нов, ингибируют нитрование тирозина и тирозинильных остатков белков нитрозильными радикалами.

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RADIATION-INDUCED CHANGES OF ENDOTHELIUM- AND NO-DEPENDENT REACTIVITY

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Epidemiological evidence indicate the connection between radiation exposure and cardiovascular diseases: the increase in the incidence of cardiovascular diseases among the population of contaminated with radionuclides areas and liquidators of the consequences on Chernobyl nuclear power station have been reported [1,2]. Radiation damage of living cells is, for the most part, due to oxidative stress. One of the most important biologically active molecules produced by endothelium is nitric oxide (NO). After ionizing radiation NO may play a dual role. On the one hand, NO might have antioxidant properties and can execute protective function, interacting with radiation-induced free-radicals and decreasing radiation injury. For instance, it has been demonstrated that in vitro NO is involved in radiation-induced immediate and reversible increase in vascular tone by scavenging O_2^-, and presence of superoxide dismutase (SOD) during irradiation significantly reduced the observed effects [3]. On the other hand, NO reacts very rapidly with superoxide leading to formation of much more potent oxidant peroxynitrite. Peroxynitrite and the subsequently formed radiacals might act as damaging agents and have a high toxicity and mutagenic properties. Interaction of NO with radiation-induced radicals might cause a decrease in NO bioavailability, inactivation of its physiological properties and thus attenuate functional stability of irradiated organism.

In the present study we have examined the effects of acute and chronic ionizing radiation in 1 Gy dose on the endothelial and NO-dependent reactivity of conductance arteries and coronary resistance vessels.

Materials and methods

Experiments were carried out on white female rats. A ^{137}Cs source was used for gamma-irradiation. Animals were allocated to one of the following treatment: whole body acute irradiation in 1 Gy dose ($9x10^{-4}$ Gy/s, 18 min, IGUR, Russia) or chronic irradiation ($2.3x10^{-7}$ Gy/s, 41 days, GAMMARID-192/120, Russia). Investigations were performed shortly after irradiation (3rd and 10th day), 1 months after radiation exposure and in the delayed term (90th day). To assess the effect of radiation on resistance vessels hearts were perfused by Langendorff and coronary flow rate was measured. After equilibration period NO-synthase inhibitor (L-NAME, 5 μM) or NO-donor sodium nitroprusside (SNP, 5 μM) were applied. Aortic rings served as a model for conductance arteries. Function of endothelium was examined by cumulative addition of carbamylcholine (CCh, 1 nM-10 μM) following precontraction with phenylephrine (PE, 1μM). After wash-up period the aortic rings were precontracted with PE and concentration-response curve for SNP (0.1 nM-10 μM) was performed.

Results

Effects of gamma-radiation on NO-component of basal coronary flow

In control L-NAME caused time-dependent decrease of basal coronary flow rate. By the 3rd day after acute gamma-irradiation coronary flow was increased on the overage 30%, and this elevation was diminished by NOS inhibition to the values of appropriate control (-L-NAME). On the 3rd and 10th days after chronic irradiation, significant reduction of basal coronary flow was observed with subsequent normalization one month later and repeated reduction 3 months after exposure. In the chronically irradiated vessels, coronary flow which was already decreased on the 3rd, 10th and 90th days of post-radiation, was unaffected by L-NAME.

These findings indicate NO-mediated increase in basal coronary flow after acute irradiation while chronic exposure seriously impairs basal NO release in coronary vessels within short and delayed terms of post-radiation period. The changes of basal coronary flow after irradiation may partly reflect changed responsiveness of the smooth muscle cells to NO. Therefore we have checked the effect of exogenous NO-donor SNP. Maximal coronary dilation to SNP in control and irradiated vessels was similar after the acute radiation during entire post-radiation period. Impact of ionizing ra-

diation with low dose rate caused a significant reduction in the maximal coronary relaxation to SNP on the 3rd and 10th day after exposure suggesting altered reactivity of the vessels to exogenous NO. One and three months after chronic irradiation, exogenous NO exerts the similar vasodilation effect in control and irradiated animals.

Endothelium-dependent and endothelium-independent vasodilation of aortic segments after irradiation

After precontraction with PE, CCh produced concentration-dependent relaxation in aorta of both control and irradiated animals. The reaction to CCh of acutely irradiated aorta was significantly elevated on the 10th day after irradiation (Figure).

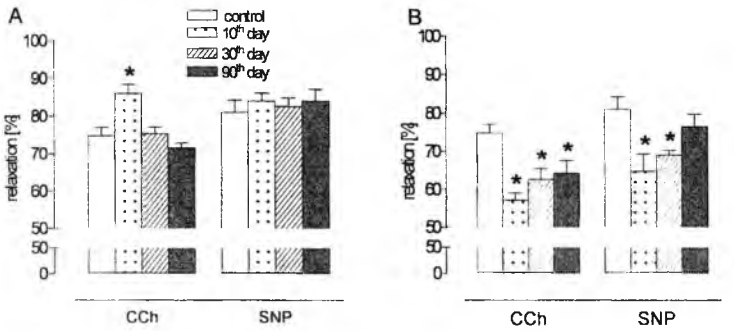

Figure. Effects of acute (A) and chronic (B) irradiation in 1 Gy dose on the maximum relaxation to CCh and NO donor SNP at different time after exposure.

In contrast, maximally induced vasorelaxation for NO- donor SNP was similar in control and irradiated animals. After chronic irradiation endothelium-dependent vasodilation was markedly attenuated in all studied terms. NO-dependent vasodilation was also impaired on the 10th and 30th day after chronic irradiation. However, three months after exposure reaction of aortic rings to the exogenous NO was similar to that of controls.

Discussion

Using a Langendorff-perfused isolated rat heart we have demonstrated that whole body irradiation in 1 Gy dose results in NO-dependent increase of coronary flow at the early stage after acute radiation exposure. Organ bath experiments revealed the significant increase of endothelium-

dependent relaxation of aortic segments to CCh shortly after radiation. Vasodilation of aorta and coronary vessels to the NO-donor SNP was unaltered within the entire experimental period. Taking together, these data suggest that the increase of coronary flow and aortic endothelium-dependent relaxation is mediated by shortly elevated after acute irradiation in 1 Gy dose NO-production.

In the early period after chronic irradiation NO component of basal coronary flow was reduced with following normalization after 1 months and repeated attenuation in the late period of post-irradiation. Aortic endothelium-dependent relaxation was markedly impaired at all studied time points after chronic irradiation.

The changes observed may be a result of diminution of NO synthesis or decreased sensitivity of smooth muscle cells to NO action. Indeed, we have found that relaxation to SNP was depressed in aorta within one month after chronic exposure and shortly after irradiation in coronary vessels suggesting that low dose rate radiation in 1 Gy dose induce the impairment of relaxing capacity of the aortic smooth muscle cells.

The other important finding, especially in the light of that 20 years have passed after Chernobyl accident, is the selective impairment of NO-mediated component of coronary flow and endothelium-dependent relaxation as the delayed effects of chronic ionizing radiation. The changes revealed may represent a basis for the cardiovascular diseases development and are of particular importance for the population exposed to the low-intensity ionizing radiation.

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