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Quinones and nitroazoles as promising inhibitors of free-radical formation of phosphatidic acid

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Abstract

It has been established earlier that lipids (phosphatidyl glycerol, phosphatidyl inositol, cardiolipin) being subjected to radiolysis undergo fragmentation via formation of hydroxyl-containing carbon-centered radicals, giving phosphatidic acids. It has been found that the accumulation of phosphatidic acid in cancer cells promotes their proliferation. Taking this into account, one can expect that the radiation-induced formation of phosphatidic acid in cancer cells should worsen the efficacy of radiotherapy in cancer patients. Compounds that can block these negative effects are expected to manifest radio sensitizing properties when introduced into cancer cells.

We have shown that quinones and nitroazoles are effective regulators of free-radical processes involving hydroxyl-containing carbon-centered radicals. These radicals are formed in homolytic reactions stimulated by γ-radiation in deaerated aqueous solutions of glycero-1-phosphate and aqueous dispersions of 1,2-dimyristoyl-glycero-3-phosphatidyl-glycerol. It was established that the studied compounds effectively inhibit the processes of glycerol-1-phosphate dephosphorylation and free radical fragmentation of 1,2-dimyristoyl-glycero-3-phosphatidyl-glycerol, suppressing the formation of phosphatidic acid – a biologically active compound that can promote the acceleration of oncocells proliferation.
The data obtained in this study allow to consider quinones and nitroazoles as promising substances to enhance efficacy of radiation therapy by blocking the radiation-induced processes leading to formation of products promoting cancer cell proliferation.

Effects of quinones and azoles on the formation of steady-state radiolysis products in aqueous solutions of glycerol-1-phosphate and aqueous dispersions of 1,2-dimyristoyl-glycero-3-phosphatidyl-glycerol has been investigated. The data obtained by LC–MS-ESI and spectrophotometric measurements shows that the compounds having quinoid structures, including the antitumor agent doxorubicin, and azoles having nitro groups effectively inhibit free-radical fragmentation of glycerol-1-phosphate and 1,2-dimyristoyl-glycero-3-phosphatidyl-glycerol, decreasing the radiation-chemical yields of either inorganic phosphate or phosphatidic acid respectively. The observed effects of blocking free-radical processes are believed to be related to the ability of the tested compounds to oxidize α-hydroxyl-containing carbon-centered radicals of starting substrates, which give rise to fragmentation reaction. The possibility of using the discovered properties of quinones, doxorubicin and nitroazoles to provide practical solutions in oncological radiotherapy and pathophysiology is discussed.

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Quinones are a class of toxicological intermediates that can create a variety of hazardous effects in a variety of organisms. Since they are prolific redox cyclers, they are primarily used for the detection, identification, analysis, etc. of chemical, biological, or pathologic processes or conditions, and are often used in the production of hydroquinones, dyes, and fungicides. Quinones are strong oxidizing agents, serve as an ingredient for photographic solutions, and can cause skin necrosis after prolonged contact. Most commonly manifested toxic reactions with quinones are skin, eye, and respiratory tract irritations. It can cause corneal ulcers after acute exposure and corneal opacities after chronic exposure. Neurotoxic effects include vision disturbances. It is a suspected germ cell mutagen. Epidemiological data do not support 1,4-benzoquinone to be carcinogenic either to humans or to experimental animals. The mechanisms by which quinones cause these effects can be quite

complex. They serve as Michael acceptors and damage cells and tissues through alkylation of crucial macromolecules (proteins and DNA). Because they are highly redox-active molecules, they can redox cycle with their semiquinone radicals, leading to the formation of highly toxic reactive oxygen species (ROS). Intracellular production of ROS can cause severe oxidative stress, leading to cell injury and cell signaling pathways that can cause various forms of cell death.