RADIOPROTECTOR MODIFYING INFLUENCE UPON THE ION TRANSPORT ATPase ACTIVITIES

S. [illegible] Yu. Egorova, I. V. Ananieva, I. A. Kulikova

[illegible] Biology
Dnipropetrovsk State University, Dnipropetrovsk, Ukraina

Study of mechanisms of chemical protection from the ionizing action is one of the main problems in modern radiobiology. It seems that significant changes in [illegible] reactions securing the endogenous biochemical background of radioresistance lead in the basis of a radioprophylactic effect[1, 2]. It's possible these reactions involve the molecular systems of ion transfer across membranes which determine the homeostatic characterizations and total functional [illegible] cell. In this connection effects of aminothiol and biogenic amine radioprotectors on the basic ion transport enzymes, such as Na, K-ATPase and Mg, Ca-ATPase activities were investigated in the tissues of numerous organs with different radiosensitivity in the Wistar rats.

In experimental series *in vivo* the intraperitoneal injections of radioprotector drugs had been given to animals in 15 min before decapitation, as following: (in mg per 1 kg of weight) 100, histamine base ("Serva", Germany); 90, dopamine hydrochloride ("Fluka", Switzerland); 60, serotonine creatinine sulfate, 5-HT ("Fluka", Switzerland); 150, β-mercaptoethanolamine hydrochloride, MEA (synthesed at the Moscow University); 250, S-2-aminoethyl-isothiourea dihydrobromide, AET·2HBr (synthesed at the Moscow University). In some series of the experiments *in vitro* the membrane preparations were incubated when [illegible] drugs were added in the washed solution to final concentrations of 5 · [illegible] M for thiols (MEA, AET) and $5 \cdot 10^{-4}$ M for biogenic amines. ATPase activities were expressed as mM Pi/mg protein per h. Experimental data were analysed statistically, significant differences were determined by "t-test for paired data" at $P < 0.05$.

Experimental results of *in vivo* studies of the chemical radioprotector effects (Table 1) showed that intraperitoneal injection of the used drugs caused preliminary inhibition of the Na, K-ATPase activity in tissues from organs with different radioresistance, but had no influence on the Mg, Ca-ATPase activity in membranes of erythrocytes and rat brain cells.

It should be pointed that thiols had the wider range of action in comparison with biogenic amines, effects of which had the selecting patterns. So, MEA

changed the Na, K-ATPase activity in cells of thymus, spleen, liver and brain, AET was effective in cells of spleen and liver, whereas S-HT influence was detected only in lymphocytes of thymus and erythrocytes, dopamine and histamine effects were observed in the membrane fraction from liver.

Table 1 Transport ATPase Activities under Radioprotector Drugs Influence *in vivo* (per cent to control value, Means±S.E.M. n=6-10)

	ATPase activities.				
	MEA	AET	5-HT	Dopamine	Histamine
a	75.0±5.6*	97.5±8.1	58.1±5.5*	96.8±6.2	97.5±10.6
b.	81.9±5.2*	129.5±2.4*	94.3±8.8	93.8±9.9	93.1±12.5
c:	110.8±5.1	92.5±5.9	108.9±1.1	98.1±6.5	101.1±5.0
d:	73.8±5.3*	53.5±4.2*	103.6±12.2	81.9±8.9*	63.2±2.2
e:	102.6±4.6	91.1±4.4	106.1±2.1	104.5±7.3	108.6±4.2
f:	86.9±1.5	97.1±3.2	95.5±2.6	90.5±6.9	119.1±2.1*
	Mg Ca-ATPase activity				
g:	98.2±3.0	100.0±0.4	80.7±2.7*	102.6±1.3	100.3±5.8
f:	88.7±4.8	90.9±4.1	95.6±6.0	102.0±6.8	102.0±6.8

a-thymus, b-spleen, c-intestinal epithelium, d-liver, e-kidney, f-brain cortex, g-erythrocytes;
*-means are significant, P≤0.05

To exclude the numerous internal organism factors influence on the net radioprotectors effects and to detail the radioprotective mechanisms we had attempted to estimate *in vitro* action of the investigated drugs upon transport ATPase activities. We had found the reduced Na, K-ATPase activities in cells of thymus, spleen, intestinal epithelium and liver, when almost each of all used radioprotector drugs was added to the medium where the plasmatic membranes were incubated (Table 2). But in the membrane fraction from brain cortex the Na, K-ATPase activity as well as the Mg, Ca-ATPase activity were enhanced by 5-HT and dopamine, whereas thiols inhibited the both of enzymatic activities. The Mg, Ca-ATPase activity wasn't affected to the radioprotector influence in membranes of erythrocytes.

Therefore it should be concluded that used radioprotector drugs being applied *in vivo* and *in vitro* inhibited generally the activities of enzymatic systems of ion transfer across membranes, excluding the excitatory membranes of nervous cells. One of the possible pathways of thiols modifying action on the ion transport ATPase activities was probably direct interaction between thiols and enzymatic protein molecules resulted the absorption, thioaetherous, amidous and disulfidous chains appearance[1]. Perhaps those interactions followed to inhibition of the active ion transport due to enzymatic systems activities in the organs and tissues, which have the higher radiosensitivity. At present the correlation between time of thiol radioprotectors treatment and kinetics of mixed disulfidous chains origin had

Table 2 Transport ATPase Activities under Rdioprotctor Drugs Influence *in vitro* (per cent to control value, Means ±S.E.M. n=6-10)

	ATPase activities				
	MEA	AET	5-HT	Dopamine	Histamine
a:	38.8±2.3*	30.4±2.6*	43.3±2.6*	36.7±3.4*	53.3±4.9*
b:	76.6±6.4*	53.2±4.4*	98.0±2.6	49.8±7.7*	63.8±2.9*
c:	77.8±1.9*	57.9±4.7*	84.9±3.6*	57.0±4.8*	104.9±3.6
d:	61.9±6.6*	52.4±6.1*	75.2±3.3*	63.9±3.6*	0*
e:	105.6±7.9	106.4±7.8	97.1±5.9	127.3±5.9*	95.2±5.8
f:	98.6±1.5	45.1±2.5*	137.9±7.7*	159.3±12.1*	90.2±5.8*
	Mg Ca-ATPase activity				
g:	98.8±2.5	106.9±2.3	98.2±2.1	98.4±2.5	106.9±3.1
f:	42.7±3.2*	86.0±3.2*	125.1±6.1*	99.5±6.3	145.4±7.4*

a-thymus, b-spleen, c-intestinal epithelium, d-liver, e-kidney, f-brain cortex, g-erythrocytes; *-means are significant, P≤0.05

been shown[1]. Thus, maximum of disulfidous chains formation was corresponded to optimum of the aminothiol radioprotection effect. Furthermore, it had been known, that injection of thiols in organisms caused an activated synthesis and release of biogenic amines, which had expressed radioprotecitve influence to be realized in several pathways, such as: at first, by hyposic effect; at second, by direct action of biogenic amines on the endogenous lipid radiosensibilization and lipid peroxidation processes; and at third, as a result of biogenic amines involving in regulation of cellular metabolism[1]. At present the mechanisms of enzymatic activities inhibition by biogenic amines are not completely clear and so, investigation of them are required in future. It seems that radioprotector inhibition of the transport ATPase activities appears as a step to storage of the cellular ATP, which is one of the factors securing the endogenous background of increased radioresistance of organism. It's necessary to take into consideration that ATP is a substrate of the bothion-transproting ATPase and adenylatcyclase activities, therefore, reduced functions of the ion-transporting enzymatic systems may lead to maintaining of defined level of cellular ATP content. Probably, when adenylatcyclases are activated by biogenic amines, ATP utilization results the occurrence of cAMP. Enhanced cAMP level increase the proteinkynase activities, and that have a modifying influence upon cellular metabolism via action on the effector systems of a cell. Under that influence the cell metabolism is transformed into resistant state and, therefore, one of mechanisms determining the endogenous background of organism radioresistance is realized[4].

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