiation incident (2) or indirect, where the molecular structures receive the energy by transfer from another molecule (3). The latter which is a predominant mechanism of injury in aqueous systems, in which the water molecules may be ionized with a subsequent transfer of energy, by the action of diffusible ions and free radicals, which are almost exclusively intermediate factors between ion pairs and final chemical products. Free radical formation almost exclu sively applies to the radiolysis of water, where most primary ionization effects occur due to the aqueous environment of biological systems. *In vivo* assessment of direct versus indirect damage to a tissue is a challenging problem in radiation chemistry because of the exceedingly rapid kinetics of the free radical interactions and the ultrashort lifetime of ion pairs, which is in the order of 10^{-18} seconds (4). These concerns remain in the realm of theoretical interest, since the ultimate result of the direct or indirect mechanism of radiation injury is the alteration of cellular morphology and function, expressed ultimately as radiation damage to the homeostatic state of the entire organism.

Radioprotective agents have no capacity for preventing direct radiation energy absorption by the aqueous intracellular environment and macromelecular structures, an exceedingly rapid mechanism of initial interactions. However, they can reduce indirect damage by facilitating the repair mechanisms leading to cell recovery, proliferation and repopulation of the radiation-induced depletion of cellular elements.

Macromolecular effects

Chemical changes to macromolecules induced by ionizing radiation, although extensively studied, remain an area of controversy, particularly in the field of identifying target sites. It has been well established that either direct or indirect deposition of radiation energy induces chemical alterations, progressing to changes in macromelecular morphology including the breakage of hydrogen bonds, macromelecular breaks and intramolecular cross linking, and intermolecular linking breakage. The combination of either of these factors may lead to irreversible functional alterations with the ultimate consequence being cell death (5). Radiosensitivity is a direct relationship with the state of the mitotic capacity of the cell (6) and the use of radioprotective agents must account for this factor, not only in the management of radiation casualties, but also in radiation therapy aimed at the protection of normal tissue, with the optimal radiation dose needed to exert a lethal effect on tumor cells, where radioprotection is much less achieved than in the mitotically highly active cellular population of the crypts of the small intestine or bone marrow (7). Most recent studies indicate that the radio-sensitivity of bone marrow stromal cells is lower than that of hematopoietic stem cells (8) clearly demonstrating the relationship between the kinetics of mitotic processes, that are governed by the macromelecular functional integrity and harmful effects of ionizing radiation in the living organism.

Radiation energy deposition in the living cell is much more likely to exert its harmful effects on the macromolecules than on the low molecular weight compounds, because the spatial configuration and size which renders the escape of macromolecules from encountering a radiation-induced event, much less probable three dimensional structure, cross-linking bonds, and the weak hydrogen bonds, easily disrupted by ionizing events, result in unfolding of secondary or tertiary molecular structures, with the ultimate loss of internal structure and function, with an effect on cellular proteins with a loss of cellular enzymatic activity. The absorbed radiation energy is not confined to the site of interaction, but can exert its effect in a distant part of a macromolecule, frequently affecting the weakest bond, or the side chain groups of amino acids in protein molecules, which act as electron traps, with similar consequences to hydrogen-bond breaks in macromolecules. DNA, not in the complex with proteins is more sensitive to radiation than a complexed molecule, with both histone and non-histone proteins. Although the RNA mechanisms of radiation injury are not as well understood, it is likely that similar mechanisms apply as those observed in DNA radiation-induced damage.

Genetic alterations of DNA are known to produce somatic mutations, resulting from the host of the macromelecular changes, including single and double strand breaks, cross--linking in both the intra and intermolecular stereochemical environment, purine and pyrimidine base degradation, which result in either uncontrolled dividing activity leading to mutagenic and teratogenic effects, or in cell functional and morphological nonviability (9).

Radiation damage to biologically critical molecules is exerted in half of the cases by indirect interactions, including the formation of ion pairs and free radicals. The lethal

effect is essentially the same as that in a direct radiation effect. Thus, the macromelecular response to direct radiation or free radical intermediates, results in the same alterations of cellular structure and function, including chemical changes in the bases, single and double strand breaks, base removal, intra and intermolecular cross-linking, and radiation death.

Effects on the cell membrane

Both direct and indirect radiation-induced changes, exert a variety of alterations on the cellular membrane by inducing structural and functional degradation of the membrane lipoproteins (10). The experimental evidence of the kinetics of radiation changes of the biological membranes has been gathered by an indirect analytical approach to overall cell dynamics. Gathering direct evidence is an exceedingly complex task owing to the rapid interaction of free radicals with the cell membrane, the effect of which occurs too soon to be attributable to macromelecular damage alone. The main mechanism of radiation-induced membrane injury appears to be peroxidation of the lipid layer by free radicals (11), leading to the formation of short chain fatty acyl metabolites and other components of lipid catabolism, with complex intermolecular interactions, including lipid to lipid and protein to protein cross-linking, aminoacid oxydation, protein denaturation and breakage of protein complexes. The membrane induced alterations at the cellular level, soon lead to the expression of radiation damage on the entire organism, by their adverse effects on homeostatic mechanisms via increased membrane permeability, release of membrane-acting biomediators, disintegration of lipoproteins and a frequently irreversible cycle of events which may lead to acute radiation syndrome, with a general malaise, hypotension, nausea, vomiting, hemorragic events and death in the event of super lethal irradiation.

Kinetics of radiation injury

The time scale of initial deposition of radiation energy to morphologic and functional tissue damage depends on various factors. Predominantly, radiation dose and expression of radiation injury may occur from picoseconds to hours after exposure (5).

The ultrafast reactions of a cellular response to radiation starts with the initial onset of chemical changes at 10^{-12} seconds after exposure. This is too rapid to allow any physicochemical kinetics interaction between radioprotective agents and the radiolytic products of water which accounts on average for 75% of the biological system. Although the precise mechanisms and kinetics of these interactions are still not completely understood, several steps of their sequence have been identified in the time scale of 10^{-9} seconds after exposure, when interactions occur between macromolecules and free radicals. This represents the time of competitive biochemical reactions between free radicals and radioprotective agents for the target sites at the critical macromolecules, which reactions commence at 10^{-7} and appear completed by 10^{-3} seconds. Radioprotective agents exert their initial action by 10^{-6} seconds, with a repair of chemical damage caused by free-radical induced oxidative injury of the macromolecules (12). The repair of chemical damage of the macromelecular structures is a slower process (10^{0}–10^{4} seconds) consisting of enzyme-mediated catabolic removal of the products of radiolysis of the aqueous intracellular environment (13). Thus, the kinetics of radioprotective agents appear strictly time-dependent and the optimal administration of a radioprotectant should ideally occur

before the exposure, since any delay, in the order of magnitude of milliseconds after irradiation will yield negative results.

Basic concepts of radioprotection

The physiological mechanisms governing the sensitivity of the organism to ionizing radiation have been considered as potential factors in the utilization of radioprotective agents. The alteration of the cellular water content was not proven a viable method since it would result in pathological intracellular changes leading to irreversible injury, in spite of theoretical justification of the aim of altering free radical formation. The oxygen effect determines the cellular radiosensitivity by the fact that it appears directly related to the degree of tissue oxygenation. Thus, the radioprotective agents that are in a reverse relationship to tissue oxygenation would enhance radioresistance of a given tissue (14). Extensive research has been focused on this radioprotective mechanism, with an impressive range of proposed radioprotective agents, identified as possessing a capacity of inducing local or generalized tissue hypoxia. Their mechanisms of action include: a) reducing oxygen supply to irradiated tissue via induced hemodynamic alteration, through inotropic or chronotropic cardiovascular mechanism; b) reducing hemoglobin-mediated transfer of oxygen to the tissue; c) inducing tissue hypoxia, by biochemical mechanisms; and d) inducing depression of the respiratory centers in the medulla oblongata (15, 16). The concept of hypoxia-induced radioprotection remains the most widely considered in the development of an extensive list of chemical, mediator and pharmacological radioprotective agents (17). However, a certain concentration of oxygen has to be present in the tissue for radioprotective actions to occur, since it is essential for the formation of some essential free radicals (18). Change of oxygen concentration from the level of atmospheric air to an oxygen free environment results in an increase in radio-resistance by a factor of two to three (19). The radiation damage exerted by a dose of 100 cGy in the atmospheric air would be produced by 200–300 cGy in an oxygen depleted environment for low LET radiations and would not apply to high LET radiations which deposit all of their energy over a short distance. Their ionization effect does not appear dependent on oxygen concentration, since their short track of ionization contains a central path of OH radicals surrounded by a wider zone of H radicals, the interaction of which results in formation of hydrogen peroxide. Thus, high LET radiation appears less effective in producing indirect chemical changes than low LET radiation where the ionization events are sufficiently distant from each other that their interactions are considerably reduced. Radioprotective agents capable of reducing the blood concentration of oxygen are confined to low LET radiation.

Basic concepts of cellular viability include the morphological integrity of all of the cellular components and their optimal functional interactions, optimal concentration and functional balance of various enzyme entities such as glutathione S-transferase, super-oxide dismutase, hydrolase, catalase, glutathione reductase, as well as mercaptan products, vitamins (C, E, beta-carotene) and water. Their quantitative relationship to the mechanisms of radiation injury is still insufficiently understood.

Mechanisms of radioprotection

Initial deposition of radiation energy in the biological systems occurs with such a rapid onset of its absorption by the aqueous endocellular environment and critical mac-

romolecules, that it remains beyond the reach of any radioprotectant to exert any inhibitory effect in this early stage of exposure. Thus, their effects remain confined to inhibiting indirect injury, to facilitating repair after either direct or indirect injury and to stimulating recovery. These effects are exerted by chemical and physiological mechanisms (20).

CHEMICAL MECHANISMS

Free-radical scavenging

The superoxide (O_2^-) and hydroxyl (OH) radicals produced from oxygen and radiation-induced hydrolysis of water are the main causative agents in radiation injury of macromolecules and membrane lipids. This concept was postulated over four decades ago as a theory of interaction between radioprotective agents and free radicals in the intracelullar environment.

Energy released by electron transfer to an outer orbit appears as radiation energy facilitating free radical formation. In its reaction with molecular oxygen it forms the superoxide radical, with potent oxidizing properties. Free radicals react avidly with biochemical entities in the cell causing severe damage to critical macromolecules and biological membranes, which in most cases are reversible processes if the repair mechanisms prevail (21). Their action is confined only to indirect effects of ionizing radiation.

Several thousand radioprotective agents tested so far belong, almost exclusively, to aminothiols and their derivatives. The particular attention of extensive research was concentrated on the compound S-2-aminopropyl-aminoethyl-phosphorothioic acid, codified as WR-2721, because of its controlled toxicity (22) and its effects in normal tissue protection (23). This substance was extensively studied in human trials (24) with reports of its favorable effects in both acute photon exposure (25), and in alleviating some of the consequences of chronic radiation effects (26). However, the practical implication of these effects has been questioned in view of the fact that the observed effects are confined to low LET radiation. The most recent reports, however, have described WR-2721 protection against irradiation with fission neutrons (27), with a demonstrated modification of neutron-induced effects, either in WR-2721/WR-3689 combination (28), or the combination with vitamin E (29), in reducing neutron effects on the hematopoietic system (30). The exact mechanisms of SH-compounds in free-radical scavenging, although postulated as aminothiols facilitating cellular repair (31), still remains an area of controversy (32), particularly regarding their auto-oxidative properties in chemical repair of the irradiated cell (33).

Hydrogen effects

The second most important mechanism of radioprotection on the molecular level involves the action of hydrogen atoms, either by process of ion transfer or donation (15). Free radicals, produced by either direct or indirect irradiation, include hydrogen atoms, hydroxyl-radicals, or an unpaired electron-induced aqueous electron which reacts in water by the formation of hydroxy ion (OH^-) and a hydrogen radical ($H^\bullet$), and can form hydrogen peroxyde (H_2O_2) by sharing their unpaired electrons. Superoxide (O_2^-) and hydroxyl ($OH^\bullet$) radicals are implied as major contributing factors in radiation-induced

alterations of macromolecules and membrane lipids, by the removal of their hydrogen atoms. Thus, radioprotective agents must replenish the hydrogen atoms in the biological targets by donating their hydrogen atoms. Hydrogen atom loss in a biological target molecule (RH) is induced by the absorption of radiation energy (hν), in an exceedingly rapid interaction in the order of magnitude of 10^{-9} to 10^{-11} seconds, in a direct,

$$R - H \xrightarrow{h\nu} R + H$$

or in an indirect reaction with free radicals.

$$OH\bullet + R\text{–}H \rightarrow R\bullet + H_2O$$

Radioprotectant action is exemplified by a hydrogen atom donation from a sulfhydril agent (P–H)

$$R\bullet + P - H \rightarrow R - H + P\bullet$$

in order to repair radiation-induced damage of the intracellular biochemical integrity.

Radical scavenging of reactive oxygen products, particularly superoxide and hydroxyl (OH) radicals has been a sustained area of experimental research (34). Most recent reports include a variety of substances with OH radical-directed scavenging properties, being studied with electron spin resonance spectroscopy, outlining a need for continued research in the area of radical scavenging therapeutic mechanisms (35). The model of reactive oxygen fixation, suggesting a possibility of DNA repair by hydrogen transfer from intracellular mercaptanes, implies oxygen-induced fixation of the radical peroxy-radical formation. While oxygen has been identified as a sensitizer to radiation injury by a free radical mechanism, recent reports have contributed to ongoing controversy on the concept of oxygen free radical scavenging of certain compounds in free radical therapeutic trials (36). Hydrogen transfer from the thiols to free radicals has been confirmed by modern techniques of pulse radiolysis, with a uniform conclusion that thiols remain superior to other agents in radiation protection, likely due to a weak covalent S–H bond, which provides for a hydrogen transfer-mediated process of radiation damage repair (20).

Radioprotectant direct binding

The main criticism of practical use of thiols in radioprotection, stems from their verified low concentration in the cell, after therapeutic dose administration. Therefore, chemical binding of radioprotective agents to radiation-vulnerable sites of critical biological molecules was advocated, in order to enhance the effectiveness of radioprotectants against free radical induced damage (37). Several theories of direct binding have been postulated, including an electrostatic bond of various radioprotectors with sugar-phosphate strands of DNA molecule, inhibition of unwinding of its double helix and stabilization of DNA secondary structure by reversible binding of polybasic radioprotective agents. Theoretical projections of the inhibition of radiation-induced strand breaks, unwinding and intermolecular reactions, with a possible facilitation of radiation repair, have not yet found their practical applications.

Mixed disulfide theory

Sulfhydril radioprotectors have been postulated to form reversible disulfide bonds between mercapto-groups of proteins and radioprotective agents (38). Mixed disulfide formation enhances the stability of proteins and enzymes whose morphological integrity, depending on disulfide and sulfhydril groups determines their functional capacity. Thus, the complex between a protein and a radioprotector yields a greater radioresistance, to either direct or indirect radiation damage.

PHYSIOLOGICAL MECHANISMS

One of the properties of a living cell is the capacity of its interaction with radioprotective agents by alterations in cell metabolism that may affect the ultimate effect of radiation injury. There are at least four physiological mechanisms experimentally proven as factors in mitigation of radiation damage, including endogenous production of radioprotectants, biochemical shock, hypoxia and hypothermia.

Endogenous radioprotectants

Chemical radioprotective agents have been used to initiate a displacement of natural endogenous radioprotectants present within the cell as mixed disulfide entities with proteins. This action has been explored mainly with thiol or disulfide radioprotectors. This theory known as the Non-protein Sulfhydril Release Hypothesis (NPSH) postulates the release of endogenous sulfhydril compounds (glutathione) resulting in radioprotection by enhancing free radical scavenging and hydrogen transfer mechanisms. This theory is based on the experimental evidence of a sulfhydril compound's capacity to increase cellular contents of NPSH resulting in an enhanced radioprotective capacity (39). Among several endogenous substances with radioprotective action, particular prominence was established for glutathione (GSH). This tripeptide, naturally present in the cell, provides resistance to peptidases, which are actively replenished by the cell in the event of its reduction. This mechanism results in an increase in the radioprotective capacity of the cell. Another substance, which has been widely studied is Vitamin E, experimentally proven to possess an inhibitory effect on free radical mediated reactions including lipid peroxidation *in vivo* (40). Thus, the effect of exogenous and endogenous radioprotectants (e.g. thiols and disulphides, as compared with glutathione) represent a mechanism involving chemical and physiological factors.

Biochemical shock theory

Bock and Van Canegham reported in 1968 that large doses of SH or SS compounds produce a sequence of intracellular reversible biochemical changes, as a cell adaptation mechanism to a large concentration of thiols (41), resulting in the formation of disulfide compounds in a reaction between radioprotective thiols and sulfhydryls in the cellular membrane. The peak event results in biochemical shock with a consequence of morphologic alterations of mitochondria endoplasmic reticulum, lysosomes and other cytoplasmic organelles, with subsequent functional changes on both the cellular and organ level. A complex cascade of homeostatic changes that follow the onset of biochemical shock include redox state changes, facilitated glycogenolysis in the hepatic parenchyma, reduce

glycolytic processes, inhibition of synthesis of DNA with delayed mitotic cycle and cell division, as well as reduced protein synthesis. The exact mechanism of biochemical shock-induced radioprotection remains unclear, but the evidence abounds on the sulfhydril compounds' effects in enhanced radioresistance and warrants further investigation (42).

Radioprotective effects of hypoxia

Oxygen concentration in the cell is one of the most effective factors in modifying radiation damage. Hypoxic range facilitates radiation survival, while an increase of oxygen concentration from 0 mmHg to 30 mmHg at 37 °C results in an increase in cellular radiation death (43). The radiation protection capacity of oxygen is LET dependent, thus requiring oxygen depletion to enhance its radiation protection effect.

While the radiation dose ratio required in the different concentrations of oxygen is constant in producing the same biological effect, the relationship between LET and OER (oxygen enhancement ratio) in modification of radiation damage has not been fully understood. It is postulated that oxygen interacts with free radicals to produce hydrogen peroxydes ($H_2O^{\cdot}$) by the radiolysis of water, and organic peroxydes in reactions with proteins, lipids and macromolecules, enhancing the indirect effects or radiation injury and exerting an inhibitory effect on molecular repair.

Hypoxia produces a radioprotective effect by decreasing the available mechanism of interaction with free radicals in an endocellular environment. Hypoxic conditions can be achieved in living tissue by several mechanisms, including cardiovascular chronotropic and inotropic mechanisms, reducing hemoglobin oxygen-carrying capacity, producing biochemical-induced tissue ischemia, increasing tissue consumption of oxygen and causing inhibition of respiratory centers in the medulla. Certain pharmacological agents may affect cellular and tissue perfusion (19), while the demonstrated effect of sulfhydril compounds in oxydative processes of thiols cause oxygen consumption, enhancing the radiation protective effect. At present, hypoxia is considered one of the most important factors inducing an increase in cellular radioresistance (14), and remains the most widely used method of radioprotection acting synergistically with radioprotective agents used by either administration of chemical and pharmacological agents or intracellular induced radioprotectors (44).

Effects of hypothermia

The experimental research on the effects of hypothermia in radioprotection has been conducted for over four decades, with a working hypothesis of cellular repair mechanisms being more complete and effective at lower body temperatures (45). The postulated mechanism included the concepts of completeness of the repair mechanisms in a reduced metabolism environment (46) and a reduced radiosensitivity and slower onset of intracellular alterations following radiation energy absorption, in the reduced thermal environment of living tissue (45). This has been a known mechanism in radiotherapy, as a factor producing ischemia with a synergistic radioprotective effect.

Contrary to the radioprotective effects of hypothermia, there has been ample evidence of increased radiosensitivity induced by hyperthermia. This phenomenology is less dependent on metabolic factors, such as pH, oxygen and nutritional status, than tissue response to ionizing radiation or chemotherapy (47).

EVALUATION OF RADIOPROTECTIVE AGENTS

The most common methods for the assessment of a radioprotectant's biological efficiency include mammalian survival curves, quantisation of the regeneration nodule in the spleen of irradiated mice and the evaluation of cell survival *in vitro* by using tissue cultures.

Mammalian lethality curves involve the use of laboratory mice which provides a conventional method, because of practical advantages of a mouse model. Experimental mice are available at a low cost in a variety of standardized breeds, requiring minimal space and care conditions, as compared with rats or rabbits and presenting an animal population with an adequate comparative criteria to other species from a viewpoint of radiation vulnerability and protective mechanism (48). The superiority of a mouse model in radioprotection research has been well established in comparison to species other than rodents, including dogs, pigs and monkeys (49). There are many factors that can determine the outcome of a survival study and they have to be considered before the use of any given animal mode (50). The main factors include the toxicity of the investigated substance, route of administration, dose and dose rate, preexposure time of the radioprotectant before radiation type, rate and LET of radiation (51). The assessment of a radioprotective substance is further analyzed by comparing control and irradiated animal's survival curves or by the calculation of a dose reduction factor (DRF) for a particular radioprotectant (52). This quantitative parameter is more complex to determine than survival studies alone, and this is the reason for the primary use of survival curves analysis as a screening method for the evaluation of a radioprotective substance, followed by the DRF method when more definitive quantisation is required. This technique implies the exposure of non-treated and treated mice to several dose levels of radiation with evaluation of survival after 30 days and an LD_{50} is established for the control group and radioprotectant treated group. The DRF value is calculated by dividing $LD_{50/30}$ of the unprotected group with $LD_{50/30}$ of the protected animals. A DRF of 2 is considered a therapeutic efficiency of twice as high radiation survival of treated versus untreated subject or experimental animals. Radioprotective effect of WR-2721 for hemopoietic death in mice has been established as a DRF of 3. This method has been found to be of considerable use in extrapolating the data obtained on experimental animals to the human use of radioprotectants.

Recovery from radiation injury, is adequately assessed by the count of macroscopic nodules in the spleen which have been found to be inversely related in their number to the radiation dose (53). Radioprotective agents have been shown to increase the number of identifiable nodules after irradiation. This method, although performed by a similar technique as mouse survival curves, and contains an end point of 10 days for the animal sacrifice after irradiation. The spleen is removed by dissection, processed by histological techniques and the nodules are counted and calculated for DRF between the control and treated groups. This method is superior to that of the study of survival curves and reduces the time for screening the efficiency of the tested substance.

CURRENT CONCEPTS ON RADIOPROTECTANTS

Among several thousand of the radioprotective substances tested in experimental and clinical trials, with a remarkable structural and functional diversity, practical and simplified classification in aminothiols and nonaminothiols offers a pragmatic approach to a

review of this complex field of their pharmacodynamics. Their current importance in radioprotection is based primarily on the DRF properties derived from $LD_{50/30}$ data established on the mice model.

The aminothiol group includes cysteine, beta-mercaptoethylamine (MEA), cystamine, amino-ethylisothiouronium (AET), WR compounds, mercaptopropionylglycine and glutathione. Nonaminothiols, albeit an oversimplified classification, include sulfur-containing compounds, cyanide derivatives, chelating agents, metabolites, hypoxia-inducing agents, immunomodulators and antioxidants. Their pharmacodynamic and radioprotective properties remain an area of active research in view of the practical concerns of their potential use in the event of tactical deployment of nuclear weapons or in the event of nuclear power plant and other industrial accidents (54), or in incidents involving medical (55) and research (56) use of ionizing radiation. The potential use of radioprotective agents may not be strategically limited to the vicinity of a major nuclear accident since final deposition in the soil is preceded by airborne quantities and patterns of radioactivity migration that can be determined by the most recent methods of global surveillance of radiation risks (57), and by risk estimation using bioindicators (58). The exact and realistic scope of the broad use of radioprotective agents still remains unanswered and warrants a thorough investigation of its practicality, risks and benefits.

1. AMINOTHIOLS

This group of agents represents the most widely studied category of radioprotective compounds, with demonstrated superiority to all other agents. All chemicals in this class are the analogs of cysteine or beta mercaptoethylamine. Their efficacy in the management of radiation injury is primarily based on $LD_{50/30}$ derived DRF values (59).

Cysteine

The radioprotective properties of this agent have been reported by *Patt and co-workers* in 1949 with experimental evidence of the statistically significant survival of mice lethally irradiated with x-rays. Its DRF of 1.7 was achieved after an intravenous administration of 1,200 mg/kg prior to x-ray exposure (60). The radioprotective capacity was found to be dose-dependent, with no effect after oral administration, and a modest effect after intraperitoneal application (61). Current reports indicate the increase of survival in whole-body irradiated rats treated with combined cysteine and vitamin E therapy (62). The mechanism of radioprotective action of cysteine is still a matter of controversy, with recent concepts of cysteine-induced effects of oxidizing substances, such as superoxyde anion ($O_2^{\bullet}$) and hydrogen peroxyde (63).

Beta-mercaptoethylamine and cystamine

One of the decarboxylated compounds of cysteine, beta-mercaptoethylamine (MEA) has been identified as an agent with significantly greater radioprotective properties than cysteine (64), providing the same DRF of 1.7 in a dose of 150 mg/kg as cysteine in a dose of 1200 mg/kg, after i.v. administration. The toxic dose for MEA was reported to be over eight times less than that for cysteine (LD_{50} 200 mg/kg vs. 1700 mg/kg, respectively). Oral administration of MEA, although unsatisfactory in overall radiation protective effect, has been slightly effective as compared to a total lack of any effect with cysteine, whereas an intraperitoneal administration of MEA yielded a better radiopro-

tective effect than cysteine (59). These properties have established MEA prominence as a standard agent as a reference drug both for design and effectiveness evaluation of other radioprotective agents.

In one of the MEA derivatives, its disulfide form - cystamine provided a major advantage by its effectiveness after oral administration, retaining similar radioprotective properties as MEA after parenteral use, with an LD_{50} of 220 mg/kg as compared to a similar value for MEA of 200 mg/kg. Protective doses of MEA and cystamine were found to be the same for both agents (150 mg/kg) with DRF of 1.7. These agents have emerged as major modulators of radiation-induced damage and future research is warranted to establish criteria of therapeutic strategies in disorders involving a role of free radicals (65).

Amineothylisothiouronium (AET)

This aminothiol compound contains a urea group responsible for the effects of the sulfur group, thus being structurally different from both MEA and cysteine. Its effectiveness is provided by its ability to form free mercaptan compounds by rearranging at the physiological pH and producing mercaptoethylguanidine (66). A distinct advantage of this compound is its effect after oral administration, which provides a prolonged radioprotective effect in mice of six hours after a single dose. LD_{50} of AET is 480 mg/kg, with the protective dose of 400 mg/kg and DRF of 2.1, with the advantage of a protracted effect. The most recent reports have demonstrated a significant radioprotective effect of AET on stromal cells in the bone marrow with a well documented capability of fibroblast, macrophages and reticular cells to provide radiation recovery of hematopoietic stem cells (8).

Although cysteine, MEA and AET provided the foundation for the extensive research of aminothiol compounds in radiation protection, their use in human therapy has been considerably limited by their toxicity and narrow therapeutic range. Numerous modifications of their structural characteristics have been found to enhance their functional efficacy, including separation of the sulfhydril group from their basic amino groups, blocking sulfur with a group that can produce free thiols after metabolic alteration resulting in reduced toxicity, modified pharmacodynamics and enhanced radioprotective properties (67). These modifications have resulted in the development of superior radioprotective compounds of the WR series.

Aminothiols of the WR-series

The aminothiols of the WR series have been developed by the US Army at Walter Reed Research Institute with significant improvement in radioprotective therapy by the advent of S-2-(3-aminopropyl- amino)ethylphosphorothioic acid, designated as WR-2721. This compound is an analog of MEA with a phosphate on the thiol group and propylamino group on nitrogen. The generic designation of ethiofos in the United States or gamafos in the former Soviet Union has not advanced to common use as the identifying name of this compound. The synthesis of this agent presents a significant milestone in radioprotective agents pharmacology because of its lower toxicity, improved radioprotection capacity and overall effectiveness when compared with other preceding agents. Its DRF of 2.7, LD_{50} of 950 mg/kg and protective dose of 500 mg/kg, together with intraperitoneal administration and effectiveness in a variety of species from mice to humans, have placed this agent in a category exceeding the properties of MEA, with the particular advantage of its radioprotective duration of over three hours. Similar to the other aminothiols,

WR-2721 demonstrates a minimal effect after oral administration (68). This agent provides significant radioprotection to most of the normal tissues, except for the central nervous system due to its lack of transfer across the blood-brain barrier. In experimentation on the rat model three of the agents of the WR series (WR-2721, WR-77913 and WR-3689) demonstrated a DMF of 1.6. The protective effect is best exerted in the immune and hematopoietic systems.

Poor clinical tolerance of WR-2721 and other sulphydril radioprotectors has been demonstrated in clinical trials (69). This has prompted studies of the synergistic action of zinc salts in combination with WR-2721 in facilitating radiation protection. This effect has been recently reported as selective radioprotection therapy to obtain effects at a lower toxicity with improved therapeutic ration than with WR-2721 alone (70). The toxicity for WR-2721 alone was found as LD_{50} of 732 mg/kg, whereas the addition of 20 mg/kg of zinc aspartate reduced the LD_{50} to 562 mg/kg. Earlier studies have reported the synergistic effects of zinc aspartate with other thiol compounds in radiation protection (71). The postulated mechanism of this combined therapy was suggested as a stabilization of endogenous and exogenous thiol complexes, while the hypothesis of zinc induced metallothionein radioprotective effect (72) was recently challenged by the evidence that metallothionein is induced relatively late after zinc administration (70). One of the adverse effects of combined zinc aspartate and WR-2721 therapy may increase the toxicity of sublethal doses of WR-2721. Further studies on synergistic protection versus synergistic toxicity will add to its clarification.

The pharmacodynamic properties of WR-2721 are based on dephosphorylation by phosphatase enzymes, producing a free thiol WR-1065, which is metabolized to a symmetrical disulfide WR-33278. Further metabolic pathway remain unclear, although several studies have attempted to identify and quantitate WR-2721 metabolites (73). Plasma clearance of WR-2721 was identified as a biphasic curve with an early fast phase of initial distribution ($t\ ^1/_2 < 10$ min) and a slow elimination phase ($t\ ^1/_2 > 60$ min), as studied by radiolabelled compounds (74).

Organ distribution of WR-2721 identified the liver, kidney and salivary glands as the sites of highest accumulation, followed by the intestine and spleen, with a minimal concentration in the central nervous system and solid tumors (75). Concentration of the drug demonstrated no correlation with its radioprotective effects. The high renal correlation of WR-2721 provides a weak radioprotection, while the bone marrow in which the radioprotective effect is most pronounced does not concentrate a high percentage of the administered agent. Similar findings apply to the immune system. Nevertheless, a general concept appears valid, that the tissues with a high concentration of WR-2721 are at least moderately protected, while low or no protection is observed in tissues with low concentrations of WR-2721 (76).

The radioprotective effects of WR-2721 for normal tissues do not apply to solid tumors. This may be the consequence of a low uptake of WR-2721 by neoplastic tissue, as demonstrated in studies on mice (74). Uptake of the agent by normal tissues rapidly rises above the serum levels with a maximum concentration at 15 minutes after administration (75), while uptake in tumors represents a slow process, not exceeding serum levels over 90 minutes after application and always remaining lower than in normal tissues. The maximum therapeutic effect of WR-2721 is achieved 15–30 minutes after mechanisms in normal tissues are mediated by the active transport against a concentration gradient (76), whereas the tumor uptake occurs as a consequence of the diffusion process, and depends on tumor cell membrane (77), tumor vascularity (23) and the hydrophylic properties of the agent (78). The mechanisms of pharmacokinetics of WR-2721 still remain poorly

understood and current international trials are being implemented to evaluate the optimal use of WR-2721 as an additional modality for tumor radiotherapy in experimental and clinical trials with: Phase 1 involving maximum tolerated doses; Phase 2 to evaluate maximum radiation dose in different organs after WR-2721 administration; and Phase 3 involving the therapeutic effects of the agent (79).

A considerable limitation in WR-2721 therapeutic use are its side-effects, including nausea, vomiting, hypocalcemia and hypotension, rendering its practical use severely limited to a controlled clinical environment. Its use with other radiosensitizing agents has been studied with various synergistic radiosensitizers specific for tumor tissue, such as azoles, which increase radioresistance by causing vascularity-moderated hypoxia. The results, however, have not proven promising.

The well documented radioprotective properties of WR-2721 against gamma radiation which suggest its adjunct role in cancer therapy (29), were considered in exploring its effects against neutrons. In recent experimental work on fission-neutron-irradiated mice the animals were given intraperitoneal injection of WR-2721 prior to radiation exposure with the report of a beneficial effect against neutron-induced delayed death. The mechanism of WR-2721 action in moderating neutron-induced carcinogenesis remains unanswered (27).

Behavioral and radioprotective effects of WR-2721 have been recently compared with a S-2 (3-methylaminopropyl)aminoethylphosphorothioic acid (WR-3689) in rats exposed to a nonlethal (5 Gy) or lethal (10 Gy) Co-60 irradiation. Neither WR-2721 nor WR-3689 produced any significant short-term protection against radiation-induced performance decrements (80).

Radioprotective effects of WR-3089 are significantly enhanced if given with vitamin E prior to irradiation (29). More recent WR-compounds, including WR-347, WR-1065, WR-2529, WR-2721, WR-3689, WR-44923, WR-151327, WR-109342 and WR-168643 have been assayed for pharmacological toxicity and hematopoietic lethality in mice after total-body irradiation with fission neutrons. While intraperitoneal administration provided no significant difference in dose modification factors, oral administration of WR-168243 provided best radioprotection with a DMF of 1.51 (81).

2. IMMUNOMODULATORS

Cell-mediated immune response ensures at the contact of an antigen with T-lymphocyte, resulting in cell-mediated immunity (CMI), similar to the B-lymphocyte mediated humeral response. Activated lymphocytes retain the capacity of responding repeatedly for a long time to the original antigen.

Cell-mediated response is more radioresistant than humeral response. Both mechanisms are interdependent. The cells that are antigen-activated at the time of the irradiation are less radiosensitive than non-activated cells. Thus, unsensitized cells are more radiosensitive (T and B lymphocytes) and the antigen-stimulated humeral response is suppressed after irradiation with moderate doses of 200–400 cGy. Final recovery from ionizing radiation is ultimately dependent on the recovery of pluripotent stem cells (PPSC). Ionizing radiation adversely affects both the humeral response and the more radioresistant cell-mediated response. The T-cells produced lymphokines stimulate a non-specific immune response, which decreases after irradiation even in the presence of surviving T-cells. This radiation-induced alteration of immune competency involves both specific and non-specific immunity, determining the survival of the organism, because of decreased defense

mechanisms against infection, hemorrhage, anemia, hypovolemic shock and death, depending on the radiation dose, ranging from reversible hematopoietic-system alterations to pancytopenia. Hematopoietic radiation syndrome can be modified by agents that facilitate the processes of hematopoietic recovery, including various natural and synthetic substances.

Natural immunomodulators

Several naturally occurring substances with demonstrated radioprotective properties include interferons Bacillus Calmette-Guerin (BCG) (82), Corynebacterium Parvum (83), Glucan, endotoxins, Interleukin-1 and peptydes of the thymus (84). Hematopoietic dose levels (200–1000 cGy) of ionizing radiation are affected by these substances, with various degrees of recovery. The prominent substrates of this group are represented by bacterial endotoxin and glucan.

Endotoxins. This group of immunomodulators are lipopolysacharides derived from the cell walls of gram negative bacteria, that possess toxic, pyrogenic and stimulatory effects. Radioprotective actions of microbial endotoxins concern their increase in immune response, either by their adjuvant action after systemic administration or after local injection with other antigens. Endotoxins may stimulate the synthesis of immunoglobulins and enhance phagocytosis by macrophages. Although their radioprotective mechanism is not fully understood, it is postulated as their capacity of nonspecific polyclonal activation of B cells as well as their capacity to enhance the specific antibody responses by their effects on T-cells. Endotoxins have been studied as radiation-protective agents in different animal species, with a well documented increase of radiation survival (85) and DRF ranging from 1.2 in mice to 1.4 in sheep and dogs (86). Their effect is optimal if applied before radiation exposure, however some of their effects of the facilitation of radiation repair have been observed in rodents up to 24 hours after irradiation with 600 cGy (87).

Glucans. Certain yeasts, such as *Saccharomyces* contain a potent immunomodulator that has been isolated from its inner cellular structures. This B-1, 3-linked polyglycan enhances hematopoietic and immune responses in either particulate (Glucan P) or soluble form (Glucan F). The source of these polysacharides is in the cell walls of *Saccharomyces cerevisiae* and glucan polymerization is catalyzed by the cell membrane enzymes (88).

While Glucan P intravenous administration has been associated with severe side-effects, Glucan F is well tolerated even in high doses in various animal species (89), including rodents, dogs and primates, when administered prior to radiation exposure, but is also effective if given after irradiation (90).

Synthetic immunomodulators

Azimexon. This agent which has been recently synthesized (compound BM-12531) has been demonstrated as a potent radioprotective agent, and increased the percentage survival in 500 cGy irradiated mice from 56 to 100% if applied prior to radiation exposure, and prolonging a mean survival time from 17.3 to 29 days. Its radioprotective effects are sustained even when administered after irradiation (91).

Levamisole. This agent has been used for over three decades as an immunomodular available for oral administration, under the commercial name of Ergamisol (levamisole hydrochloride). It was reported that this agent provides significant radiation protection (92). Although its mechanism of action is not known it is postulated that its function

involves free radical interactions as well as antioxydant properties. Levamisole use has been associated with severe and sometimes fatal agranulocytosis, which necessitates comprehensive hematological monitoring during its administration. However neutropenia is reversible following discontinuation of therapy (93). Levamisole appears to restore a compromised immune system (94) and does not elevate the immune response to a higher level than before immunocompromise (95).

Serotoninergic agents. Among several serotoninergic drugs (96), including 5-hydroxytryptophan, 5-methoxytryptamine (mexamine) and 5-hydroxytryptamine (serotonin), the leading radioprotective properties have been demonstrated by mexamine. The recent reports of Russian investigators indicate mexamine radioprotective effects in mice after fractionated irradiation (97), reduced radiation injuries during embryogenesis in total-body irradiated mice (98), and increased survival rates in total-body irradiated mice (99). However, it failed to show modification of long-term radiation effects with either life span or tumor incidence in rats (100). The effects of mexamine on decrease of intestinal radiation death was not demonstrated in a single agent therapy in mice (101). Combined use of oral mexamine and bone marrow shielding proved efficient in the radioprotection of dogs irradiated with 400 rad high energy photons during a space flight (102).

Although the use of mexamine has not demonstrated a consistent radioprotective effect as a single agent therapy (100), it has shown relatively high radioprotective effectiveness in mice when used in combination with gutimine and ethyrone (103). The development of multicomponent radioprotective preparation has been studied in a mathematical model using the data of cystamine, thiophosphates, ethiron, gutimine and mexamine, with the optimization of their radioprotective effectiveness and toxicity (104). The most effective action of mexamine has been reported in the radioprotection of the skin, where it demonstrated the reduction of radiation injury by over 50 percent (105).

Diethyldithiocarbamate (DDC). This agent has been recently approved for clinical use, in August of 1992. It contains sulfur groups and appears to exert its radioprotective properties through free-radical action mechanisms. It also possesses chelating agent properties and may act as a radiosensitizing agent by the inhibition of antioxidant enzymes (superoxide dismutase). Its therapeutic advantage is its radioprotective action after radiation exposure (106).

3. ANTIOXIDANTS

Any substance that can react with free radicals can be considered a free radical scavenger. Molecules with such properties react with free radicals to neutralize their action before they can exert adverse effects to the cells after radiation exposure. Biochemical defense mechanisms are a part of all living systems developed in the process of evolution and allow unchallenged survival in the biosphere that is constantly exposed to ionizing radiation from cosmic and terrestrial sources of radiation.

Free radicals exert their effects in the biological system by toxic effects on critical biological molecules, with the consequent pathologic alteration of cells. A mechanism of biochemical oxidant defense counteracts free radical concentration in the cells, with a consequent protective effect against ionizing radiation. Two major categories of radioprotective agents in the group of antioxidants are best represented by free radical scavenging low molecular weight compounds and the enzymes that neutralize the adverse effects of free radicals.

Radioprotective effects of hypoxic gas mixtures have been enhanced after administration of antihypoxic agents, in the experiments on mice, by affording a better tolerance to hypoxia (106).

Low Molecular Weight Compounds – Vitamins

Vitamin E. Alpha-tocopherol penetrates the cell membrane owing to its liposolubility and demonstrates a scavenging interaction with various species of free radicals (107), with a pronounced effect of protective action of the membrane lipid layers against peroxidation damage (108). Vitamin E plasma concentration has been extensively studied in radiation exposure before bone marrow transplantation, with recent reports of its radioprotective effects in combined radiation and chemotherapy (109).

Vitamin A. Another liposoluble agent, beta-carotene has been identified as a potent free-radical scavenger, with the capacity for inhibitory effects on peroxidation damage of membrane lipids. Liposoluble vitamins have been used in individual drug trials, and in the combination of ascorbic acid, beta-carotene and alpha tocopherol, with recently reported prevention of tissue damage exerted by reactive oxidants (110). Its therapeutic properties have been studied as a preventative agent for free-radical induced tissue alterations in malignant disease (111), atherosclerosis and radiation damage (112) with a recent clinical trial of the use of beta-carotene in correcting the immunosuppressive effects of radiation exposure of Chernobyl children (113). The demonstrated immunomodulating antioxidant effects of Beta-carotene warrant further research on its effects on immune function-induced radioprotection (114).

Vitamin C. Ascorbic acid has been postulated as an agent with potent free radical scavenging properties, as a sinergistic effect with vitamin E. The mechanism of action appears to be associated with its antioxidant function in reactions with vitamin E radicals and the restoration of alpha-tocopherol to its active reduced state (112). The effects of ascorbic acid are limited to the aqueous compartmental environment because of its hydrosolubility.

Glutathione. Glutathione (GSH) is a tripeptide molecule composed of the amino acids, glutamate, glycine and cysteine. It is an abundant protein sulfhydryl substance present in millimolar range in living tissue, where it appears a part of various metabolic functions. GSH is an integral part of cysteine metabolism which is a known radioprotective substance of the aminothiol group. The sulfhydryl group of cysteine is the acting component of its molecular radioprotective action. It is a water soluble substance with a potent free-radical quenching reaction in aqueous medium. GSH in living tissue is present in the form of reduced thiol (95 percent) with only five percent in the oxidized form of glutathione disulfide (GSSG), with a conversion catalyzed by glutathione reductase. GSSG is a toxic substance and its conversion to GSH via glutathione reductase occurs by the NADPH mechanism. GSH radioprotective properties are well demonstrated and postulated as a free-radical mediated radioprotection (115).

Enzymes

Glutathione Peroxidase. Glutathione radioprotective properties in free radical defense action are associated with glutathione peroxidase, the activity of which is dependent on

the selenium ion. This enzyme is interdependent with NADPH reaction, and its radiation protection effect has been well demonstrated in the reaction of converting H_2O_2 to water through the oxidation of GSH and of converting lipid peroxidases to unreactive short chain fatty acids (116).

Catalase. This enzyme also removes H_2O_2 to water, producing its lower tissue concentration in synergistic action with glutathione peroxidase, thus reducing the potential of H_2O_2 producing more reactive species of free radicals. Both catalase and glutathione peroxidase act with superoxide dismutase reducing the concentration of superoxide anions to H_2O_2 and oxygen. Three active forms of catalase have been identified in eukariotic and prokariotic cells with their action identified by their copper, zinc or manganese ion.

OTHER RADICAL SCAVENGING AGENTS

Repair of tissue damage by the free-radical-scavenging substances includes several recently reported compounds, including disaccharide mannitol and dextran (117). The controversy over the dextran mechanism of action involves its organ preservation via the mechanism of improved microcirculation and remains an area of current research. Free radical scavenging mechanisms which have been earlier implied in the pathogenesis of neuron degeneration in certain neurological disorders have recently been reconsidered by evidence that circulating glutathione peroxidase, reductase, transferase, superoxide dismutase and catalase do not have an effect on the mechanisms of dopamine neuron regeneration (118).

Current multidisciplinary research on free-radical scavenging agents is considerably improved by the utilization of highly advanced technology, including the most recent improvements in the evaluation criteria by the electron spin resonance spectroscopy (119). New agents are being identified and studied (120), including the free-radical scavenging activity of papaya extracts (121), carnosine (122), thiol-containing angiotensin enzyme inhibitors (123), some of the new flavonoid complexes (124), several compounds from the eliptiane series (125), as well as free-radical scavenging substances isolated from various bacterial species. Recent experimental evidence indicates promising radioprotective effects of carazostatin, isolated in Japan from *Streptomyces* species chromofuscus (126).

New compounds including thiocarbamides (127), calcium antagonists (128), mercaptoacetamidine (129) and some benzodiazepine compounds, have demonstrated some radioprotective effects, with the reports of diltiazem effects on radiation survival in mice after parenteral administration (128). Recent reports on the radioprotective effects of synthetic antioxidants of dihydropyridine series (130) and studies of the radioprotection of hematopoietic system by the prostaglandin synthesis inhibitors (131) provide a sustained contribution to the search for the optimal radioprotective agents. Their practical use in radioprotective therapy remains to be further ascertained in experimental and clinical trials.

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Sažetak

RADIOPROTEKTIVNA SREDSTVA U MEDICINI

Odnedavna smanjena vjerojatnost strateške primjene nuklearnog oružja smanjila je i opasnost od masovnih ljudskih gubitaka kao posljedice ionizirajućeg zračenja. Time se briga oko liječenja radijacijskih sindroma svodi na realnije područje planirane primjene zaštite od zračenja, u industriji, tehnologiji, znanosti i medicini. Skorašnja iskustva o posljedicama nesreća u nuklearnoj industriji, kao i neriješeno pitanje radioaktivnog otpada, postavljaju složeno pitanje pred medicinu i znanost o smanjenju štetnih posljedica zračenja u povećanoj primjeni nuklearne energije.

Kako nije moguće predvidjeti nuklearnu nesreću, zaštita od njezinih posljedica prelazi okvire medicinske znanosti. Stalna pozornost o svim pojedinostima primjene nuklearne energije ima biti striktno kontrolirana prema najstrožim kriterijima tehnologije. Time se medicinska zaštita od zračenja usmjeruje na liječenje i na zaštitu organizma u široku području od akutnih sindroma radijacijske bolesti do kroničnih promjena na staničnoj ili molekulskoj razini, uzrokovanih dugotrajnim izlaganjem manjim dozama zračenja ili internom kontaminacijom. Sadašnja multidisciplinarna suradnja na području zaštite od zračenja uključuje široko područje temeljnih i kliničkih istraživanja, od subatomskih mehanizama, stvaranja slobodnih radikala, makromolekularnih i intracelularnih promjena. Na razini fizioloških i biokemijskih promjena homeostaze, temeljna se saznanja prenose u područje kliničkih istraživanja i liječenja radijacijske bolesti u zdravstvenim ustanovama.

Radioprotektivna sredstva unatoč intenzivnom proučavanju u više od protekla četiri desetljeća još nisu dovoljno upoznata da bi medicinskoj znanosti pružila sve potrebne elemente koji se traže od lijeka za primjenu u praksi. To uključuje učinak, toksičnost, raspoloživost, specifično djelovanje i podnošljivost.

Članak razmatra sadašnje stanje zaštite od zračenja u različitim oblicima medicinske primjene i naglašava nužnost nastavljanja istraživanja o liječenju ozračenih osoba u svijetu koji na kraju ovog tisućljeća sve više ovisi o nuklearnoj energiji.

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Ključne riječi: aminotioli, antioksidansi, imunomodulatori, ionizirajuće zračenje, kemijsko-molekulski mehanizmi, lipidi u membrani, makromolekule, proteini