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Research Article

Derivatives of 3-Hydroxypyridine in The Correction of Disorders in The Structural and Functional Properties of Erythrocytes in Experimental Acute Destructive Pancreatitis Due to Chronic Ethanol Intoxication

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Abstract. At present, acute pancreatitis only in some areas is a rather well-studied disease of the abdominal organs, however, the destructive forms of this disease have various developmental patterns, complications and, often unfavorable outcomes. The aim of the research is to establish the possibilities to correct the disorders in the functional and structural features of erythrocytes by 3-hydroxypyridine derivatives in experimental acute destructive pancreatitis due to chronic ethanol intoxication. In experimental acute destructive pancreatitis due to a 60-day ethanol intoxication there was a decrease in the content of proteins (a - ? ß -spectrin, ankyrin, anion transport protein, actin, gyceraldehyde-3-phosphate dehydrogenase, glutation-S transferase) and lipids (phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, glycerophospholipids, sphingomyelin, phospholipids, triacylglycerol, sum of mono- and diacylglycerol), an elevated level of band 4.1 and 4.5 proteins, pallidin, dematin, tropomyosin and lipids (lysophosphatidylcholine, cholesterol, it's esters, non-esterified fatty acids), a disorder in intrinsic cellular metabolism of erythrocytes (an increased concentration of lipid peroxidation products, a decreased activity of catalase, superoxide dismutase, degree of stable metabolites of nitrogen oxide and sorption indicators of membrane) in the erythrocyte membrane. The study has revealed that the greatest efficiency in correction of disorders in the functional and structural feutures of erythrocytes from among the derivatives of 3-hydroxypyridine has a compound ß - hydroxynicotinoylhydrazon 2-methyl-3-hydroxy-4-formyl-5-oxymethylpyrydine dihydrochloride, and the least one - 2-ethyl-6-methyl-3-hydroxypyrydine malate (etoxydol), the administration of 2-ethyl-6-methyl-3-hydroxypyrydine succinate (mexidol) has shown an intermediate result.

Keywords: Acute Destructive Pancreatitis, Ethanol, Derivatives of 3-Hydroxypyridine, Erythrocytes.

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1. INTRODUCTION

Despite the existing diagnostic and therapeutic algorithms, the volume and methods of pharmacotherapy aimed at stopping the rise in pancreatic lesions, the development of its individual complications has not been finally resolved. Experimental and clinical studies have shown the development of predominantly destructive forms of acute pancreatitis in close relation to alcohol intake. Destructive pancreatitis of alcoholic etiology is known to be characterized by more severe damages to the nervous, cardiovascular and digestive systems, and primarily the hepatic parenchyma[1-3]. In presence of chronic alcohol intoxication (CAI) there develop cytolytic, cholestatic, liver cell failure biochemical syndromes of hepatocytes damage, the lipid peroxidation activation (LPO) and blood coagulation processes is observed, a drop in the whole number of circulating erythrocytes and their membrane sorption parameters, the emergence of secondary alcohol-associated immunodeficiency is noted[4,5]. Pathogenic mechanisms of tissue damage, due to the growth of oxidative stress, in particular, are also characteristic of acute pancreatitis when LPO processes cause damages not only to pancreatic cells, but also to the hepatocytes membranes, peripheral blood cells, erythrocytes, in particular[6]. In recent decades, various authors in their studies have established a significant role of erythrocytes in the regulation of various elements of homeostasis not only in the normal conditions, but also in pathological conditions, including the diseases of the hepatopancreatobiliary system[3,4]. At the same time, there are practically no data on changes in the structural components of the erythrocytes membrane due to the isolated effect of ethanol and acute pancreatitis in presence of alcohol intoxication, and the arising activation of LPO in such a case and damage to cell membranes results in microcirculatory disorders and tissue hypoxia, which negatively affect the processes of reparative regeneration which underlie the infectious complications of destructive pancreatitis. Thus, there is no doubt about the pathogenetic role of changes in the erythrocytes membrane and oxidative disorders in acute pancreatitis, especially in presence of prolonged alcoholization, however, the issues of their correction in many aspects remain open: there are no clear terms and ways of these disorders removal, and preparations with antioxidant effects are often not administered and are not included in the standards of this disease treatment [3,7]. Multi-year researches have resulted in the synthesis of several compounds and creation of several original domestic medicinal substances, which belong to 3- hydroxypyridine (3-HOP) class and possess antioxidant, antihypoxic, membrane-protective and other properties: 2-ethyl-6-methyl-3-HOP hydrochloride (emoxipine), 2-ethyl-6-methyl-3-HOP succinate (mexidol, mexicor), 2-ethyl-6-methyl-3-HOP malate (ethoxidol), the compound β -hydroxynicotinoylhydrazone 2-methyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine dihydrochloride[1,2,8]. Together with 3-HOP derivatives, they have not been investigated for the possibility to correct the structural and functional properties of erythrocytes in experimental acute destructive pancreatitis (ADP) in presence of chronic ethanol intoxication. The aim of the research is to establish the possibilities to correction the disorders in the functional and structural feutures of erythrocytes by 3-hydroxypyridine derivatives in experimental acute destructive pancreatitis due to chronic ethanol intoxication.

2. MATERIALS AND METHODS

This current study were performed on 110 healthy mature Wistar rats with 130-180 g weights. We used the animals that underwent quarantine in the vivarium of Kursk State Medical University and had no external signs of any diseases. All research were performed at the similar time, from 8 a.m. to 12 p.m., according to the regulations of laboratory practice of Russia (Animal usage approval order No. 267 of the Ministry of Health of Russia, dated 19th June 2003). In this research the following 3-HOP derivatives were studied: ethylmethylhydroxypyridine malate by SINTEZ AKO OAO (Kurgan, the RF); ethylmethylhydroxypyridine succinate (2-ethyl-6-methyl-3-HOP succinate, mexidol) by ZAO "ALSI Pharma" (Moscow, the RF) and the compound β -hydroxynicotinoylhydrazone 2-methyl-3-hydroxy-4-formyl-5-oxymethylpyridine dihydrochloride (DONAHP). All the studied derivatives of 3-HOP were intraperitoneally introduced within fifteen days, from the 16th day of ethanol intoxication, in 24 hours followed mexidol and ethoxidol at a dose of 50 mg/ kg, DONAHP compound at a dose of 35 mg/ kg. The preparations dosages used were based on the recommendations of the "Register of Medicinal Remedies in Russia" (2010) and instructions for their administration. The combination DONAHP was used according to the authors of the patent recommendations for the compound [9]. CAI underwent modelling through forced intragastric administration of 20% ethanol solution at a dose of 3 ml/ kg in 24 hours for 60 days. ADP was induced on the 55th day of ethanol administration by the ducts ligation of the pancreas left and right, followed by stimulation with proserin at a dose of 0.2 mg/ kg three times in 60 min. Experimental animals were split into five classifications with 10-11 animals in each one: the 1st group (control) - healthy rats; the 2nd one – ADP in presence of CAI; the 3rd group - ADP in presence of CAI, the introduction of ethoxidol; the 4th group - ADP in presence of CAI, the introduction of mexidol; the 5th group - ADP in presence of CAI, the introduction of DONAHP. The rats were killed in 24 hours after the last introduction of ethanol and 3-HOP derivatives. The mortality rate of experimental animals within 5 days following ADP modeling in the 2nd group was 70% and in the 3rd, 4th and 5th groups 59%, 48% and 41%., respectively, Erythrocytes and plasma were obtained from 5 ml of heparinized blood; for this purpose, the blood being centrifuged, the plasma was separated, and the packed erythrocytes were defecated twice in 20 ml of 10 mM Na-phosphate buffer (pH = 7.4) having 0.9% sodium chloride and 3% dextran T-500 for 30 min at a 37° C temperature. Following the centrifugation the supernatant has been eliminated by aspiration, and the packed erythrocytes were exposed to further purification on a chromatographic column through HBS-cellulose, followed by the evaluation of the sorption capacity of their glycocalyx (SCG) and the sorption capacity of erythrocytes (SCE)[8,10]. The erythrocyte membranes have been isolated by the Dodge method[11], the membrane lipids were defined by the approach of thin-layer chromatography[5,9,12]. Protein electrophoresis was performed in the lack of sodium dodecyl sulphate in vertical plates of polyacrylamide gel based on the Laemmli method[2,4,10], proteins were stained with Kumasi blue R-250. The intensity of LPO procedures was evaluated by the curb of acyl hydroperoxides (AHP) and malonyldialdehyde (MDA) in erythrocytes, forming a colored complex accompanied with thiobarbituric acid. The evaluation of AHP and MDA was performed by a "TBK-Agat" kit (Agat-Med, Russia), utilizing an "Apel-330" spectrophotometer (Japan) at wavelength of 535 nm and 570 nm. The status of the antioxidant system was defined by the approach of competitive enzyme-linked

immunosorbent assay (ELISA) with the reaction products' detection at wavelengths ranging from 405 to 630 nm with the aid of ready-made kits to evaluate the action of SOD generated by "Bender Medsystems" (Austria) and to evaluate the action of catalase generated by "Cayman Chemical" (USA). All the ELISA outcomes were registered utilizing a Sunrise microplate photometer (Tecan, Austria). Statistical procedure of the outcomes was performed based on the commonly admitted standards of the variable-bases statistical analysis with the determination of the the mean deviation (m), mean values (M) applying the Microsoft Excel software package, 2010. The importance of the differences was evaluated by Mann-Whitney U test. The differences were deemed significant at $p<0.05$.

3. RESULTS AND DISCUSSION

When modeling ADP in presence of CAI, there was a decrease in the content of α - and β -spectrin, ankyrin, anion transport protein (ATP), actin, glyceraldehyde-3-phosphate dehydrogenase (G-3-PD), glutathione-S-transferase (G-S-T) and an increase in the level of bands 4.1 and 4.5 proteins, pallidin, dematin, tropomyosin. The introduction of ethoxidol normalizes the level of pallidin, the level of band 4.5 protein, corrects the representativeness of the band 4.1 protein, actin, tropomyosin, and G-S-T towards the values of healthy animals. The use of mexidol, compared to ethoxidol, additionally normalizes the content of ATP, dematin, tropomyosin and corrects the level of α -spectrin, ankyrin, G-3-PD. The use of DONAHP, in comparison with mexidol, additionally normalizes the representativeness of the band 4.1 protein and corrects the count of β -spectrin and actin (Table 1).

Table 1. Correction of Disorders in Protein Content of Erythrocyte Membrane with 3-HOP Derivatives in ADP Associated with CAI (M ± m)

Indicators	1	2	3	4	5
	Control	-	Introduction of ethoxidol	Introduction of mexidol	Inroduction of DONAHP
α -spectrin	108,3±4,2	82,1±3,3*1	83,0±2,3*1	95,1±2,8*1-3	94,1±3,1*1-3
β -spectrin	103,1±3,3	86,3±2,2*1	83,9±2,9*1	84,3±3,5*1	92,9±2,5*1-4
Ankyrin	89,0±3,0	75,2±1,6*1	73,8±2,1*1	80,3±1,9*1-3	83,1±2,2*1-3
ATP	171,6±4,2	160,2±3,7*1	161,4±2,2*1	173,9±3,9*2,3	175,4±3,6*2,3
4.1	70,4±3,2	88,3±2,4*1	76,3±1,9*1,2	75,9±2,1*1,2	71,5±2,2*2-4
Pallidin	92,1±4,1	100,1±3,2*1	91,3±2,6*2	89,8±3,8*2	88,3±4,1*2
4.5	79,8±3,1	84,5±2,0*1	80,2±1,5*2	78,9±3,1*2	77,4±2,3*2
Dematin	91,2±3,1	104,4±3,5*1	101,3±2,8*1	87,2±3,0*2,3	86,2±2,9*2,3
Actin	88,1±3,2	69,2±2,4*1	72,5±2,2*1,2	73,9±2,9*1,2	79,3±2,2*1-4
G-3-PD	54,3±2,0	44,0±2,1*1	40,3±2,1*1	49,3±1,8*1-3	50,0±2,1*1-3
Tropomiosine	63,7±3,1	85,0±2,7*1	69,3±2,2*1,2	65,3±1,7*2,3	64,1±2,2*2,3
G-S-T	61,2±2,5	42,4±1,4*1	54,9±2,0*1,2	57,1±2,5*1,2	56,8±2,3*1,2

Note: asterisk (*) marks significant differences in medians (p<0.05).

When simulating ADP associated with chronic alcoholization in animals, there was a decrease in phosphatidylcholine (PC), phosphatidylethanolamine(PE),phosphatidylserine(PS), phosphatidylinositol (PI), glycerophospholipids (GPL is the sum of PC, LPC, PE, PS and PI), sphingomyelin (SM), phospholipids (PL - the sum of GPL and SM), triacylglycerols (TAG), the sum of mono- and diacylglycerols (DAG, MAG), a rise in the degree of lysophospatidylcholine (LPC), cholesterol (C) and its esters (CE), and nonesterified fatty acids (NEFA) in the erythrocyte membrane. The introduction of ethoxidol normalizes the EC content and corrects, but not the control values, the representativeness of PC, PI, SM, PL, NEFA. The use of mexidol, compared to ethoxidol, additionally normalizes the content of PS, PI, GPL, MAG+DAG, brings the representativeness of LPC, FE, PL, C and NEFA closer to the healthy animals' values[1,11,13]. The administration of DONAHP compared to mexidol additionally normalizes the level of PC, PE, GPL, PL, C, NEFA and corrects the content of SM (Table 2).

Table 2. Correction of Disorders in Lipids Content of Erythrocyte Membrane with 3-HOP Derivatives in ADP Associated with CAI (M ± m)

Indicators	1	2	3	4	5
	Control	-	Introduction of ethoxidol	Introduction of mexidol	Inroduction of DONAHP
PC	24,0±0,7	20,1±0,2*1	21,7±0,6*1,2	22,3±0,4*1,2	25,8±1,3*2-4
LPC	3,9±0,05	6,2±0,1*1	6,0±0,1*1	5,2±0,04*1-3	5,1±0,06*1-3
PE	24,6±1,0	19,6±1,0*1	19,2±1,1*1	22,4±0,8*1-3	24,7±1,4*2-4
PS	19,7±0,7	18,3±0,4*1	18,1±0,5*1	19,4±0,3*2,3	19,5±0,6*2,3
PI	4,6±0,05	3,3±0,04*1	3,7±0,03*1,2	4,5±0,08*2,3	4,7±0,2*2,3
GPL	76,8±2,2	67,5±1,3*1	68,7±1,8*1	73,8±1,4*2,3	79,8±2,2*2-4
SM	12,2±0,5	7,3±0,4*1	9,4±0,2*1,2	9,1±0,3*1,2	10,9±0,3*1-3
PL	89,0±2,0	74,8±1,7*1	78,1±2,1*1,2	82,9±1,9*1-3	90,7±1,5*2-4
C	44 ,8±2,1	61,8±0,6*1	60,6±1,4*1	57,4±1,2*1-3	48,5±2,1*2-4
CE	40,0±2,2	44,1±1,2*1	41,7±1,3*2	41,4±1,2*2	40,4±2,1*2

TAG	14,5±0,7	12,3±0,3*1	11,0±1,1*1	11,6±1,0*1	13,9±0,8*2-4
DAG+MAG	9,6±0,2	8,3±0,3*1	8,0±0,5*1	9,3±0,6*2,3	10,0±0,9*2,3
NEFA	2,9±0,05	4,2±0,03*1	4,0±0,07*1,2	3,5±0,04*1-3	3,0±0,06*2-4

Note: asterisk (*) marks significant differences in medians (p<0.05).

When assessing the parameters of erythrocytes metabolism, it has been established that in presence of ADP and CAI, the concentration of LPO products (MDA, AHP) in the red blood cells increases, the activity of catalase, SOD, the level of SM_{NO} and the sorption parameters of erythrocyte membrane (SCE and SCG) decrease. The introduction of ethoxidol brings all the studied metabolic parameters of erythrocytes closer to the control values[2,9,14]. The use of mexidol additionally normalizes the activity of catalase and increases, but not to the parameters of the norm, the concentration of SM_{NO}. The use of DONAHP, in comparison with mexidol, additionally normalizes the level of LPO products, SM_{NO} and corrects SOD activity (Table 3).

Table 3. Correction of Disorders in Metabolic Status of Erythrocytes with 3-HOP Derivatives in ADP Associated with CAI (M ± m)

Indicators	1	2	3	4	5
	Control	-	Introduction of ethoxidol	Introduction of mexidol	Inroduction of DONAHP
MDA, μmol/L	0,37±0,06	0,98±0,02*1	0,56±0,04*1,2	0,61±0,3*1,2	0,46±0,03*2-4
AHP, RU	0,13±0,01	0,65±0,02*1	0,3±0,02*1,2	0,28±0,03*1,2	0,14±0,02*2-4
Catalase, mcat/L	12,4±0,9	7,2±0,8*1	8,9±0,4*1.2	11,4±0,6*2,3	12,7±1,1*2,3
SOD, RU /ml	30,1±1,4	11,4±1,1*1	18,0±1,5*1,2	16,2±2,0*1,2	23,5±2,1*1-4
SM_{NO}, μmol/L	4,9±0,1	2,1±0,07*1	3,1±0,1*1,2	3,9±0,04*1-3	5,0±0,2*2-4
SCG, 10^{12} gram/erythrocytes	52,5±0,6	27,0±2,0*1	32,5±1,1*1,2	31,4±1,4*1,2	33,3±2,2*1,2
SCE, %	2,8±0,03	1,3±0,08*1	1,8±0,04*1,2	1,9±0,09*1,2	1,7±0,1*1,2

Note: asterisk (*) marks significant differences in medians (p<0.05).

Thus, in ADP associated with CAI 100% of the parameters of the structural and functional properties of erythrocytes turned out to be different in content from the values of healthy animals. The changes affected both the peripheral proteins responsible for the structure formation and stabilization of the erythrocyte membrane, morphogenesis and the membrane flexibility (actin, tropomyosin), and integral proteins responsible for the intrinsic cellular metabolism (ATP, G-3-PD, G-S-T, band 4.5 protein)[13-15]. As for the determined disorders of the lipid profile content, first of all, a drop in the content of membrane SM and PL, forming the fundation of the double lipid framework of the cell membrane and have a substantial role in the protein macromolecules alignment and erythrocytes normal metabolism[3,7,12], along with the changes in the proteins architectonics, disrupted the intrinsic cellular metabolism and functional properties of peripheral blood erythrocytes. The introduction of ethoxidol normalized 9.4% of the changed parameters, corrected, but not to the normal values, 50.0%, and 40.6% of the parameters remained unchanged. The administration of mexidol normalized and corrected 34.3% and 59.4% of indicators, respectively, having no effect on 6.3% of the parameter. The most effective compound turned out to be DONAHP, since its use in the context of ADP associated with CAI normalized 65.6% and corrected 34.4% of the indicators of the functional and structural features of erythrocytes[4,13,16]. The main components in the disturbance of the organ functional activity in pancreatitis are the development of systemic oxidative stress, acceleration of LPO processes, an increase in phospholipase activity, which bring about the destabilization of cell membranes not only of pancreatic cells, but also of erythrocytes[6,8,17]. Disarrangement of cell membrane lipids, which are a substrate for peroxidation and enzymic hydrolysis, results in the disruption of antioxidant homeostasis, a decrease in the activity of transport and enzyme proteins and, ultimately, to irreversible structural and functional changes[4,7,11]

4. CONCLUSIONS

Based on the results of the study, it can be concluded that

1. In the erythrocyte membrane of experimental animals with acute destructive pancreatitis in presence of a 60-day ethanol intoxication, there were changes in the content of all the studied proteins and lipids, the intrinsic cellular metabolism of red blood cells is disrupted.

2. The highest efficiency in correcting disorders of the structural and functional properties of erythrocytes among the derivatives of 3-hydroxypyridine belongs to the compound β - hydroxynicotinoylhydrazone 2-methyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine dihydrochloride, the administration of ethoxidol has the least efficacy, and the use of mexidol gives an intermediate result.

5. Authors' Contribution Statement

E.S. Litvinova, and A.V. Kharchenko, conceived of the presented idea. N.S. Razinkova, and V.A. Ragulina developed the theory and performed the computations. All authors discussed the results and contributed to the final manuscript.

6. CONFLICT OF INTEREST

Conflict of interest declared none.

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