HUMAN ECOLOGY

Glutamic Acid in Treatment of Alcohol Intoxication Aggravated by Ecologically Unfavorable Factors

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Alcohol intoxication aggravated by exposure to ecologically unfavorable factors (methanol and furfural vapors) induced pronounced desynchronization of hematologic processes, dramatic disturbance of carbohydrate metabolism, and considerable structural changes in internal organs. Treatment with glutamic acid reduced pathological manifestations and increased the adaptive capacities of the organism. Functional and morphological changes observed in laboratory animals after treatment with the neurometabolic compound glutamic acid could be classified as reversible.

Key Words: *alcohol intoxication; ecologically unfavorable factors; glutamic acid*

Amino acids, in particular, glutamic acid (Glu) and its salts are considered to be promising compounds for the treatment of chronic alcohol intoxication (CAI): they inhibit ethanol metabolism, reduce the accumulation of the most toxic metabolic products, and accelerate their elimination with urine [1]. Glu modulates activity of enzymes responsible for ethanol and acetaldehyde transformations and elevates tissue content of endogenous ethanol. The absence of endogenous ethanol is considered to be a pathological factor in the development of alcohol addiction. Glu prevents dramatic changes in the cerebral content of some amino acids induced by alcohol intoxication [1].

Pharmacological correction of alcohol-induced somatic disturbances is a pressing problem, especially when alcohol intoxication is aggravated by the influence of different xenobiotics. There are no published data on the use of nootropics for the correction of somatic disturbances induced by combined effects of alcohol and toxic compounds.

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The aim of the present study was to describe changes in hematologic indices, carbohydrate metabolism, and histology of internal organs after exposure to alcohol and toxic agents and to assess the possibility of their correction with Glu.

MATERIALS AND METHODS

The study was carried out on 120 male albino rats kept under standard vivarium conditions. Early manifestations of CAI were modeled by daily administration of ethanol for 28 days and aggravated by inhalation of methanol and furfural widely used in chemical and other industries. Two experimental series were performed: in series I, group 1 animals received intragastric ethanol (40%, $^1/_2$ LD_{50}); group 2 rats were exposed for 4 h to methanol and furfural vapors in concentrations 2-3-fold exceeding the permissible doses for human and animals [3] (this model approximates real conditions of alcohol production by hydrolysis), and group 3 rats received intragastric ethanol (40%, $^1/_4$ LD_{50}) in combination with exposure to toxic methanol and furfural vapors. In series II, the animals of each group

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were additionally treated with Glu in a dose of 1 mg/g (oral administration). The control animals received an equal volume of intragastric water instead of ethanol.

The count and mean volume of erythrocytes (V_e) were determined on a Picoscale hematoanalyzer, hemoglobin content was measured by a photometric technique using hemoglobin-cyanide reaction. The color index, mean saturation with hemoglobin, and mean content and concentration of hemoglobin in erythrocytes were calculated [2]. The count of reticulocytes, daily erythropoiesis, and the mean erythrocyte lifetime (MELT) were determined [4], serum glucose was measured colorimetrically with o-toluidine reagent. Liver glycogen was evaluated after hydrolysis by the content of glucose (colorimetrically with o-toluidine reagent). The heart, liver, brain, lungs, and kidneys were examined histologically. Sections were stained with hematoxylin and eosin, sudan-III, azure-eosin, by Van-Gieson's method and with Schiff reagent. The data were processed statistically using Student's *t* test.

RESULTS

In series I, all experimental groups revealed a decreased hemoglobin content. The maximum drop (to 78.5%) was observed in group 3 exposed to combined intoxication (Table 1). In this group, erythrocyte count was significantly reduced (to 85%), while in groups 1 and 2 it tended to increase. All groups showed increased V_e, the maximum enlargement (to 118%) was noted in group 3. In all experimental groups the percentage of reticulocytes surpassed the control value, while MELT was slightly below the control. Daily erythropoiesis significantly exceeded the control in groups 1 and 2, but was suppressed in the animals exposed to combined intoxication (80.9%, $p<0.01$).

Thus, changes in hematologic indices depended on the model of intoxication. It should be noted that CAI in relatively small doses in combination methanol and furfural desynchronized hematologic processes and caused anemia. Under these conditions, the defense and compensatory mechanisms were unable to maintain homeostasis in the organism.

Administration of Glu considerably enhanced daily erythropoiesis in all experimental groups (Table 2). In rats subjected to combined intoxication, peripheral blood reticulocyte count was significantly higher than in other experimental and control groups. The decrease in hemoglobin content was less pronounced than in series I (the lowest value was observed in group 3 with combined intoxication), MELT tended to decrease in both experimental groups compared to the control (Table 2).

Thus, all experimental groups treated with Glu developed moderate anemia. The comparison of groups 3 in series I and II showed that Glu improved hematologic indices. Therefore, under conditions of alcohol intoxication aggravated by ecologically unfavorable factors Glu enhanced body adaptive capacities probably due to its antihypoxic and stress-protective activity.

Hyperglycemia was revealed in all experimental animals. Intragastric administration of ethanol activated glycogenolysis (in group 1 glycogen content was reduced to 90.1%, $p<0.05$) and induced hyperglycemia (113.68% compared to the control). Activation of glycogenolysis could be caused by enhanced secretion of adrenaline due to ethanol intoxication-induced stress. Etha-

TABLE 1. Hematologic Indices in Different Intoxication Models (*M±m*)

Index	Control	Experimental groups		
		1	2	3
Daily erythropoiesis, 10^7	265.54±6.64	320.79±38.23	369.27±10.68*	214.77±18.26**
Reticulocyte count, %	1.83±0.07	2.09±0.13***	2.15±0.08**	2.03±0.13
Hemoglobin, g/liter	145.14±5.21	141.20±18.6	136.66±6.91	114.00±7.36*
Erythrocyte count, 10^{12}/liter	6.53±0.11	6.57±0.13	6.66±0.11	5.56±0.35**
Color index	0.66±0.02	0.64±0.02	0.61±0.02	0.62±0.03
V_e, μ^3	75.69±1.52	81.19±7.57	76.29±1.92	89.45±6.59***
Erythrocyte hemoglobin content, pg	22.22±0.59	21.24±0.82	20.49±0.77	20.56±0.86**
Erythrocyte hemoglobin concentration, pg/μ^3	0.290±0.006	0.27±0.03	0.27±0.01	0.23±0.02**
Erythrocyte saturation with hemoglobin	0.77±0.02	0.72±0.08	0.71±0.03	0.61±0.04**
Erythrocyte lifetime, days	24.27±0.67	19.27±1.20*	18.12±0.77**	13.46±28.79

Note. Here and in Table 2: *$p<0.001$; **$p<0.01$; ***$p<0.05$ in comparison with the control.

TABLE 2. Hematologic Indices in Different Models of Intoxication after Treatment with Glutamic Acid (*M±m*)

Index	Control	Glu	Experimental groups		
			1	2	3
Daily erythropoiesis, 10^7	221.26±4.31	271.28±6.76*	287.13±4.39***	306.17±13.20*	300.42±7.31*
Reticulocyte count, %	1.85±0.04	1.12±0.05*	1.91±0.04	1.97±0.03**	2.07±0.04*
Hemoglobin, g/liter	147.44±1.38	141.36±1.13**	147.68±3.08	143.75±2.7	134.16±2.80*
Erythrocyte count, 10^{12}/liter	6.87±0.1	6.69±0.06	6.7±0.11	6.45±0.08	6.17±0.11**
Color index	0.640±0.007	0.630±0.003	0.650±0.005***	0.660±0.008***	0.650±0.009
V_e, μ^3	72.80±0.72	70.23±0.65**	74.83±0.62***	68.69±1.27**	79.59±0.75*
Erythrocyte hemoglobin content, pg	21.48±0.22	21.140±0.095*	22.00±0.17***	22.28±0.26***	21.73±0.29
Erythrocyte hemoglobin concentration, pg/μ^3	0.295±0.002	0.300±0.003**	0.290±0.002	0.320±0.005*	0.270±0.003*
Erythrocyte saturation with hemoglobin	0.770±0.006	0.790±0.007***	0.770±0.007	0.850±0.015***	0.720±0.007*
Erythrocyte lifetime, days	31.11±0.71	24.77±0.79*	23.40±0.55*	21.06±0.25*	20.65±0.71*

nol lowers blood insulin by suppressing the function of pancreatic β-cells [7,8]. Moreover, ethanol stimulates the development of insulin resistance, which disturbs glucose utilization and leads to hyperglycemia [9].

The most dramatic changes in carbohydrate metabolism were observed after combined exposure to alcohol and toxic vapors (group 3). Both liver glycogen and blood glucose were significantly elevated to 518.5% ($p<0.001$) and 125.2%. ($p<0.05$), respectively, which implies blockade of tissue utilization of energy substrates.

Simultaneous pronounced increase in the blood glucose and liver glycogen content can also result from enhanced gluconeogenesis due to activation of the pituitary-adrenal system in response to intoxication stress [6].

Considerable activation of gluconeogenesis after combined exposure to ethanol, methanol, and furfural suggests the development of the distress syndrome or adaptation disease, when inadequate reactions to stimuli initiate further pathological changes in the organism. This can be explained by additive effects of harmful factors which leads to the breakdown of adaptive mechanisms.

Treatment with Glu slightly increased liver glycogen and lowered blood glucose, which suggests the improvement of carbohydrate metabolism and glucose utilization.

Morphological changes in internal organs after CAI included microcirculation disturbances, edema, diffuse degeneration, and acute focal inflammation. Inhalation of methanol-furfural vapors induced mild, variable, and nonspecific structural changes in all examined organs except lungs, where inflammation rapidly spread from bronchi to peribronchial tissues. Combined intoxication produced more dramatic pathological changes. In the brain, diffuse microcirculatory disturbances were accompanied by neuronal death (the presence of ghost cells), microinfarctions, and solitary postinfarction cysts. In the heart, atrophy and cell homogenization were revealed in some regions along with general myocardium degeneration. In the liver, cell necrosis was observed against the background of diffuse fatty degeneration and pronounced inflammatory changes. In the kidney, progressive hydropic and granular degeneration was accompanied by diffuse parenchymal hemorrhages and focal changes, similar to acute exudative or proliferative glomerulonephritis. In the lungs, catarrhal and purulent processes in the small and medium bronchi and alveoli were accompanied by diffuse alterations in blood vessels.

Thus, dystrophic changes of varying degree constituted the structural basis for lesions observed in internal organs after the exposure to toxic compounds. These changes tended to increase after combined intoxication. The histological picture of internal organs in group 3 was characterized by the most pronounced signs of toxic lesions. This additive effect can be explained by two factors: first, the organotropic effect of ethanol could be enhanced due to changes in general reactivity; second, ethanol as a universal solvent could facilitate the diffusion of xenogenics in organs and tissues.

Animals treated with Glu exhibited less pronounced pathomorphological changes. The signs of pathology in the brain were limited by degeneration; no microinfarctions and only focal encephalitis were observed. Myocardial degeneration was relatively

mild; focal myocarditis and diapedesis were observed only in animals exposed to combined intoxication. No signs of necrosis or acute hepatitis were seen in the liver, despite the presence of all types of degeneration. In the kidney, only some loops in glomerular capillaries were affected, degenerative changes were infrequent or completely absent (inhalation of methanol-furfural vapors without ethanol).

Thus, histological picture and changes in hematologic indices and carbohydrate metabolism depended on the model of intoxication. Glu alleviated intoxication-induced pathology, structural changes in internal organs were partially reversible. It can be concluded that under these conditions neurometabolic drugs with membrane-protective and metabolic activity enhance adaptive capacities of the organism exposed to unfavorable environmental factors.

REFERENCES

1. Yu. V. Burov, S. E. Metkalova, and L. E. Davydova, *Vopr. Narkol.*, No. 4, 50-56 (1994).
2. I. A. Kassirskii and G. A. Alekseev, *Clinical Hematology* [in Russian], Moscow (1970).
3. G. I. Krasovskii and O. R. Sobinyakova, *Gigiena i Sanitariya,* No. 4, 29-34 (1970).
4. E. N. Mosyagina, *Erythrocyte Balance in Norm and Pathology* [in Russian], Moscow (1962).
5. A. G. Solov'ev, G. N. Degteva, and P. I. Sidorov, *Byull. Eksp. Biol. Med.*, **96**, No. 8, 195-197 (1983).
6. A. M. Khokha, *Uspekhi Sovrem. Biol.*, No. 5, 573-580 (1994).
7. M. Hardman, P. Jeyarathar, and K. Hitson, *Alcohol Clin. Exp. Res.*, No. 2, 212 (1994).
8. C. Lang, P. Molina, and N. Skrepnick, *Am. J. Physiol.*, No. 6, 863-869 (1994).
9. Z. Spolarics, G. Bagly, and P. Pekala, *Ibid.*, No. 6, 886-891 (1994).