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Possible hepatostabilizing properties of the cluster rhenium compound in tumor-bearing rats

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ABSTRACT

The influence of the cluster rhenium compound in liposome form and cisplatin on the functional activity of hepatocytes of rats with Guerin's (T8) carcinoma has been studied. It was shown that the increase of enzymatic activity of some diagnostic enzymes in liver under tumor development and cisplatin therapy that was the consequence of hepatocytes destruction. Introduction of the rhenium compound led to a decrease of the enzymatic activity that confirms the possible hepatoprotective properties of rhenium compounds.

Key words: cluster rhenium compound, cisplatin, liposomes, hepatocytes, liver, aminotransferases, dehydrogenases, Guerin's (T8) carcinoma.

INTRODUCTION

The liver is an organ, where the majority of cytostatics are metabolized during anticancer therapy [1,2]. Most of the antitumor preparations don't have any specific influence, that's why its hepatotoxicity [4,7,9,10]. For example, cisplatin - an effective antitumor agent which is widely used in the oncological practice - alongside with high effectiveness has an essential cytotoxic effect on normal tissues of liver [6,9]. In our previous works [11-14] it was shown that cluster rhenium compounds exhibit antiradical, antihemolytic activity in the models *in vitro* and *in vivo* and revealed themselves as biochemical modulators of cisplatin action. In those works the influence of rhenium compounds on the state of red blood system was studied along with antitumor properties, but the influence of the cluster rhenium compound in liposome form on the indices of the fermentative activity of some enzymes - markers of cytolysis of hepatocytes: aspartate aminotransferases (AsAT), alanine aminotransferases (AlAT), lactate dehydrogenases (LDG) in the homogenate of rat liver tissues.

MATERIALS AND METHODS

Cisplatin and cluster rhenium compound - dichlorotetra-(isobutylrhenium(III)) with formula: $[\text{Re}_4(\text{f-C}_3\text{H}_7\text{CO}_2)_4\text{Cl}_2]$, where $\text{f-C}_3\text{H}_7\text{CO}_2\text{R}$ = isobutyric, - (ReI) were used according to procedure described in [14]. Wistar rats were inoculated by tumor Guerin's carcinoma (T8) cells. Tumor transplantation was performed by subcutaneous injection of 20% Guerin's carcinoma cell suspension in the thigh area. A single intraperitoneal administration of cisplatin at the dose of 8 mg/kg was made on the 9 day after the tumor inoculation. The intraperitoneal administration of

the ReI at the dose of 7 $\mu\text{M/kg}$ in liposome forms began on the 3 day after the inoculation of the tumor cells and was repeated every 2 days until day 21. Homogenate of liver tissues was obtained by means of its homogenization in 10 ml of physiological solution. Fermentative activity AsAT, AlAT, LDG was determined in oversediment liquid which was obtained after homogenate centrifuging. To determine ferment activity, generally accepted methods with use of the set of reagents (phosphatase - Diagnostics, Ukraine) were used. The statistical analysis of the obtained data was conducted with application of Student's t-criteria, estimating the probability of the obtained results at the level of significance not less than 95 per cent ($P < 0.05$). The data were expressed as $\text{M} \pm \text{m}$. The results at $P < 0.05$ were considered as reliable.

RESULTS AND DISCUSSION

It was demonstrated that the development of Guerin carcinoma in experimental animals (group No 2) is accompanied by increase of the enzymatic activity in comparison with the control group (figures 1 and 2).

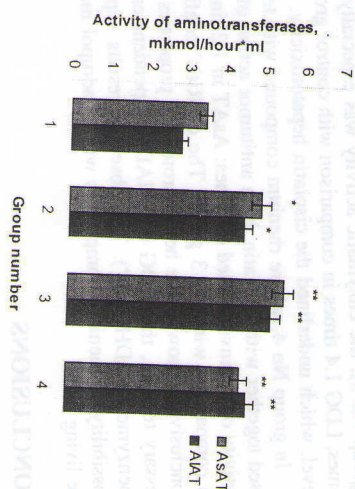


Figure 1. Activity AsAT and AlAT (mkmol/hour·ml) of hepatocytes of rats 1-control, 2-tumor, 3-cis-Pl, 4-liposome form $\text{Re}_4(\text{f-C}_3\text{H}_7\text{COO})_4\text{Cl}_2$ (* $P < 0.01$, ** $P < 0.05$).

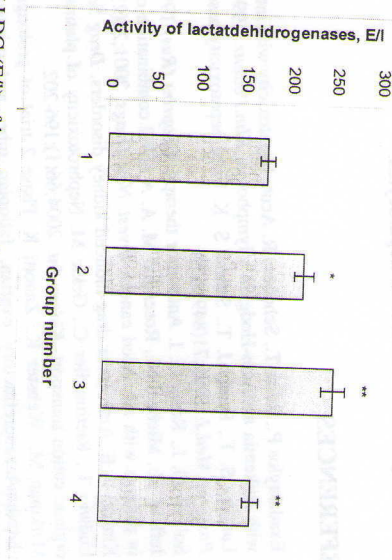


Figure 2. Activity of LDG (E/l) of hepatocytes of rats 1-control, 2-tumor, 3-cis-Pl, 4-liposome form $\text{Re}_4(\text{f-C}_3\text{H}_7\text{COO})_4\text{Cl}_2$ (* $P < 0.01$, ** $P < 0.05$).

The increase of enzymatic activity such as AIAT, AsAT and LDG in liver tissues takes place due to the damage of hepatocytes and outcome of these enzymes from the cells. In the hepatocytes the investigated enzymes are situated in different subcellular compartments: 2/3 of AsAT is situated in cytosol, 1/3 AsAT - in mitochondria; AIAT is a cytosolic enzyme. The extent of hepatocyte damage may be estimated by activity of these enzymes and is used in medicinal practice [15].

The ratio of values of activities of AsAT / AIAT (de Ritis' coefficient) points to the extent of hepatocyte damage and may be explained in such a way: a hepatocyte contains more AsAT than AIAT, but the first enzyme is situated in cytosol and in mitochondria; AIAT - only in cytosol. In the case of pathological state which leads to the hepatocyte damage, the cytosolic enzymes easier come out from the cells, the AIAT activity is higher and de Ritis' coefficient becomes lower. The Ritis' coefficient which is at normal state 1.21, reached the value 1.09 in the group 2 and points to the cytolysis of hepatocytes.

In the acute forms of hepatitis and many other diseases LDG activity in the intercellular space increases [17]; this is also due to hepatocytes damage. This is a glycolytic, cytosolic, zinc-containing enzyme which inversely catalyses the lactate oxidation into pyruvate. Under influence of tumor growth the LDG activity increased in comparison with control.

Nevertheless that substantial breaking of tumor growth took place under the action of cisplatin (group No 3), the enzymatic activity was especially large: AsAT increased 1.6 times, AIAT 1.8 times, LDG 1.4 times in comparison with control group. The Ritis' coefficient decreases to a 1.06 level, which underlined the cisplatin hepatotoxicity.

In group No 4, where rhenium compound with tetraisobutylate ligand in a liposome form was used together with cisplatin, high antitumor action of the system was followed by decrease of the activity of the investigated enzymes: AsAT in 1.2 times, AIAT in 1.1 times and LDG in 1.5 times in comparison with the 3 group. The de Ritis' coefficient increased to the level of 0.96, which conclusively showed the hepatoprotective properties of the cluster rhenium compound. It is necessary to note, that LDG is a NAD - dependent enzyme, which uses the reduced form of the coenzyme (NADH + H⁺). The observed results supported our previous assumption [14] about the possibility of rhenium compounds with quadrupol metal-to-metal bond to regulate redox state of the living cells.

CONCLUSIONS

Increase of enzymatic activity of some diagnostic enzymes in liver under tumor development and cisplatin therapy and ability of the cluster rhenium compound to stabilize their level were shown. Possible hepatoprotective properties of the rhenium compounds may be explained by its ability to regulate redox state in hepatocytes.

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