Pharmacological approaches to the correction of radiation-induced endothelial dysfunction

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INTRODUCTION

The effect of radioactive radiation on biological objects was classically considered in terms of mutagenic, oncogenic, and teratogenic effects. However, clinical experience has created prerequisites for studying the problem of the ionizing radiation contribution to the etiology and pathogenesis of cardiovascular pathology. Exposure to radiation can occur in manmade disasters, work on nuclear power plants, submarines, rent offices, etc. It is especially important that ionizing radiation is widely used in the treatment of cancer diseases that affect all age and social groups.

At the end of the past century, the analysis of the long-term effects of people exposed to radiation during large-scale manmade disasters such as the accident at the Chernobyl nuclear power plant. In all these cases, the relationship with cardiovascular diseases, and mainly with atherosclerotic vascular lesion, was revealed. At the same time, as with classical atherosclerosis, many researchers assign a key role to endothelial dysfunction.

It is known that the endothelium is the largest endocrine organ and its functional activity is associated with the regulation of hemodynamics, coagulation, local inflammation, angiogenesis, and many other processes. Endothelial dysfunction leads to hypertension, disruption of normal tissue perfusion, the appearance of a tendency to thrombosis, and pathological changes in the anatomy of the vascular network. Changes in the spectrum of molecules secreted and expressed by the endothelium and a violation of its barrier function ultimately lead to infiltration of the vascular wall with atheromatous masses and the formation of atherosclerotic plaques.

The pathophysiological basis of endothelial dysfunction induced by radioactive radiation is associated with the activation of free radical oxidation, activation...
of pro-inflammatory immunological cascades, damage to the endocrine system, and disruption of vascular wall cells at the level of genetic and epigenetic regulation. At the same time, systemic changes associated with multiorgan disorders and massive release of a wide range of humoral factors are summed up with the direct effect of ionizing radiation on endothelial cells and their microenvironment.

SYSTEMIC RADIATION EXPOSURE AND ENDOTHELIAL DYSFUNCTION

The impact of a stressing factor of extreme intensity leads to the formation of systemic maladaptation of executive and regulatory systems. These processes develop to a certain extent stereotypically in accordance with the concept of stress Selye. At the same time, initially, the mobilization of the adaptation resources of the body and the activation of stress-limiting systems, which then give way to decompensation with the development of functional and structural disorders that form pathological cascades.

Typical changes at the cellular and subcellular levels, which are manifested in the disorganization of organelles, disruption of the structure of deoxyribonucleic acid (DNA) and chromatin, as well as damage to the plasma membranes, lead to disruption of the processes of cellular life support. Genotoxic stress induces the development of the so-called secretory phenotype associated with aging (from the English senescence-associated secretory phenotype). In essence, this means that the cell is prone to hyperproduction of a wide range of pro-inflammatory cytokines and chemokines, matrix proteases, and growth factors, and is also in a state of oxidative stress.

DIRECT DAMAGE TO ENDOTHELIOCYTES

When exposed to intense radioactive radiation on the cells, the most likely target for radiolysis is H₂O, as the most common molecule in the cell. The hydroxyl radical (OH) formed from it causes damage to DNA and other macromolecules [Figure 1]. Genotoxic stress at the same time leads to effects equivalent to the natural aging of cells, which is accompanied by a decrease in antioxidant potential and even greater activation of oxidative stress. Interestingly, the induction of cellular aging of endotheliocytes is considered an important mechanism for the suppression of tumors since it stops the growth of genetically damaged cells with critically shortened telomeres or permanent DNA damage and also prevents angiogenesis. Studies on cell cultures have shown that radiation (2–10 Gy) induces apoptosis of endothelial cells in a dose-dependent manner, and the critical level of radiation depends on the cytokine microenvironment.

Morphological studies of tissues exposed to radiation show that there is evidence of the prothrombotic effects of radiation, which may be the cause of increased platelet adhesion and thrombus formation observed in irradiated capillaries and arteries. Ionizing radiation activates inducible nitric oxide synthase transcription and increase nitrite content. Along with this, a decrease in the concentration of L-arginine occurs. Since the inducible form of NO synthase has a very high activity, there is a rapid depletion of L-arginine, and the resulting NO interacts with ROS, increasing nitrosative stress [Figure 1].

POSSIBILITIES OF PHARMACOLOGICAL CORRECTION

Based on the pathogenetic basis of the processes occurring during exposure to radioactive radiation, several fundamental approaches to pharmacological effects can be proposed.

Statins
Due to its pleiotropic effects including antioxidant, anti-inflammatory, and antiapoptotic effects, as well as proven efficacy in correcting and preventing endothelial dysfunction, statins can be recommended as pharmacological agents effective in this pathology. Non-lipid-lowering effects of β-hydroxy β-methylglutaryl-CoA reductase inhibitors are explained by the fact that they interfere with the synthesis of farnesyl pyrophosphate and geranylgeranyl pyrophosphate. These molecules activate GTPases Ras, Rho, and Rac1, the increased activity of which induces apoptosis, inflammation, oxidative stress, and other undesirable consequences, leading to cell death. In the context of this topic, it is especially important that through these enzymes, proapoptotic kinases p21 and p53 induced by irradiation work.

Figure 1: Schematic illustration of endothelial damage when exposed to ionizing radiation (original designed). eNOS: Endothelial NO synthase, ROS: Reactive oxygen species, IL-1: Interleukin-1, IL-6: Interleukin-6, TGF-β: Transforming growth factor-β
Antioxidants
Given the critical role of oxidative and nitrosative stress by the action of ionizing radiation, it seems advisable to consider drugs with antioxidant orientation as endothelioprotectors in case of radiation damage. It was shown that transgenic animals with overexpression of the antioxidant enzyme superoxide dismutase 2 demonstrate high resistance to ionizing radiation, which is manifested in the reduction of apoptosis, inflammatory organ infiltration, and the production of proinflammatory cytokines. Oxidative and nitrosative stress triggered by ionizing radiation and their role in the formation of endothelial dysfunction is a direct prerequisite for the use of antioxidant agents in radiation-induced lesions. R rexod (superoxide dismutase), 3-hydroxyypyridine derivatives, acetylcysteine, flavonoids, carnosine, and Skulachev ion (SkQ) can be referred to drugs of this group.

Angiotsin-converting Enzyme Inhibitors
The renin–angiotensin system is one of the important participants in radiation-induced lesions. The endothelium protective effects of angiotensin-converting enzyme (ACE) inhibitors have been repeatedly proven in clinical and experimental studies. Its radioprotective activity was investigated in relation to the lungs, kidneys, brain, skin, as well as the hematopoiesis system. ACE inhibitors have demonstrated high efficacy in the treatment of such experimental pathologies as radiation-induced pulmonary endothelial dysfunction, radiation pneumonitis, and fibrosis. Prophylactic administration of captopril led to a decrease in systemic arterial pressure and an improvement in renal function after exposure to radiation in an experiment and a decrease in chronic renal failure in patients after radiation therapy. Captopril and perindopril were effective in correcting radiation-induced hematopoietic syndrome, normalizing the level of erythrocytes, reticulocytes, leukocytes, and platelets. The mechanism of reducing radiation injury caused by captopril is not installed, but in part, it is attributed to the fact that in addition to the classical targets, ACE destroys the N-acetyl-seryl-asparyl-lylsyl-proline molecule. Finally, captopril has a direct cytoprotective effect in vivo experiments, reducing the degree of apoptosis and inflammation, as well as affecting the life cycle of cells after exposure to radiation.

Erythropoietin (EPO)
Recombinant EPO has been approved by the Food and Drug Administration as a drug for treating anemia. However, its universal cytoprotective activity has been proven in many experimental models including ischemia of almost all organs and mechanical trauma. It has been shown that EPO not only regulates the physiological contour of blood formation, being excreted by the kidneys into the systemic circulation, but also performs various functions in other organs and tissues that produce this glycoprotein and its receptors. The discovery of EPO and its receptors in the nervous and vascular systems has attracted interest in studying its effectiveness against a variety of diseases such as Alzheimer’s disease and heart failure. A further search revealed the possibility of EPO production by some other organs including endothelium.

Thus, the pharmacological activity of EPO allows us to consider it as an agent possessing a potential endothelioprotective effect in radiation-induced endothelial dysfunction.

Sulfur-containing compounds
Cystamine belongs to the group of aminothiols. Radioprotective activity is due to its ability to bind free radicals and impart resistance to ionizing radiation to some macromolecules, currently used in medical practice for the prevention and treatment of radio-associated lesions. In addition, cystamine blocks specific transglutaminase enzymes that catalyze the formation of ε-N-(γ-glutamyl)-lyl cross-links between proteins.

Melatonin
Tryptophan derivative melatonin is most widely known as an endogenous regulator of circadian rhythms. However, in recent years, melatonin has been shown to have a large number of pleiotropic effects manifested by antioxidant, oncosuppressive, anti-inflammatory, immunoregulatory, and metabotropic activity. At present, a wide evidence base has been accumulated, confirming both the radioprotective and endothelioprotective orientation in the action of melatonin.

Unfortunately, our knowledge of radiation-induced lesions of the vascular wall is currently fragmentary and insufficient, but it does allow us to find some potentially effective molecules for pharmacological effects including statins, antioxidants, ACE inhibitors, EPO drugs, and some other endothelioprotectors.

CONCLUSION
At the present moment, scientific and technical progress has led to the widespread occurrence of various types of radiation sources. Nuclear power plants and submarines, the exploration of outer space and the upper layers of the atmosphere, and X-ray diagnostic methods - all these can cause exposure to ionizing radiation. However, the most common cause of radiation damage is radiation therapy of tumors
since the increase in the overall life expectancy of the population has led to an increase in the number of oncological diseases. At the same time, the improvement of methods for diagnosing and treating neoplasms has led to an increase in the survival of these patients. Therefore, remote complications of radiotherapy, among which the cardiovascular system occupy a leading position, are becoming increasingly important.

REFERENCES


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