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PHENFORMIN ATTENUATES THE OXIDATIVE-NITROSATIVE STRESS IN THE LIVER OF RATS UNDER LONG-TERM ETHANOL ADMINISTRATION

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Modulation of the AMP-activated protein kinase (AMPK) pathway activity is considered to be a promising option in the development of approaches to chronic alcoholic hepatitis treatment. Phenformin, which is a biguanide, has been reported to increase AMPK activity. The aim of this work was to estimate the effect of phenformin as AMPK activator on the development of oxidative-nitrosative stress in the liver of rats under conditions of long-term ethanol administration. The experiments were performed on 24 male Wistar rats, divided into 4 groups: control; animals, which received phenformin hydrochloride orally at a dose of 10 mg/kg daily for 63 days; animals with a forced intermittent alcoholization for 5 days by intraperitoneal administration of 16.5% ethanol solution in 5% glucose at the rate of 4 ml/kg b.w. and subsequent transfer to 10% ethanol as the only source of drinking; animals with chronic alcohol hepatitis simulation and phenformin administration. Superoxide dismutase, catalase, NO synthase isoforms activity, superoxide anion radical production, concentration of malonic dialdehyde, peroxynitrite, nitrites, nitrosothiols concentration and oxidative modification of proteins (OMP) were estimated in liver homogenates. The increased production of oxygen and nitrogen active forms and OMP intensification in the liver of rats under long-term administration of ethanol was detected. Phenformin introduction under long-term ethanol administration was shown to limit the excess peroxynitrite formation and to prevent oxidative damage to rat liver proteins.

K e y w o r d s: liver, chronic alcoholic hepatitis, phenformin, oxidative and nitrosative stress, AMP-activated protein kinase.

Chronic alcohol consumption can lead to steatosis, hepatitis, fibrosis and cirrhosis of the liver and even hepatocellular carcinoma [1]. The main biochemical mechanisms of the development of alcoholic fatty liver disease largely depend on the ability of ethanol to inhibit the oxidation of fatty acids and change the redox potential in the liver [2]. During its biotransformation, ethanol changes the metabolism of hepatocytes and their energy balance: 1) Alcohol dehydrogenase of the ADH1B class, cytochrome P450 2E1 (CYP2E1) and peroxisomal catalase oxidize ethanol to acetaldehyde, which is classified as a category 2 carcinogen, which, under the action of aldehyde dehydrogenase isoform ALDH2, is converted to acetic acid, which with the help of ATP-dependent acetyl-CoA synthetase forms a universal metabolite acetyl-CoA, a substrate of the tricarboxylic acid cycle [3]. 2) The formation of a large amount of reactive oxygen species (ROS) during ethanol metabolism activates lipid peroxidation, oxidative modification of proteins and reduces the antioxidant capacity of hepatocytes [4]. 3) Alcohol-activated casein kinase phosphorylates methionine acyltransferase α1 (MATα1), promoting the interaction of MATα1 with prolyl cis-trans isomerase 1 (PIN1) and reducing the concentration of MATα1 in mitochondria. As a result, MATα1 is not involved in the mitochondrial cycle of tricarboxylic acids, oxidative phosphorylation and β-oxidation of fatty acids, which leads to lipid accumulation and the development of mitochondrial dysfunction in hepatocytes [5]. In addition, because CYP2E1 has high NADPH oxidase activity, it can stimulate the transport of NADPH to mitochondria, increase ROS generation,

increase mitochondrial DNA damage, and further inhibit β-oxidation of fatty acids [6]. 4) Induced nitric oxide synthesis, which is regulated by signal transducer and activator of transcription 3 (STAT3), accelerates the development of hepatitis and liver fibrosis through excessive synthesis of NO, which, under conditions of high ROS generation, can turn into peroxynitrite and increase hepatocyte damage [7].

In both in vivo and in vitro alcohol-induced hepatocyte experiments, AMP-activated protein kinase (AMPK) activity was reduced as an adaptive response to alcohol-mediated fatty liver disease. At the same time, the sensitivity of the liver to changes in the AMP/ATP ratio decreases [8]. AMPK activity can be increased by phosphorylation of the Thr172 site of the AMPK α-subunit by Liver kinase B1 (LKB1) or Ca^{2+}/calmodulin-dependent protein kinase kinase-β (CaMKKβ) or by pharmacological activators (metformin, 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR)) [9]. In addition, AMPK activity is significantly affected by the intracellular AMP/ATP ratio: an increase in AMP/ATP contributes to the activation of AMRK, inhibiting lipid synthesis and promoting fatty acid oxidation [10]. AMPK by phosphorylation at Ser871 inhibits the activity of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR), which plays a key role in the regulation of cholesterol synthesis [11]. In addition, the following major pathways are known by which AMPK reduces lipid accumulation in the liver: 1) Activated AMPK inhibits acetyl-CoA carboxylase by phosphorylation, which prevents its dimerization and, as a result, reduces fatty acid synthesis [10]; 2) Malonyl-CoA is not only a precursor of fatty acid synthesis, but also a powerful inhibitor of carnitine acyltransferase1 (CPT1). AMPK phosphorylates acetyl-CoA carboxylase to inactivate it, reducing malonyl-CoA synthesis, which promotes CPT1 expression and thus increases fatty acid oxidation [8]. Thus, AMPK can reduce lipid accumulation, promote fatty acid oxidation, and inhibit cholesterol and fatty acid synthesis. Therefore, pharmacological modulation of the activity of the AMPK pathway may be a promising option in the development of drugs for the treatment of chronic alcoholic hepatitis.

The purpose of this work is to establish the effect of activation of AMP-activated protein kinase on the development of oxidative-nitrosative stress in the liver of rats under the conditions of long-term ethanol administration.

Materials and methods

Animals. The experiments were performed on 24 male Wistar rats weighing 180-220 g. The animals were divided into 4 groups (6 animals in each): I – control group; II – group animals, which received phenformin hydrochloride (phenformin, Sigma-Aldrich), as an activator of AMP-activated protein kinase, orally at a dose of 10 mg/kg [12] daily for 63 days (AMPK activation group); III group – animals, on which we simulated alcoholic hepatitis ($n = 6$) by forced intermittent alcoholization for 5 days, with repetition after two days by intraperitoneal administration of 16.5% ethanol solution in 5% glucose solution, at the rate of 4 ml/kg body weight. Then, they were converted to 10% ethanol as the only source of drinking water, first proposed by Yu. M. Stepanov [13, 14] (Alcoholic hepatitis group). IV group – animals, on which we simulated chronic alcohol hepatitis as in group III and administered phenformin according to the scheme of group II (Alcoholic hepatitis with AMPK activation group).

The control group included animals that were subjected to similar manipulations throughout the study period, but were injected with a physiological solution (0.9% sodium chloride). The conditions for keeping animals in the vivarium were standard.

Bioethics. The experiments followed the recommendations of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 1986) in accordance with the "General Principles of Animal Experiments" approved by the First National Congress of Bioethics of Ukraine (September 2001), and the requirements of the "Procedure for scientific research, animal experiments" (2012). The animals were kept in a vivarium accredited in accordance with the "Standard rules of order, equipment and maintenance of experimental biological clinics (vivarium)". Devices used for research were subject to metrological control.

All manipulations with laboratory animals were approved by bioethical committee of Poltava State Medical University (Record No 197 from 23.09.2021).

Removal of animals from the experiment occurred on day 63 by taking blood from the right ventricle of the heart under thiopental anesthesia. Serum and liver were immediately studied.

Biochemical studies. General NO-synthase activity (gNOS) was evaluated by the increase of

nitrites after incubation of 10% liver homogenate (0.2 ml) for 30 min in the incubation solution (2.5 ml of 0.1 M Tris buffer, 0.3 ml of 320 mM aqueous solution of L-arginine and 0.1 ml of 1 mM NADPH+H^+ solution). To determine the activity of constitutive NOS (cNOS), 1% solution of aminoguanidine hydrochloride was used, and the incubation time was extended to 60 min [15]. The activity of inducible NOS (iNOS) was calculated by the formula: iNOS= gNOS-cNOS.

Adrenaline auto-oxidation reaction in an alkaline environment with the generation of superoxide was used to determine SOD activity [16]. The method of catalase activity estimation was based on the determination of colored products formed by the reaction of hydrogen peroxide with ammonium molybdate [17].

Free malonic dialdehyde specifically reacts with 1-methyl-2-phenyl-indole in a mixture of methanol and acetonitrile to form chromogen (carbocyanine dye) with a maximum light absorption at a wavelength of 586 nm [18]. Peroxynitrite concentration was measured by using its reaction with potassium iodide under pH 7.0 in 0.2 M phosphate buffer with the same pH, which yields I3 with maximum absorbance at 355 nm wavelength [15].

The method for the determination of nitrosothiols was based on the determination of the difference in the concentration of nitrites (NO_2^-) using Griess reagent (modified by Ilosvay) before and after oxidation of nitrosothiol complexes (SNO) to nitrites with a solution of mercuric chloride ($HgCl_2$) [19]. Sulfides specifically react with N-N-dimethyl-paraphenylenediamine in the presence of Fe^{3+} and excess of hydrochloric acid to form a red-pink chromogen with a maximum light absorption at a wavelength of 667 nm [20].

The concentration of oxidized proteins was determined spectrophotometrically (Ulab 101, China). The principle of the method is that 2,4-dinitrophenylhydrazine reacts with the carbonyl groups of oxidized proteins to form dinitrophenylhydrazones which are then detected [21].

The method for estimation of superoxide anion radical production was based on Nitroblue tetrazolium (NBT) reduction by superoxide with the formation of diformazan, a dark blue insoluble precipitate [22].

In the serum of rats we determined the activity of γ-glutamyltranspeptidase (γ-GGT) using a diagnostic kit, manufacturer NPP "Philisit-Diagnostics".

Statistics. Statistical processing of biochemical research results was performed using Kruskal–Wallis one-way analysis of variance with the following pairwise comparison using the Mann-Whitney U-test. In order to avoid multiple comparison errors, we used correction by the Bonferroni method. All statistical calculations were performed in Microsoft Office Excel and its extension Real Statistics 2019. The difference was considered statistically significant at $P < 0.05$.

Results

Analyzing the marker enzyme of liver cell damage in blood serum, we found that the activity of γ-GGT in rats under the conditions of phenformin administration decreased by 2.2 times ($P = 0.0022$), in animals under conditions of chronic alcoholic hepatitis it decreased by 5.58 times ($P = 0.0022$), and under the conditions of AMPK activation by against the background of chronic alcoholic hepatitis it decreased by 2.31 ($P = 0.0022$) times compared to the control group of rats (Fig.).

Effect of phenformin as activator of AMP-activated protein kinase on biochemical parameters of rat liver. The analysis of the data obtained as a result of experimental studies allowed us to establish the following changes in the liver of rats under the conditions of the introduction of phenformin as an activator of AMP-activated protein kinase: cNOS activity increased by 2.11 times ($P = 0.0022$), SOD activity increased by 1.12 times ($P = 0.026$), MDA concentration increased by 1.53 times ($P = 0.0022$), OMP increased by 2.68 times ($P = 0,0022$), peroxynitrite elevated by 6.09 times ($P = 0.0022$), sulfide anion increased by 3.8 times ($P = 0.0022$) compared to the control group of rats. The production of the superoxide anion radical in the liver of rats under the conditions of phenformin administration decreased by 1.15 times ($P = 0.0022$), the concentration of nitrosothiols decreased by 3.83 times ($P = 0.0022$) and nitrites by 2.61 ($P = 0.0022$) times in relation to the control group of rats (Table).

Changes in the biochemical indicators of the liver of rats under the conditions of phenformin administration as activator of AMP-activated protein kinase against the background of chronic alcoholic hepatitis modeling. In the group of animals injected with phenformin to activate AMPK against the background of chronic alcoholic hepatitis, the iNOS activity in the liver increased by 5.06 times ($P = 0.0022$), cNOS activity increased by 1.63 times

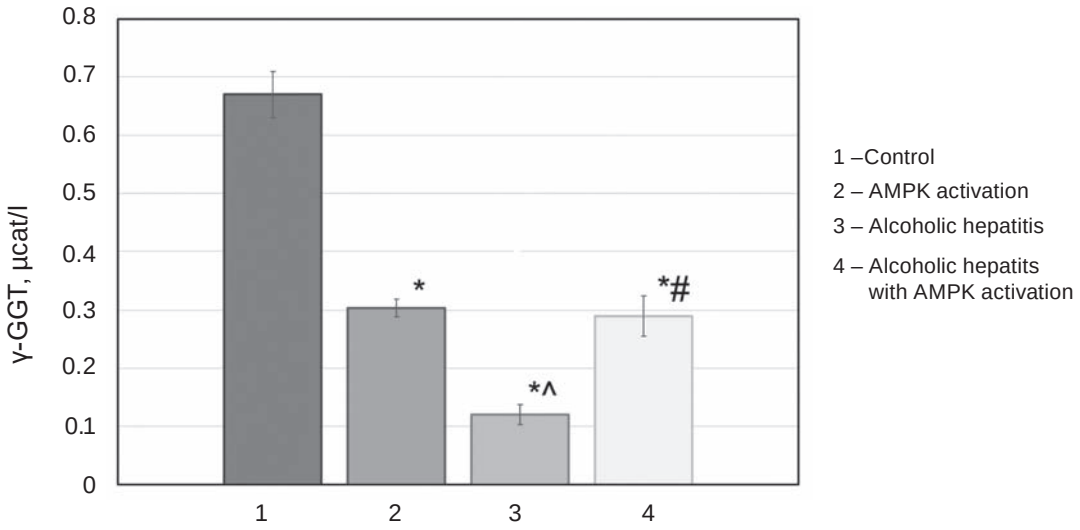

*Fig. Activity of γ-glutamyltranspeptidase (γ-GGT) in blood serum of rats under conditions of phenformin administration and simulation of chronic alcoholic hepatitis, μcat / l. *P < 0.01 compared to the control group; ^P < 0.01 compared to AMPK activation group; #P < 0.01 compared to alcoholic hepatitis group*

Table. Biochemical indicators in the liver of rats under conditions of phenformin as an activator of AMP-activated protein kinase and chronic alcoholic hepatitis (M ± m, n = 6)

Biochemical parameters	Groups			
	Control	AMPK activation	Alcoholic hepatitis	Alcoholic hepatitis with AMPK activation
Inducible NO synthase activity, μmol/min per g of protein	0.16 ± 0.02	0.170 ± 0.007	0.72 ± 0.07*^	0.81 ± 0.09*^
Constitutive NO synthases activity, μmol/ min per g of protein	0.027 ± 0.0003	0.057 ± 0.002*	0.044 ±0.0009*^	0.044 ± 0.002*^
Superoxide dismutase activity, c.u.	12.34 ± 0.55	13.83 ± 0.30*	12.23 ± 1.03	7.75 ± 0.32*^#
Catalase activity, μkat/g	0.376 ± 0.008	0.365 ± 0.011	0.23±0.01*^	0.41 ± 0.001*#
Malonic dialdehyde concentration, μmol/g	12.32 ± 0.11	18.90 ± 0.28*	15.91 ± 0.32*^	33.04 ± 0.19*^#
Superoxide anion radical production, nmol/s per g	1.84 ± 0.004	1.60 ± 0.06*	2.71 ± 0.03*^	3.02 ± 0.08*^#
$ONOO^-$ concentration, μmol/g	0.45 ± 0.01	2.74 ± 0.13*	4.26±0.03*^	3.60 ± 0.03*^#
S-NO concentration, μmol/g	0.36 ± 0.019	0.094 ± 0.003*	0.18 ± 0.034*^	0.101 ± 0.004*#
NO_2 concentration, nmol/g	7.14 ± 0.17	2.74 ± 0.11*	5.67 ± 0.34*^	6.18 ± 0.56^
Sulfide anion, μmol/g	7.23 ± 0.17	27.47 ± 0.89*	15.01 ± 0.32*^	38.38 ± 1.15*^#
OMP concentration, c.u.	0.04 ± 0.002	0.107 ± 0.001*	0.34 ± 0.007*^	0.131 ± 0.001*^#

Note. *P < 0.05 compared to the control group; ^P < 0.05 compared to the AMPK activation group; #P < 0.05 compared to alcoholic hepatitis group

(P = 0.0022) compared to the control group of rats (Table), and in relation to the group of animals in which AMPK was activated, the activity of iNOS increased by 4.76 times (P = 0.0022), the activity of cNOS decreased by 1.3 times (P = 0.0022). The activity of SOD in the liver of a group of rats with AMPK activation under the conditions of chronic alcoholic hepatitis modeling decreased by 1.59 times (P = 0.0022) compared to the control, by 1.78 times (P = 0.0022) compared to the group of animals activated by AMPK, and by 1.58 times (P = 0.0022) compared to the group animals with chronic alcoholic hepatitis. In contrast, the catalase activity increased 1.09 times (P = 0.0022) in relation to the control and 1.78 times (P = 0.0022) in relation to the group of rats with chronic alcoholic hepatitis. Under these conditions, the concentration of MDA in the liver increased by 2.68 times (P = 0.0022) in relation to the control, by 1.75 times (P = 0.022) in relation to the group of AMPK activation and by 2.08 times (P = 0.0022) in relation to the group of rats with chronic alcoholic hepatitis. The production of superoxide anion in the liver of rats of the group of animals with AMPK activation against the background of chronic alcoholic hepatitis modeling increased by 1.64 times (P = 0.0022) in relation to the control, by 1.89 times (P = 0.0022) in relation to the AMPK activation group and by 1.11 times (P = 0.0022) in relation to the group rats with chronic alcoholic hepatitis. The concentration of peroxynitrite in the liver of rats increased by 8 times (P = 0.0022) in the group of animals with AMPK activation under the conditions of chronic alcoholic hepatitis modeling compared to the control, by 1.31 times (P = 0.0022) in relation to the group of AMPK activation and decreased by 1.18 times (P = 0.0022) in relation to the group of rats with chronic alcoholic hepatitis. The concentration of nitrosothiols in the liver of rats decreased by 3.56 times (P = 0.0022) in relation to the control and by 1.78 times (P = 0.015) in relation to the group of rats with chronic alcoholic hepatitis. The concentration of NO_2 in the liver of rats increased by 2.26 times (P = 0.0022) in the group of animals with AMPK activation under the conditions of chronic alcoholic hepatitis simulation compared to the group of AMPK activation. The concentration of HS- in the liver of rats increased by 5.31 times (P = 0.0022) in the group of animals with AMPK activation under the conditions of chronic alcoholic hepatitis modeling compared to control, by 1.4 times (P = 0.0022) compared to the group of AMPK activation and by 2.56 times (P = 0.0022) in relation to the group of rats with chronic alcoholic hepatitis. The concentration of OMP in the liver of rats increased by 3.28 times (P = 0.0022) in the group of animals with AMPK activation under the conditions of chronic alcoholic hepatitis modeling compared to the control, by 1.22 times (P = 0.0022) in relation to the group of AMPK activation and decreased by 2.6 times (P = 0.0022) in relation to the group of rats with chronic alcoholic hepatitis.

Discussion

Most studies related to the study of the effect of chronic alcohol consumption on the activity of γ-GGT in the blood plasma indicate an increase in the activity of this enzyme [23, 24]. However, there are also data in the scientific literature indicating that the activity of γ-GGT in the blood plasma under conditions of chronic alcohol abuse reaches its peak at the stage of alcoholic fatty liver dystrophy and begins to decrease with the increase of fibrotic changes in the liver [25]. Also, research by Baros A.M. et al. showed that on the 6th week of alcohol abuse, a decrease in the activity of γ-GGT in the blood plasma was noted, which continued until the 12th week [26]. Therefore, the decrease in the activity of γ-GGT in the blood plasma observed in our study may be a consequence of exhaustion of the body's adaptive systems, which is accompanied by a decrease in the synthesis of γ-GGT in the liver, or an increase in fibrotic changes in the liver tissues.

The development of oxidative damage to lipids and proteins of the liver under the conditions of AMPK activation by phenformin indicates the toxicity of the drug, which is due to its biotransformation in the liver. Phenformin (1-(diaminomethylidene)-2-(2-phenylethyl)guanidine) is a guanidine derivative that was first obtained from *Galega officinalis* [27]. The toxicity of guanidine derivatives is associated with the development of vitamin B_{12} deficiency, which develops with long-term use of drugs of this series [27]. Other negative phenomena that develop under the conditions of long-term excess intake of guanidines to the body are the development of metabolic acidosis due to the accumulation of lactic acid [27]. Also, under conditions of renal insufficiency, the accumulation of guanidine drugs is possible, even under the conditions of their use in non-toxic (therapeutic) doses [27].

The main mechanism of the effect of guanidine derivatives (biguanides), such as phenformin

and metformin, on the activity of the AMPK cascade is the inhibition of mitochondrial complex I, which leads to an increase in the AMP/ATP ratio and substrate-induced activation of AMPK [28]. Another mechanism of action of biguanides on AMPK is the inhibition of the signaling cascade mediated by mammalian target of rapamycin (mTOR), which, according to scientific literature, makes biguanides potential drugs for combination with cytostatics in antitumor therapy [28]. Studies by Huang L. and others have shown that the use of phenformin in combination with sorafenib makes liver tumor cells particularly sensitive to the action of sorafenib [29].

It is worth noting that the mTOR cascade in hepatocytes performs several functions: activation of mTORC1 promotes the development of insulin resistance and lipid formation, while activation of mTORC2 leads to a reduction in insulin resistance [30]. The non-selectivity of biguanides in relation to the blockade of the mTOR cascade in the liver may explain the development of oxidative damage to biological polymers, which is observed in the phenformin group, since the activation of mTORC2 is accompanied by the activation of the Akt cascade, which, in turn, activates the antioxidant transcription factor Nrf2 [28, 31].

The lack of effect of phenformin administration on the activity of the inducible isoform of NO-synthase in the liver of rats may indicate that phenformin has no effect on the activity of transcriptional cascades that control this enzyme, such as activating protein-1 (AP-1) or NF-κB. In the group of phenformin administration, there is a decrease in the content of deposited forms of nitric oxide (nitrosothiols and nitrites), which is possibly associated with the development of acidosis in the liver under the influence of phenformin, which creates conditions for the non-enzymatic recovery of deposited forms of nitric oxide [27]. It is worth noting that the excess of nitric oxide, which is formed by the reductase pathway, probably goes to the formation of peroxynitrite, which causes an increase in peroxynitrite in the phenformin administration group.

The lack of effect of phenformin on the transcriptional cascades that control the activity of the inducible isoform of NO-synthase in the liver persists even under the conditions of a combination of the action of phenformin and chronic ethanol intake. The tendency to increase the reductive formation of nitric oxide also persists when combining alcohol with phenformin, which explains the low level of nitrosothiols in this group. An increase in the concentration of nitrites in a group of animals with a combination of long-term excessive intake of alcohol and the administration of phenformin may be due to increased production of nitric oxide from the inducible isoform of NO-synthase as a result of alcohol-induced activation of pro-inflammatory transcription factors [32].

The increase in the intensity of lipid peroxidation in the group of combined exposure to phenformin and alcoholization of animals to levels higher than alcohol intoxication and those observed in the phenformin administration group may be related to increased toxicity of phenformin due to alcohol-induced impairment of kidney function [33]. Less damage to the protein structures of the liver in the group of rats with a combination of chronic ethanol intake with the introduction of phenformin can be explained by the reduced intensity of protein synthesis due to the activation of AMPK and the inhibition of mTORC1 under the influence of phenformin [34]. A possible decrease in protein synthesis in the liver and a decrease in oxidative damage to protein molecules under the influence of phenformin is a positive phenomenon, as it will reduce the risk of fibrosis by slowing down collagenogenesis and other extracellular proteins. The ability of AMPK to limit fibrosis may be related to inhibition of oxidative stress, inflammation, aerobic glycolysis, and promotion of mitophagy and mitochondrial biogenesis; in addition to its antifibrotic role, AMPK improves liver function and attenuates hepatocyte apoptosis, indicating that it has hepatoprotective and antifibrotic properties [35].

Conclusions. Activation of AMP-activated protein kinase by phenformin leads to increased production of nitric oxide from constitutive isoforms of NO synthase and enhances the formation of peroxynitrite in the liver of rats. The introduction of phenformin for the activation of AMP-activated protein kinase is accompanied by the development of oxidative stress due to the increase in the formation of reactive oxygen species against the background of a compensatory increase in the activity of superoxide dismutase in the liver of rats.

Long-term administration of ethanol leads to an increase in the production of active forms of oxygen and nitrogen in the liver of rats, which leads to increased damage to biological membranes and protein structures due to the development of oxidative-nitrosative stress in hepatocytes.

Activation of AMP-activated protein kinase by phenformin under the conditions of long-term administration of ethanol limits excess peroxynitrite formation and prevents oxidative damage to rat liver proteins.

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ФЕНФОРМІН ЗАПОБІГАЄ РОЗВИТКУ ОКСИДАТИВНО-НІТРОЗАТИВНОГО СТРЕСУ У ПЕЧІНЦІ ЩУРІВ ЗА ТРИВАЛОГО ВВЕДЕННЯ ЕТАНОЛУ

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Модуляція активності АМФ-активованого протеїнкіназного шляху (АМФК) вважається перспективним варіантом у розробці підходів до лікування хронічного алкогольного гепатиту. Відомо, що фенформін, який є бігуанідом, підвищує активність АМФК. Метою роботи було оцінити вплив фенформіну як активатора АМФК на розвиток оксидативно-нітрозативного стресу в печінці щурів за умов тривалого введення етанолу. Досліди проводили на 24 щурах-самцях лінії Wistar, розділених на 4 групи: контрольна; тварини, які отримували фенформін гідрохлорид перорально в дозі 10 мг/кг щоденно протягом 63 днів; тварини, які піддавалися примусовій перерівистій алкоголізації протягом 5 діб, з повтором через дві доби шляхом внутрішньоочеревинного введення 16,5% розчину етанолу на 5% розчині глюкози, з розрахунку 4 мл/кг маси тіла і подальшим переходом на 10% розчин етанолу як єдиного джерела пиття; тварин із симуляцією хронічного алкогольного гепатиту та введенням фенформіну. У гомогенаті печінки оцінювали активність супероксиддисмутази, каталази, ізоформ NO-синтази, продукцію супероксид-аніон-радикалу, концентрацію малонового діальдегіду, пероксинітриту, нітритів, нітрозотіолів та окислювальну модифікацію протеїнів (ОМП). Виявлено підвищення продукції активних форм кисню та азоту і інтенсифікацію ОМП у печінці щурів за тривалого введення етанолу. Показано, що введення фенформіну під час тривалого введення етанолу обмежує надлишкове утворення пероксинітриту та запобігає окисному пошкодженню протеїнів печінки щурів.

Ключові слова: печінка, хронічний алкогольний гепатит, фенформін, оксидативний та нітрозативний стрес, АМФ-активована протеїнкіназа.

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