

MECHANISMS OF ETHANOL LIVER DAMAGE IN RATS WITH DIFFERENT EMOTIONALITY

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Abstract

Alcoholic liver disease is associated with liver injury ranging from steatosis to steatohepatitis, fibrosis and cirrhosis. One of the mechanisms of organs damage is cytokines influences. The intensity of injury depends on individual reactivity.

The aim of the study was to evaluate changes in the blood of interleukins in the heart of high- and low-emotional (HE, LE) male rats with ethanol hepatosis, hepatitis, fibrosis and cirrhosis of the liver and to determine the degree of liver and heart damage.

Material and methods of investigation. The experiments were performed on 72 HE and LE outbred male rats aged 4 months ((control 1, glucose 7 days, acute ethanol hepatitis – EH) and 120 HE and LE outbred male rats aged 5.5-6.5 months (control 2, glucose 67 days, ethanol hepatosis – EHs, ethanol fibrosis – EF, ethanol cirrhosis – EC). The emotionality was determined by "open field" method.

Determined in the blood serum Tumor Necrosis Factor Alpha (TNF- α), Interleukin 1 Beta (IL-1 β), Interleukin 4 (IL-4), Interleukin 10 (IL-10), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP). All animals underwent histological examination of the liver and heart, right and left ventricles (RV, LV), and ventricular septum (VS) square.

Results. In EH increase IL-1 β , IL-10 and decrease TNF- α in LE rats. In EHs, EF and EC were decrease of IL-1 β , IL-4 and IL-10 in HE rats and decrease of TNF- α , IL-4 and IL-10 in LE rats. In EH decrease ALT (more in LE), AST (more in HE) and increase AP. In HE rats in EHs, EF and EC decreased ALT, in EC increased AST. AP in HE rats increased in EHs; decreased in EF and EC. In LE rats ALT was increased in EHs, and decreased in EC; AST was increased in EC; AP was increased in EHs. In both groups of animals at ethanol damage of a liver remodeling of heart is observed. The earlier and bigger is observed in HE rats.

Conclusion. The degree of ethanol damage to the liver and heart depends on the emotionality of the animals and the severity of the simulated pathology, which is more pronounced in highly emotional rats. In the mechanisms of ethanol damage of organism of different emotionality rats take place cytokines changes. In hepatitis increase IL-1 β , IL-10 and decrease TNF- α in low emotions rats. In hepatosis, fibrosis and cirrhosis were decrease of IL-1 β , IL-4 and IL-10 in high emotional rats and decrease of TNF- α , IL-4 and IL-10 in low emotional rats.

Key words: cytokines; transaminase; liver; heart; ethanol; rats

Introduction. Alcoholic liver disease (ALD) is associated with a spectrum of liver injury ranging from steatosis to steatohepatitis, fibrosis and cirrhosis. Enhanced inflammation in the liver during ethanol exposure is a major feature of ALD. Proinflammatory and anti-inflammatory cytokines play an important role in ALD development. Exposure to alcohol leads to predominantly pro-inflammatory cytokine secretion and liver damage, and IL-10 counteracts them by limiting damage by inhibiting TNF- α production by monocytes [1, 2, 3]. Alcohol potentiated the increase of aspartate aminotransferase and alanine aminotransferase enzyme activity in wild-type IL-10 knock-out mice. The higher histological effects of liver steatosis are in the knock-out mice. It were demonstrated, that pro-inflammatory cytokine tumor necrosis factor (TNF- α) is one of the key factors in the various aspects of pathophysiology of ALD, but TNF- α and IL-1beta levels are not affected by alcohol alone. The IL-10 plasma levels play roles in exerting hepatic protective effects. Adiponectin prevents alcohol-induced liver injury via suppression of TNF- α expression and induction of anti-inflammatory cytokines such as IL-10 [2, 3].

TNF- α has a pro-inflammatory, proatherogenic effect, causing endothelial dysfunction. IL-1 provides intercellular interactions that cause an inflammatory response through the expression of acute inflammatory proteins in hepatocytes, activation of neutrophils, action on T-helpers and their stimulation, effects on endothelial, smooth muscle

cells, macrophages [4]. Increased production of TNF- α by monocytes and Kupffer cells on the background of ALD is associated with mortality [5]. Increased production of TNF- α by monocytes and Kupffer cells on the background of ALD is associated with mortality [5].

At chronic consumption of ethanol proinflammatory mechanisms are included, and at acute moderate consumption the anti-inflammatory effect is noted. The mechanism of such action is as follows. Prolonged alcoholism increases the basal level of nuclear factor kappaB (NF-kappaB) in the liver of mice, with acute use decreases lipopolysaccharide-induced production of NFkappaB in the liver, and in serum induces the synthesis of TNF- α [6].

In alcoholic hepatitis is a higher value of TNF- α compared with alcoholic cirrhosis and those who regularly consume alcohol and have no liver pathology. With normal renal function, TNF- α levels are lower. Low cytokine content is also important for normal liver regeneration [4]. Damage to dendritic cells occurs with prolonged use of ethanol, resulting in a violation of the cellular immune response required for the normal implementation of clearance functions [7].

Alcohol is an immunosuppressant. Acute ethanol-induced immunosuppression occurs in part due to inhibition of TNF- α production due to the action of ethanol on posttranscriptional processes [8]. Under the action of ethanol decreases the production of TNF- α , which creates the conditions for a compromised immune response [9]. From the standpoint of neuroimmune action, ethanol has the greatest effect on the cardiovascular system and liver [10]. However, not all individuals suffer equally from the development of pathology of the internal organs during alcohol abuse, as it depends on individual reactivity.

The aim of the study was to evaluate changes in the blood of interleukins in the heart of high- and low-emotional (HE, LE) male rats with ethanol hepatosis, hepatitis, fibrosis and cirrhosis of the liver and to determine the degree of liver and heart damage.

Material and methods of investigation. The experiments were performed on 72 HE and LE outbred male rats aged 4 months and 120 HE and LE outbred male rats aged 5.5-6.5 months. Animals were divided into groups – control (1, 2), glucose (7 days, 67 days), acute ethanol hepatitis (EH), ethanol hepatosis (EHs), ethanol fibrosis (EF) and ethanol cirrhosis (EC). Control 1, glucose 7 days, EH was simulated in 4 months old rats; the experiments were performed in February. Control 2, glucose 67 days, EH_z, EF, EC were simulated in rats from 4 months of age, the experiments were performed from February to May.

The emotionality of rats was determined at 3-3.5 months by the method of "open field", which allows assessing the physiological response to the new environment, provides information about the motor, research and emotional activity of animals [11]. HE animals

included those with high horizontal and vertical activity, intensive study of holes in the bottom of the test chamber, infrequent fading. Conversely, LE included those, who had low motor activity, a large number of fading and increasing their duration, avoidance of central squares by animals, which indicates a high level of anxiety.

Control groups 1 and 2 were kept on the standard diet of the vivarium throughout the simulation period in other groups EH, EHs, EF and EC, with free access to water.

Animals of the glucose group were in standard vivarium conditions for 7 days with free access to food, but instead of drinking water received a 5% glucose solution. To simulate EH, experimental animals were administered intragastrically 12.5 ml/kg of 40% ethanol solution on 5% glucose for 7 days. Rats were in standard vivarium conditions with free access to water and food [12].

Animals of the glucose group were in standard vivarium conditions for 67 days with free access to food, but instead of drinking water were given a 5% glucose solution. To simulate EHs, rats were given 60 days of 10% ethanol solution in 5% glucose solution as the sole source of drink (having previously become accustomed to ethanol with 5% ethanol solution in 5% glucose solution for 7 days). Rats were in standard vivarium conditions with free access to food [13]. For modeling EF and EC previously adapted to alcohol: in the first week the animals received in drinking bowls instead of water 5% ethanol solution diluted with 5% glucose solution, in the second week – 15% ethanol solution diluted with 5% glucose solution without dietary restrictions. From the third week, there was an intensive alcoholization with 96% ethanol solution on slices of white bread for 12 weeks 14 g/kg (for EF) and 18 g/kg of weight (for EC) without restrictions in water. Twice a week the animals were given oats [14, 15]. All animals underwent histological examination of the liver and heart to confirm the simulated pathology, right and left ventricles (RV, LV), and ventricular septum (VS) square was determined.

All experiments were performed in the morning in a specially designated room at a temperature of 18-22 °C, a relative humidity of 40-60% and an illumination of 250 lux. All animals kept in one room on a standard diet and vivarium regime. The experiments were performed in compliance with the norms of the Council of Europe Convention on the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes (Strasbourg, 18.03.1986), the resolution of the First National Congress on Bioethics (Kyiv, 2001) and the Ministry of Health of Ukraine № 690 of September 23, 2009.

Euthanasia of rats was performed by total bloodletting from the heart after previous thiopental-sodium anesthesia (60 mg/kg, intraperitoneally). For further experimental study in

the blood serum were determined the concentration of interleukins [16]. Determination in the blood serum of cytokines levels was performed using by immunophermment method with standard reagent, adapted for white rats “Enzyme-linked Immunosorbent Assay; Kits for Rat: Tumor Necrosis Factor Alpha (TNF- α), Interleukin 1 Beta (IL-1 β), Interleukin 4 (IL-4), Interleukin 10 (IL-10)”, Uscn, Life Science Inc., E90133Ra, E90563Ra, CSB–E04635r, CSB–E04595r on the analyzer STAT FAX 303 plus.

The content of alanine aminotransferase (ALT) [17] and aspartate aminotransferase (AST) [18], alkaline phosphatase (AP) [19] was determined by conventional methods.

Statistical processing of digital data was performed using the program "STATISTICA" 6.0 ("Statsoft", USA) [20].

Results and discussion. In the control of 4-month-old HE rats, compared with LE showed higher 25.6% ($p < 0.01$) values of the anti-inflammatory cytokine IL-10 (table 1).

Table 1 – The value of interleukins in the serum of high- and low-emotional rats with the development of ethanol hepatitis, $M \pm m$, $n = 12$

Index	Group	
	High-emotional rats	Low-emotional rats
Control 1		
TNF- α , pg/ml	3.47 ± 0.16	3.63 ± 0.11
IL-1 β , pg/ml	2.08 ± 0.10	1.83 ± 0.12
IL-4, pg/ml	6.61 ± 0.31	6.30 ± 0.22
IL-10, pg/ml	7.12 ± 0.60	$5.30 \pm 0.18^{**}$
TNF- α / IL-1 β	1.73 ± 0.14	2.06 ± 0.13
Glucose, 7 days		
TNF- α , pg/ml	3.38 ± 0.17	$3.20 \pm 0.18^*$
IL-1 β , pg/ml	2.12 ± 0.10	$2.74 \pm 0.13^{*,**}$
IL-4, pg/ml	5.96 ± 0.24	$7.28 \pm 0.32^{*,**}$
IL-10, pg/ml	$10.04 \pm 0.79^*$	$12.37 \pm 1.08^*$
TNF- α / IL-1 β	1.63 ± 0.11	$1.17 \pm 0.04^{*,**}$
Ethanol hepatitis		
TNF- α , pg/ml	3.50 ± 0.18	$3.09 \pm 0.09^{*,**}$
IL-1 β , pg/ml	2.07 ± 0.13	$2.33 \pm 0.10^{*,\#}$
IL-4, pg/ml	6.58 ± 0.22	6.53 ± 0.20
IL-10, pg/ml	7.48 ± 0.68	$7.76 \pm 0.70^{*,\#}$
TNF- α / IL-1 β	1.78 ± 0.15	$1.34 \pm 0.05^{*,**,\#}$
– indexes are reliable, compared to control; – indexes are reliable, compared to HE rats; – indexes are reliable, compared to glucose.		

In the Glucose 7 days group, HE IL-10 increased by 40.9% ($p < 0.01$). In LE increased IL-1 β by 49.5% ($p < 0.001$), IL-4 by 15.5% ($p < 0.02$), IL-10 by 2.3 times ($p < 0.001$), decreased

TNF- α by 11.9% ($p < 0.05$), the ratio of TNF- α /IL-1 β by 43.2% ($p < 0.001$). Comparing the results between HE and LE, LE showed higher values of IL-1 β by 29% ($p < 0.001$), IL-4 by 22.1% ($p < 0.002$), and in HE – the ratio of TNF- α /IL-1 β at 28.1% ($p < 0.001$). From the obtained data it follows that HE animals are more resistant to glucose load, and in LE it caused a violation of the immune system, apparently due to the activation of macrophages. Activation of anti-inflammatory interleukins may be due to the fact that in LE, which is less active and more anxious, glucose has become an additional source of energy, which intensified inflammatory reactions, but reduced the destructive changes.

In EH in HE animals, cytokine values did not differ from control values. In LE compared with the control were lower values of TNF- α by 14.9% ($p < 0.001$), the ratio of TNF- α /IL-1 β by 34.8% ($p < 0.001$), increased IL-1 β by 27.7 % ($p < 0.002$), IL-10 by 46.4% ($p < 0.001$). LE, compared with HE, had lower values of TNF- α by 11.7% ($p < 0.05$), the ratio of TNF- α /IL-1 β by 24.7% ($p < 0.01$). In LE with hepatitis, compared with the group Glucose 7 days were lower values of IL-1 β by 27.3% ($p < 0,02$), IL-10 by 46,4% ($p < 0,001$), but a higher ratio of TNF- α /IL-1 β at 34.8% ($p < 0.01$). The results indicate an increase in inflammation in the body of LE rats and, compared with glucose consumption, increased destructive processes, which are apparently associated with the destruction of hepatocytes.

In the control of 6-month-old animals (table 2) in LE rats, compared with HE, there were higher values of TNF- α by 15% ($p < 0.001$), the ratio of TNF- α /IL-1 β by 26.7% ($p < 0.001$), lower IL-1 β by 8.8% ($p < 0.001$), IL-4 by 6.7% ($p < 0.002$).

67-day glucose consumption led to a decrease in IL-4 by 17.7% ($p < 0.001$) and an increase in IL-10 by 27.4% ($p < 0.002$) in HE rats, and in LE – to a decrease in IL-4 by 5.1% ($p < 0.05$). LE rats, compared with HE, had higher values of TNF- α by 12.8% ($p < 0.05$), IL-4 by 17.6% ($p < 0.01$), the ratio of TNF- α /IL- 1 β by 18% ($p < 0.05$), lower IL-10 by 16.7% ($p < 0.01$).

In EHs, compared with the control, the HE rat values of IL-1 β decreased by 17.3% ($p < 0.001$), IL-4 by 30.1% ($p < 0.001$), IL-10 by 15.6% ($p < 0.05$), the ratio of TNF- α /IL-1 β increased by 27.4% ($p < 0.001$). Compared with glucose, 67 days in the HE animals remained lower values of IL-1 β by 16.7% ($p < 0.001$), IL-4 by 15% ($p < 0.001$), IL-10 by 33.8% ($p < 0.001$). In LE-animals with EHs, compared with the control, there were lower TNF- α by 21.9% ($p < 0.01$), IL-4 by 24.2% ($p < 0.001$), IL-10 by 19.1 % ($p < 0.05$), and the values of TNF- α by 17.3% ($p < 0.05$), IL-4 by 20.2% ($p < 0.001$), were lower compared to the glucose group 67 days. The obtained results can be explained by the growth of destructive processes and the reduction of inflammatory reactions and responses to them in HE; in LE-animals, the

response of the immune system to the development of the pathological process, including the destruction of hepatocytes, has obviously decreased. In EHs, compared with non-ethanol steatohepatosis, the animals had less pro-inflammatory interleukins, as well as less damage to the body to both HE and LE rats.

Table 2 – The value of interleukins in the serum of high- and low-emotional rats with the development of ethanol liver damage, $M \pm m$, $n = 12$

Index	Group	
	High-emotional rats	Low-emotional rats
Control 2		
TNF- α , pg/ml	3.11 \pm 0.13	3.58 \pm 0.06**
IL-1 β , pg/ml	2.75 \pm 0.04	2.51 \pm 0.06**
IL-4, pg/ml	8.62 \pm 0.11	8.04 \pm 0.14**
IL-10, pg/ml	10.89 \pm 0.57	11.97 \pm 0.52
TNF- α / IL-1 β	1.13 \pm 0.04	1.43 \pm 0.04**
Glucose, 67 days		
TNF- α , pg/ml	2.99 \pm 0.14	3.37 \pm 0.10**
IL-1 β , pg/ml	2.73 \pm 0.08	2.58 \pm 0.07
IL-4, pg/ml	7.09 \pm 0.15*	7.63 \pm 0.13*,**
IL-10, pg/ml	13.88 \pm 0.73*	11.55 \pm 0.37**
TNF- α / IL-1 β	1.11 \pm 0.07	1.31 \pm 0.05**
Ethanol hepatitis		
TNF- α , pg/ml	3.28 \pm 0.11	2.79 \pm 0.25* [#]
IL-1 β , pg/ml	2.28 \pm 0.05* [#]	2.18 \pm 0.21
IL-4, pg/ml	6.03 \pm 0.17* [#]	6.09 \pm 0.41* [#]
IL-10, pg/ml	9.19 \pm 0.58* [#]	9.68 \pm 0.97*
TNF- α / IL-1 β	1.44 \pm 0.04* [#]	1.33 \pm 0.10
Ethanol fibrosis		
TNF- α , pg/ml	3.08 \pm 0.09	3.18 \pm 0.09*
IL-1 β , pg/ml	2.38 \pm 0.08*	2.42 \pm 0.05
IL-4, pg/ml	5.72 \pm 0.16*	6.18 \pm 0.21*
IL-10, pg/ml	9.27 \pm 0.50*	9.39 \pm 0.48*
TNF- α / IL-1 β	1.30 \pm 0.03* ^{##}	1.32 \pm 0.05
Ethanol cirrhosis		
TNF- α , pg/ml	3.19 \pm 0.07	3.11 \pm 0.10*
IL-1 β , pg/ml	2.58 \pm 0.03* ^{##,***}	2.38 \pm 0.07**
IL-4, pg/ml	5.87 \pm 0.10*	5.62 \pm 0.25*
IL-10, pg/ml	8.33 \pm 0.54*	10.64 \pm 0.28* ^{##,***}
TNF- α / IL-1 β	1.24 \pm 0.03* ^{##}	1.31 \pm 0.05
– indexes are reliable, compared to control; – indexes are reliable, compared to HE rats; 3. # – indexes are reliable, compared to glucose; 4. ## – indexes are reliable, compared to hepatitis; 5. *** – indexes are reliable, compared to fibrosis.		

In EF of liver, compared with the control, in the HE rats decreased the values of IL-1 β by 13.3% (p<0.001), IL-4 by 33.7% (p<0.001), IL-10 by 14.9 % (p<0.05), the ratio of TNF- α /IL-1 β increased by 15% (p<0,002). Also in EF, compared with EHs, in HE rats the ratio of TNF- α /IL-1 β was lower by 9.7% (p<0.01). In LE rats with EF, compared with controls, there were lower values of TNF- α by 11% (p<0.001), IL-4 by 23.1% (p<0.001), IL-10 by 21.5% (p<0.001). The results obtained may indicate a suppression of the immune system response in animals.

In EC of the liver, compared with the control, in the HE rat values of IL-1 β decreased by 6.4% (p<0.001), IL-4 by 31.9% (p<0.001), IL-10 by 23.5 % (p<0,002), the ratio of TNF- α /IL-1 β increased by 9.7% (p<0.05). Also in EC, compared with EF, increased IL-1 β by 8% (p<0.02), and compared with EHs, increased IL-1 β by 13.2% (p<0.001). The ratio of TNF- α /IL-1 β by 13.8% (p<0.001) was less. LE-rats had lower TNF- α levels by 13.1% (p<0.001), IL-4 by 30.2% (p<0.001), and IL-10 by 11.1% (p<0.02) compared to controls, and compared with EF increased IL-10 by 13.3% (p<0.02). The results obtained may indicate the suppression of the immune response in animals. Comparing the results in rats with different emotionality, it was found that IL-1 β was higher in the HE of animals by 7.4% (p<0.01), and IL-10 – in LE by 27.7% (p<0.001). The results obtained may indicate suppression of the immune system response in animals, secondary alteration in HE rat, and the compensatory response of anti-inflammatory cytokines in LE rats.

The degree of liver damage was determined by the content of ALT, AST and AP (tables 3, 4).

It should be noted that there was no difference in the indicators between HE and LE animals in group Control 1. In the group of Glucose 7 days there was a decrease in AST in HE rats by 30.6% (p<0.001) and LE animals by 23.9% (p<0.001) and an increase in AP by 11.3% (p<0.05) in HE . Moreover, ALT was higher by 16.7% (p<0.001) in LE rats. Apparently, glucose caused a decrease in cytolytic processes in the membranes of cardiomyocytes, improving the energy supply and operation of ion pumps, but caused disturbances in hepatocytes HE, causing the development of steatosis. ALT relative to control did not change, so its higher concentration in LE rats can be regarded as an inflammatory process, which is confirmed by higher values of IL-1 β .

At EH in comparison with control were decrease in ALT, AST level, but increase in AP in HE and LE animals. That is, ethanol, compared with glucose drink, caused a decrease in ALT in animals with different emotions, respectively, by 15.6% (p<0.05) and 33.5% (p<0.001), and AST in HE rat by 50.4% (p<0.001), and AP in LE-rats by 14.6% (p<0.05). In

HE animals, AST changed more, and in LE – ALT, which, accordingly, indicates more damage to the heart in HE, and liver in LE. A decrease in ALT can be observed in necrosis of hepatocytes, cirrhosis of the liver, ie when the number of cells capable of synthesizing ALT decreases in vitamin B6 deficiency. Decreased AST may also be in hepatocyte necrosis, vitamin B6 deficiency. A decrease in both aminotransferases indicates an unfavorable prognosis.

Table 3 – Changes in the degree of cell cytolysis in high- and low-emotion rats with the development of ethanol hepatitis, $M \pm m$, $n=12$

Index	Group	
	High-emotional rats	Low-emotional rats
Control 1		
ALT, units/ml	104.32 ± 6.54	109.03 ± 3.37
AST, units/ml	229.35 ± 8.14	227.67 ± 4.51
AP, units/ml	388.47 ± 11.92	409.09 ± 13.79
Glucose, 7 days		
ALT, units/ml	98.11 ± 1.98	114.58 ± 1.98**
AST, units/ml	159.27 ± 9.52*	173.32 ± 9.95*
AP, units/ml	432.23 ± 16.13*	423.93 ± 20.90
Ethanol hepatitis		
ALT, units/ml	88.06 ± 4.32* [#]	72.56 ± 1.76* ^{*,#}
AST, units/ml	113.87 ± 6.69* [#]	159.15 ± 11.02* ^{**,#}
AP, units/ml	460.89 ± 16.71*	468.99 ± 7.83* ^{*,#}
– indexes are reliable, compared to control; – indexes are reliable, compared to HE rats; – indexes are reliable, compared to glucose.		

In Control 2, HE rat had a 18.7% ($p < 0.001$) higher ALT activity compared to LE, which may be associated with more intense proinflammatory responses because IL-1 β was also predominant in them (Table 4). In the group of glucose 67 days there was an increase by 27.3% ($p < 0.001$) AST and a decrease by 6.5% ($p < 0.05$) of AP in HE rats, an increase of 19.2% ($p < 0.001$) ALT in LE animals. Such indexes indicate more damage in the heart of HE animals, and liver in LE. At EHs in HE rats decreased by 40.8% ($p < 0.001$) ALT and increased by 10.8% ($p < 0.01$) AP, and at LE – increased ALT by 73.4% ($p < 0.001$) and AP by 18.5% ($p < 0.001$), which indicated more damage to the inflammatory genesis of the liver in LE, and destructive – in HE, which was consistent with a significant increase in TNF- α /IL-1 β in HE rats.

At EF in HE rats decreased ALT by 31.4% ($p < 0.001$) and AP by 15.3% ($p < 0.001$), and in LE rats the indicators did not differ from the control, which indicated more liver

damage in HE. The increase in TNF- α /IL-1 β in HE, compared with control values, and the decrease in ALT and AP can be regarded as significant destruction of hepatocytes.

Table 4 – Changes in the degree of cell cytolysis in high- and low-emotion rats with the development of ethanol liver damage, M \pm m, n = 12

Index	Group	
	High-emotional rats	Low-emotional rats
Control 2		
ALT, units/ml	83,05 \pm 2,46	67,50 \pm 1,55**
AST, units/ml	122,77 \pm 5,47	137,77 \pm 7,27
AP, units/ml	232,28 \pm 6,85	215,38 \pm 9,02
Glucose, 67 days		
ALT, units/ml	84,66 \pm 2,38	80,46 \pm 0,61*
AST, units/ml	156,35 \pm 4,60*	131,42 \pm 7,81**
AP, units/ml	217,12 \pm 2,07*	212,67 \pm 14,05
Ethanol hepatitis		
ALT, units/ml	49,18 \pm 1,79* [#]	117,07 \pm 4,64* ^{*,**,#}
AST, units/ml	115,92 \pm 4,72 [#]	127,31 \pm 7,01
AP, units/ml	257,467 \pm 5,86* [#]	255,18 \pm 2,92* [#]
Ethanol fibrosis		
ALT, units/ml	57,02 \pm 1,27* ^{*,##,###}	72,32 \pm 2,61* ^{*,##,###}
AST, units/ml	139,57 \pm 7,47 ^{##}	142,65 \pm 5,19
AP, units/ml	196,69 \pm 8,15* ^{*,##,###}	212,97 \pm 13,84 ^{##}
Ethanol cirrhosis		
ALT, units/ml	63,93 \pm 0,86* ^{*,##,###,***}	61,30 \pm 0,86* ^{*,##,###,***}
AST, units/ml	148,05 \pm 6,60* ^{*,##}	164,90 \pm 9,88* ^{*,##}
AP, units/ml	194,00 \pm 6,90* ^{*,##,###}	210,42 \pm 6,06 ^{##}
– indexes are reliable, compared to control; – indexes are reliable, compared to HE rats; 3. # – indexes are reliable, compared to glucose; 4. ## – indexes are reliable, compared to hepatitis; 5. *** – indexes are reliable, compared to fibrosis.		

At EC in HE rats were decreased by 23% (p<0.001) ALT and by 16,5% (p<0.001) AP, increased by 20,6% (p<0.01) AST. In LE rats with EC were decreased by 9.2% (p<0.001) ALT, increased by 19.7% (p<0.05) AST, which indicated damage to the heart muscle in all animals, but greater changes in the liver in HE. It is obvious that at HE animals considerable damage of an organism develops already since EHs, and at LE rats – at EC.

We found damage of the heart muscle, that's why we examined changes in the square of the right and left ventricles, and ventricular septum (table 5). In control 1, LE rats had a larger square of the RV. In the group of glucose 7 days and EH, compared with the control, in the HE rat increased the square of the RV, and in the LE – the VS. At EH in HE the square of

the RV increased, and in LE it decreased, but the area of the VS increased, which indicates heart remodeling. Such indicators can be regarded as the development of right ventricular failure in HE and left ventricular failure in LE.

Table 5 – Changes in morphometric parameters in high- and low-emotional rats with the development of ethanol liver damage, M±m, n=12

Group	Area, mm ²		
	Right ventricle	Ventricular septum	Left ventricle
Control 1			
HE	94,2±3,7	51,7±2,2	136,4±7,2
LE	113,7±3,2 ^{**}	52,4±1,5	136,7±4,1
Glucose 7 days			
HE	111,2±5,3 [*]	57,8±2,5	125,8±5,2
LE	114,8±5,4	62,5±4,1 [*]	131,4±4,5
Ethanol hepatitis			
HE	110,5±3,3 [*]	52,7±1,8	126,8±4,6
LE	95,0±2,2 ^{*,#}	58,4±2,4 [*]	130,7±4,0
Control 2			
HE	143,7±2,5	76,2±1,9	129,6±4,2
LE	151,2±5,7	88,5±1,7 ^{**}	156,8±6,9
Glucose 67 days			
HE	120,9±2,0 [*]	83,3±2,2 [*]	140,6±2,6 [*]
LE	144,5±4,5 ^{**}	72,3±3,5 ^{*,**}	146,2±4,2
Ethanol hepatothosis			
HE	110.0 ± 3.1 ^{*,#}	63,5±4,0 ^{*,#}	114,0±3,7 ^{*,#}
LE	125.3 ± 5.2 ^{*,**, #}	81,6±3,3 ^{**}	126,8±3,7 ^{*,**, #}
Ethanol fibrosis			
HE	116.0 ± 3.9 [*]	75.6 ± 3.7 ^{##}	122,7±4,6 ^{*,#}
LE	117.2 ± 5.5 ^{*,#}	81.2 ± 3.3	139,2±4,8 ^{*,**, ##}
Ethanol cirrhosis			
HE	116.4 ± 3.7 [*]	67.7 ± 3.3 ^{*,#}	134,2±6,3 ^{*,##}
LE	118.7 ± 4.6 ^{*,#}	86.5 ± 3.9 ^{**, #}	122,4±3,9 ^{*,#,***}
– indexes are reliable, compared to control; – indexes are reliable, compared to HE rats; – indexes are reliable, compared to glucose; – indexes are reliable, compared to hepatitis; * – indexes are reliable, compared to fibrosis.			

In adult LE rats in control, a larger area of VS was observed. Consumption of glucose for drinking for 67 days in the HE animals caused a decrease in the area of the RV s, but an increase in the area of the VS and LV. In LE-rats, the area of VS decreased. In LE-animals, compared with HE, the area of the RV was larger, and VS – smaller. At EHs at HE rats all

investigated parameters, and at LE rats only the area of ventricles decreased. In LE-animals, compared with HE, the areas of the ventricles and VS were larger.

At EF in HE rats the areas of both ventricles appeared smaller, and in LE only RV area decreased. In LE-animals, compared with HE rats, the area of the LV was larger. At EC in HE rats the areas of RV and VS decreased and the area of LV increased. At EC in LE rats the area of both ventricles decreased. In LE-animals, compared with HE rats, the area of VS was larger. From the received data it follows that in both groups of animals at ethanol damage of a liver remodeling of heart is observed. The earlier and bigger is observed in HE rats.

Conclusion. The degree of ethanol damage to the liver and heart depends on the emotionality of the animals and the severity of the simulated pathology, which is more pronounced in highly emotional rats. In the mechanisms of ethanol damage of organism of different emotionality rats take place cytokines changes. In hepatitis increase IL-1 β , IL-10 and decrease TNF- α in low emotions rats. In hepatosis, fibrosis and cirrhosis were decrease of IL-1 β , IL-4 and IL-10 in high emotional rats and decrease of TNF- α , IL-4 and IL-10 in low emotional rats.

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