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TOXIC LIVER DAMAGE IN ACUTE PHASE OF ETHANOL INTOXICATION AND ITS EXPERIMENTAL CORRECTION WITH CHELATE ZINC COMPOUND

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Absract: *It was established, that ethanol in the dose of 12 g/kg in experimental animals (white non-inbred male rats) had expressed damaging effect on the liver, that is shown in statistically significant increase of activity of hepatic enzymes (alanine aminotransferase, alkaline phosphatase), hypoglycemia, development of albuminous and hydropic degeneration. It is proved, that application of new chelate zinc (2, 8, 9-trigidrotsinkatrane) in experimental correction of acute ethanol poisoning promotes reduction of metabolic and morphological derangements.*

Keywords: *toxic liver damage, acute ethanol poisoning, alcohol dehydrogenase, 2, 8, 9-trihydrozincatrane.*

Introduction: Approximately 80,000 cases of acute ethanol poisoning (AOE) are registered annually in the world [1, 4]. Significant mortality rates from them are due to the large scale of alcoholization of the population, as well as the amount of low-quality alcoholic beverages and technical alcohol-containing liquids consumed. Acute ethanol poisoning is a serious medical and biological problem. [5]. The severity of AOE is determined by the degree of damage to internal organs, which is associated both with non-specific physicochemical properties and the membranotropic effect of primary low molecular weight alcohols, and with specific effects on the structures of the central nervous system, to which they exhibit increased affinity (neurotropism, neurotoxicity, narcotic effect) [9, 20,21]. Morphologically, the most significant changes are observed in parenchymal organs (liver, kidneys, lungs), the damage to which largely determines the picture and severity of ethanol poisoning in its acute phase [18, 19,22].In recent years, certain successes have been achieved in the study of the pathogenesis of AOE [8,23]. However, the still high mortality rate suggests the need for a more in-depth study of pathogenetic mechanisms and further search for ways to treat this most dangerous social disease, especially since the treatment of AOE does not involve the use of specific procedures and is carried out according to the general rules for the treatment of poisoning [3].At the same time, earlier, as a result of experimental biological modeling with a single intragastric administration of ethanol at a dose of 12 g/kg, we found that the use of a new zinc chelate compound 2,8,9-trihydrozincatran (2,8,9-THCA) in the experimental Correction of BAE contributes to an increase in the survival rate of experimental animals [17]. In the study [7], it was proved that 2, 8, 9-THCA, used as a protector in OAE, almost completely normalizes the parameters of the metabolic system "lipid peroxidation - antioxidant protection" and lipid metabolism.

The purpose of this study was to study the functions of the liver in the conditions of modeling BOE with the elucidation of the possible corrective effects of 2,8,9-THCA on the liver of experimental animals as the main organ of ethanol metabolism.

Materials and methods All studies were performed on 108 white non-linear male rats weighing 180–220 g, bred in a specialized vivarium (veterinary certificate 238 No. 0018942). Throughout the experiment, rats were kept in plastic cages under natural light, with free access to balanced briquetted compound feed and water.

To avoid the influence of daily biorhythms on the values of parameters, blood sampling after decapitation was carried out at the same time (10.00–10.30). All animals were divided into three series of 36 rats each: 1) intact control (n = 12); 2) positive control (n = 12), animals were administered only ethanol (40 vol.%) orally at a dose of 12 g/kg, once; 3) experimental rats (n = 12), which, immediately after the modeling of BAE, were intragastrically injected once with an ethanolic (5 vol.%) solution of 2,8,9-THCA (experimental correction) at a protective dose of 4 mg/kg. Intact animals received only water from drinkers in the free access mode.

The zinc chelate compound 2,8,9-THCA is an intramolecular tricyclic complex of tris(2-hydroxyethyl)amine (triethanolamine) with zinc diacetate corresponding to the formula (CH 3 COO) 2 Zn · [(CH 2 CH 2 OH) 3 N]. The compound under study was synthesized at the Irkutsk Institute of Chemistry. A.E. Favorsky and provided by the technology implementation center "Innokom" (Irkutsk). It is a white powder, poorly soluble in water and soluble in ethanol (5% vol.). The ratio of triethanolamine with zinc diacetate is 1:1.

The authenticity of the chemical structure of 2,8,9-THCA was confirmed by NMR spectroscopy and elemental analysis. All studies were performed in accordance with the ethical requirements for working with experimental animals, set out in the following regulatory documents: "Rules for carrying out work using experimental animals" (Appendix to the order of the Ministry of Health of the USSR No. 755 of August 12, 1977) [11], "Rules of laboratory practice" (appendix to the order of the Ministry of Health of the Russian Federation No. 708n dated August 23, 2010) [12].

The biosubstrate was taken in vivo from experimental and control animals, except for the period of 3 days (from surviving animals). In the blood serum of experimental and control animals, the activity of alanine aminotransferase (AlAT, U/L) and alkaline phosphatase (AP, mmol R/h·l) - by the kinetic method, glucose levels (mmol/l) - by the glucose oxidase method, total protein (g/l) - by the biuret method. The ALP activity in the liver homogenate was determined according to the method of A. Bodansky [14].

Sodium β-glycerophosphate in medial buffer (pH = 9.6) was taken as a substrate. Enzyme activity was expressed as mg of inorganic phosphorus cleaved from sodium β-glycerophosphate during one hour of incubation at 37°C per 1 g of raw tissue (mg P/h·g). The content of glycogen in the liver homogenate was determined by the method of S. Seifter [14]. The method is based on the ability of glycogen to give with anthrone in concentrated sulfuric acid when heated, a blue color, the intensity of which is proportional to the concentration of glycogen.

The glycogen content was expressed in g/kg wet tissue. The material for histological and histochemical studies was fragments of the liver of experimental and control rats. The organs were fixed in 10% neutral formalin, wired and embedded in paraffin + wax. Serial sections (5 μm) were obtained from each block and stained with hematoxylin-eosin [10].

In unfixed liver sections (10 μm) prepared on a cryostat, the content of total lipids (Sudan III), glycogen (according to McManus), activity of alkaline phosphatase (according to Burston), succinate dehydrogenase (SDH, Nachlas), and monominoxidase (MAO, according to Glenner), lactate dehydrogenase (LDH, according to Hess, Scarpelli, and Pierce) [13]. Pathological studies were carried out at the Department of Toxicology of the Research Institute of Biophysics of the Angarsk State Technical Academy (D.Sc., Professor V.V. Benemansky).

Statistical analysis of the obtained results was carried out using the STATISTICA 6.1 licensed software package. (StatSoft Inc., USA); license holder FGBU "Scientific Center for Family Health and Human Reproduction" SB RAMS (Irkutsk). The arithmetic mean value (M) and the standard error of the arithmetic mean value (m) were calculated.A preliminary expert evaluation was carried out for the applicability of the parametric Student's t-test and Fisher's F-test. In the case when differences between quantitative traits were identified by both the t- and F-criteria (the Fisher-Behrens problem), the nonparametric Mann-Whitney U-test was used.Differences between the experimental data obtained in the experimental and control groups were considered statistically significant at $p < 0.05$. RESULTS AND DISCUSSION 30 minutes after the animals received solutions of ethanol and 2,8,9-THCA, the ALT level in the experiment did not differ from that in the intact control ($p > 0.05$), while the enzyme activity in the positive control significantly exceeded the experimental values (ethanol + 2,8,9-THCA) and intact control data - by 28.3% and 32.8%, respectively.

Thus, a single intragastric administration of 2,8,9-THCA into the body of experimental rats has a positive effect on the indicators of the state of liver functions in AOE, stimulating the processes of gluconeogenesis and helping to restore the total protein content in blood serum tolevelofintactcontrol.

The data obtained during the experimental study made it possible to establish that ethanol at a dose of 12 g/kg in all experimental animals has a pronounced damaging effect on the liver, which manifests itself in a statistically significant increase in the activity of liver enzymes (AlAT, alkaline phosphatase), hypoglycemia, and morphologically - in the development proteinaceous and hydropic dystrophy.

It has been proven that the use of 2,8,9-THCA in the experimental correction of BAE helps to reduce metabolic and morphological disorders, resulting in a significant increase in the survival rate of experimental animals. The zinc-containing protector 2,8,9-THCA and the method for treating BOE using it are protected by a patent [17], which creates the basis for clinical trials of this chemical compound and its subsequent introduction into medical practice.

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