Participation of NAD-dependent Mechanisms in the Hemopoiesis Regulatory Activity of p-Tyrosol

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The regulation of hemopoiesis by physiological and pathological stimuli is one of the most important problem to be solved in biology and pathophysiology. It is commonly believed that antitumour agents, including anthracycline antibiotics, possess at the same time the antitumour effect and cytotoxic activity in rapidly renewing cell systems, particularly in the bone marrow, that results in the disturbances of endogenous regulation of bone marrow cell proliferation and programmed cell death (apoptosis). In this connection one of the most topical problem of oncopharmacology is the search of agents which raise the antitumour resistance of organism and prevent toxical action of antitumour agents on normal bone marrow cells. Substances of vegetable origin can be referred to such agents. They possess the adaptogenic properties which can be used to raise organism resistance to different disturbing factors.

The purpose of this experimental work was to investigate the protective effect of new drug p-tyrosol – a synthetic analogue of one biologically active component from *Rhodiola rosea* (higher plant from *Crassulaceae* family), – under the oxidative stress induced by doxorubicin.

The diffusion chamber technique was used for bone marrow cells culturing. The colonie- and clusterforming ability of cells and the percentage of cells with morphological features of apoptosis was evaluated.

In our experiments doxorubicin ($1x10^{-6}$ M, $5x10^{-6}$ M) dose-dependently suppressed the colonie- and clusterforming ability of cells and induced increase of percentage of bone marrow cells bearing morphological features of apoptosis. The cytotoxic effect of doxorubicin was blocked by p-tyrosol (10^{-4} g/ml) whose adaptogenic properties are close to that of *Rhodiola rosea* extract. P-tyrosol was effective both at the addition in the incubation medium *in vitro* and at the 10-day course of prophylactic treatment of mice (100 mg/kg, i.m.) *in vivo*.

It is commonly believed that the rearrangement of the intracellular pool of pyridine nucleotides because of an activation of poly-ADP-ribosylpolymerase, which facilitate the repair of DNA damaged by reactive oxygen species, is one of the key process in the pathogenesis of the cytotoxic action of xenobiotics – inducers of oxidative stress. The effectiveness of p-tyrosol in the prevention of doxorubicin-induced disturbance of bone marrow cell proliferation allows to suggest the participation of NAD-dependent processes in the hemopoiesis regulatory activity of p-tyrosol. Indeed, in our experimental model nicotinamide, substrate inhibitor of poly-ADP-ribosylpolymerase increases the specific action of p-tyrosol.

Thus, application of p-tyrosol seems to be pathogenetically based method for correction of cytotoxic activity of antitumour agents in actively proliferating cells.