PECULIARITIES OF THE CHEMICAL AND PHYSICAL FACTORS INFLUENCE OF THE PRODUCTION ENVIRONMENT ON THE CARBOHYDRATE AND ENERGY METABOLISM OF THE EXPERIMENTAL ANIMALS' LIVER

MukaddaskhonKhamrakulova, Doctor of Medical Sciences, Head of the Laboratory of Medical and Biological Research in Hygiene, Research Institute of Sanitation, Hygiene and Occupational Diseases of the Ministry of Health of RU, Uzbekistan.

SabirovaGulchehra, PhD doctoral student, Research Institute of Sanitation, Hygiene and Occupational Diseases of the Ministry of Health of RU, Uzbekistan

SadikovAskar, Doctor of Medical Sciences, Professor, Research Institute of Sanitation, Hygiene and Occupational Diseases of the MH of RU, Uzbekistan

SadikovKhumoyun, Tashkent Medical Academy, Uzbekistan

NavruzovErnazar, PhD of Medical Sciences, Senior Researcher, Research Institute of Sanitation, Hygiene and Occupational Diseases of the Ministry of Health of RU, Uzbekistan

Abstract:

The energy supply of liver functions is carried out mainly by aerobic mitochondrial processes. We have studied some aspects of carbohydrate energy metabolism in mitochondria of the liver at the chronic influence of dichloroethane complex of factors, noise and vibration on experimental animals' organism. The research aims to study some parameters of carbohydrate energy metabolism in mitochondria of the liver under the chronic influence of dichloroethane, noise and vibration. The researchers carried out experiments on 98 purebred white male rats weighing 160-180 g. Dichloroethane in the form of 10% oily solution was injected into the animal's stomach in a dose of 1/20 LD50 (255 mg/kg), in conditions of noise (95-110dBa) and vibration (2-16dBa) during 15 and 90 days. After the experiments end in 15, 30, 60 and 90 days after exposure cessation to chemical and physical factors, the rats were decapitated and determined some indicators of carbohydrate and energy metabolism in the liver and blood of experimental animals. Presented results of experimental studies show that at repeated exposure to dichloroethane, noise and vibration there was observed an increase in the intensity of anaerobic glycolysis in blood, which is confirmed by the accumulation of lactic acid and reduction of glycogen. Similar changes were observed in the reduction of activity of alkaline phosphatase in the liver. Inhibition of enzyme activity (dehydrogenase) in all studied biospheres can be explained by the influence of dichloroethane, noise and vibration on enzyme functional activity. Inhibition of enzymes GDG, MDG, SDG and alkaline phosphatase in the liver is observed at multiple effects of dichloroethane, noise and vibration. As a result of the reduction of redox enzymes, under-oxidized products of anaerobic glycolysis of lactic, pyruvic acid are accumulated and the level of glycogen is reduced. Prolonged exposure to various chemical and physical factors in concentrations causing external effects in the experimental animals' organism is manifested by hidden changes in several physiological reactions, biochemical indicators of the individual organs function and systems. Confirming

influence of xenobiotics on cellular structures, mainly in the discoordination of functional activity of organs and specific enzyme systems.

Keywords: Liver, dichloroethane, noise and vibration, carbohydrate energy exchange.

Introduction:

Near the researchers, it was shown that some chemicals are hepatotropic, in particular, dichloroethane, which causes a disturbance of oxidation processes in the liver [5, p. 12; 2, p. 8]. However, the mechanism of complex influence of chemical and physical factors (dichloroethane, noise and vibration) on the energy apparatus of mitochondria has not been finally clarified so far [6, p. 38; 8, p. 45].

The liver is most exposed to the harmful effects of chemical and physical factors [1, p.707-709; 4, p. 63]. It is the main organ performing metabolism of toxic and other chemical compounds. When intoxicated by various harmful chemical and physical factors, the liver suffers first of all from internal organs, its multiple functions and structures are violated [7, p. 38; 3, p. 12].

According to current data, the liver plays a vital role in the catabolism of atherogenic lipoproteins (LP). Here, oxidation and synthesis of triglycerides, cholesterol, phospholipids, the formation of acetone bodies, bile acids take place.

Since the energy supply of liver functions is carried out mainly by aerobic mitochondrial processes, we have studied some aspects of carbohydrate energy metabolism in mitochondria of the liver under the chronic influence of complex factors dichloroethane, noise and vibration on the organism of experimental animals [11, p. 740].

The work aims to study some indicators of carbohydrate and energy metabolism in mitochondria of the liver under chronic exposure to dichloroethane, noise and vibration.

The research was performed within the grant project ADBC - 15.17.3.

The research materials and methods. Experimental studies were conducted to study the mechanism of toxic effects of the studied factors, widely used in the oil and gas industry.

Experimental studies were conducted on white male rats. Animals taken for the experiment were kept in laboratory quarantine for 20 days: control animals were kept in the same conditions as the experimental ones. The animals were given a common diet with a sufficient content of proteins, fats, carbohydrates, vitamins, salts and trace elements. All studied parameters in experimental animals were compared with parameters in control group animals.

The studies were conducted in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental or Other Scientific Purposes (Strasbourg, March 18, 1986) ETS N 123. All animals were kept in the vivarium and in the laboratory for medical and biological studies in hygiene at the Research Institute of SSPPZ of MH RU.

The study of mechanism of biological action of dichloroethane, noise and vibration was carried out in chronic experience. The mechanism of biological action of hepatotropic factors in chronic experience was studied during each 15, 30, 45, 60 and 90 days.

The experiments were carried out on 98 purebred white male rats weighing 160-180 years. Dichloroethane in the form of 10% oily solution was injected into the stomach of animals in a dose of 1/20 LD50 (255 mg/kg), under the influence of noise (95-110dBa) and vibration (2-16dBa) during 15 and 90 days.

After the end of experiments in 15, 30, 60 and 90 days after cessation of exposure to chemical and physical factors, rats were decapitated. The content of the following substrates was determined spectrophotometrically in liver tissue: pyruvate, lactate and glycogen. Simultaneously, the activity of respiratory enzymes of liver mitochondria: glutamate dehydrogenase (GDG), lactate dehydrogenase (LDG), malate dehydrogenase (MDG), succinate dehydrogenase (SDG) was determined in parallel groups of animals [9, p. 10]. Mitochondria were isolated from the liver by differential centrifugation in 0.25 M saccharose solution containing 1 mM EDTA, pH 7.4 with double washing [6]. To increase the access of substrates to enzymes, the mitochondrial membrane was destroyed by three times freezing. The enzyme activity was expressed in μmol/g.h.

The content of total protein, cholesterol, total and free bilirubin and activity of alanine transferase (ALT), asparaginamin transferase in blood serum of experimental animals who received intragastric 1/20 LD50 dose of dichloroethane under the conditions of 90 - 105 dBA noise and 5 - 15 dBA vibration were studied.

The contents of total protein, total and direct bilirubin, cholesterol, enzyme activity under the influence of dichloroethane, noise and vibration in blood serum were determined in biochemical analyzer [10, p. 15].

Results. Our studies investigated the content of total protein, total and direct bilirubin, cholesterol, the activity of enzymes alanine transferase, (ALT), asparagine transferase (AST) under the influence of dichloroethane, noise and vibration in the liver and serum.

Determination of metabolites of carbohydrate metabolism and activity of enzymes involved in the cycle of tricarboxylic acids were carried out on 15, 30, 60 and 90 days of inoculation.

At repeated injection of dichloroethane within 90 days in a dose of 1/20 LD50 (255 mg/kg) the content of lactic acid in whole blood from 15 to 90 days of exposure was significantly increased to 254.5; 246.0; 277.7 and 237.4%.

The content of pyruvic acid in all experimental periods increased from 143.5 to 166 μmol/l in comparison with the control group (109.0 ± 6.72 μmol/l). The content of glycogen in blood under the influence of complex of chemical and physical factors during 90 days decreased and made 10.3 ± 0.56; 10.46 ± 0.53; 9.45 = 0.47; 10.2 ± 0.56 mg/l on 15, 30 60 and 90 days of experiment, respectively (Table 1).

It is evident from the obtained data that at repeated exposure to dichloroethane, noise and vibration there was observed an increase of intensity of anaerobic glycolysis in blood, which is confirmed by lactic acid accumulation and glycogen reduction.

The study of dichloroethane effect, noise and vibration on the activity of tricarboxylic acid cycle enzymes in blood serum revealed inhibition of GDG, SDH, MDH and increased activity of alkaline phosphatase.

The table shows that under repeated exposure to dichloroethane, noise and vibration, the activity of GDG decreased in all study terms (15, 30, 60 90 days) to 54.9; 46.6%, 33.8 and 39.8% respectively.

Table 1.

Influence of dichloroethane, noise and vibration on metabolites of carbohydrate and energy metabolites in blood

№	Indicators	Статистическиепо казатели	Control group	Day 15	Day 30	Day 60	Day 90
1.	Lactic acid (μmol/l)	Mcp ± m %	0,99 ± 0,08	2,52 ± 1,64*** 254,5%	2,44 ± 0,17*** 246%	2,75 ± 0,17*** 277,7%	2,35 ± 0,15*** 237,4%
2.	Pyruvic acid (μmol/l)	Mcp ± m %	109,0 ± 6,72	155 ± 9,90** 142,2%	166,0 ± 11,0*** 152,2%	143,5 ± 8,37* 131,6%	155,2 ± 6,72*** 142,3%
3.	Glycogen (mg/l)	Mcp ± m %	13,0 ± 0,74	10,3 ± 0,56* 79,2%	10,46 ± 0,53* 80,5%	9,45 ± 0,47** 72,7%	10,2 ± 0,56** 78,5%
4.	GDG (μmol/l.h.)	Mcp ± m %	11,0 ± 0,95	6,04 ± 0,60*** 54,9%	5,13 ± 0,59*** 46,6%	5,92 ± 0,49** 53,8%	4,38 ± 0,46 39,8%
5.	SDG (μmol/l.ch.)	Mcp ± m %	24,0 ± 2,64	17,3 ± 2,02* 72,1%	14,17 ± 1,39** 59%	14,0 ± 1,37** 58,3%	30,8 ± 29,3
6.	MDG (μmol/l.h.)	Mcp ± m %	15,0 ± 1,00	10,49 ± 1,19* 69,9%	8,03 ± 0,64*** 53,5%	10,3 ± 1,31*** 68,6%	10,32 ±1,24 68,8%
7.	Alkaline phosphatase (μmol/l.ch.)	Mcp ± m %	0,79 ± 0,05	1,60 ± 0,13*** 202,5%	1,91 ± 0,14*** 241,2%	1,74 ± 0,15*** 220,2%	1,67 ± 0,1 165,3%

*Note: Reliability: * - P<0,05; ** - P<0,01; *** - P<0,001 in relation to the control group*

Similar phenomena have been detected when dichloroethane, noise and vibration affect the serum activity of SDH. The enzyme activity was reduced to 72.1; 59.0; 58.3 and 73.6%.

In the course of experimental studies, it was found that repeated exposure to dichloroethane, noise and vibration on animals changed the activity of MDH. Under the influence of complex hepatotoxic factors, the change of enzyme activity was in all terms of research.

Particularly sharp changes in the activity of alkaline phosphatase were determined in blood serum under the influence of dichloroethane, noise and vibration on white rats. At the same time, the enzyme activity reliably increased in all the terms of the experiment up to 165.3 - 241.2%.

Thus, under repeated exposure to dichloroethane, noise and vibration there was observed inhibition of redox enzymes GDG, SDH and MDG and increased activity of alkaline phosphatase, resulting in increased metabolites of carbohydrate metabolism: lactic, pyruvic acids and decreased glycogen level in blood.

Our studies have shown that in chronic dichloroethane poisoning under the conditions of noise and vibration, an increase in cholesterol content and activity of AST and ALT and a decrease in the total protein in liver tissue were observed in all periods of experience (Table 2). Reduction of entire protein content and reliable increase of cholesterol level in liver tissue in all terms (15, 30, 60 90 days) of the experiment was noted, reliable change was observed up to 137,3 - 160,3%. The level of total protein decreased to 75.2; 69.6; 78.7; 81.8%.

The determination of reamination activity between α- ketoglutar, alanine and asparagine aminotransaminases in the liver was very important for our studies.

The activity of AST decreased during all the study periods (15, 30, 60 and 90 days) to 74.4 - 55.4% in liver tissue under repeated exposure to dichloroethane, noise and vibration. ALT activity on the 15th, 30th and 60th days of the study was reduced to 81.1 - 70.8%. By the 90th day of the experiment the enzyme activity sharply increased up to 1645% in comparison with the control group. This increase in ALT activity at the end of 90 days under the influence of dichloroethane, noise and vibration indicates the possibility of hepatocyte dysfunction, which may result in liver cirrhosis.

Table 2

The complex of chemical (dichloroethane) and physical (noise, vibration) factors influence on some biochemical parameters in liver tissue

№	Indicators	Statistic indicators	Control	Day 15	Day 30	Day 60	Day 90
1.	Total protein (y/y)	Mcp ± m %	85,9 ± 2,51	64,6 ± 2,19*** 75,2%	60,09 ± 2,81*** 69,9%	67,6 ± 3,24*** 78,7%	70,3 ± 3,40*** 81,8%
2.	Cholesterol (µmol/g.h.)	Mcp ± m %	26,5 ± 1,95	36,4 ± 1,62 137,3% t-3,91	39,36 ± 1,90*** 148,5%	42,47 ± 2,22 160,3% t-5,39	38,1 ± 2,54** 143,7%
3.	AST (µmol/g.h.)	Mcp ± m %	55,9 ± 3,17	41,6 ± 2,51** 74,4%	31,0 ± 1,57*** 55,4%	35,5 ± 3,44*** 63,5%	52,2 ± 2,85* 93,4%
4.	ALT (µmol/g.h.)	Mcp ± m %	38,1 ± 1,76	30,9 ± 2,23* 81,1%	27,6 ± 2,10** 72,4%	27,0 ± 1,48*** 70,8%	63,5 ± 3,21*** 166,6%

*Note: Reliability: * - P<0,05; ** - P<0,01; *** - P<0,001 in relation to the control group*

Study of cholesterol showed that in all periods of 15, 30, 60 and 90 days of exposure to dichloroethane, noise and vibration in the liver of experimental rats, its content increases to 137.3; 39.36; 42.47; 38.1% concerning the control group. The level of total protein at chronic exposure to hepatotropic chemical and physical factors on 15 - 60 days of the experiment decreases to 69.9-81.8%, which indicates a violation of the protein-synthetic function of the liver.

Thus, the conducted researches allowed to establish that changes in some aspects of the metabolism of carbohydrate and energy metabolism under the influence of dichloroethane, noise and vibration testify to the increase of enzymatic activity of ALT, AST, the content of total protein, cholesterol in liver tissues.

The activity of AST in all study dates (15, 30, 60 and 90 days) was significantly increased in serum compared to the control group to 227.7; 419.4; 228 and 252.7% (Table 3).

The activity of ALT in serum under chronic exposure to dichloroethane, noise and vibration also increases to 188.6 - 239.6%.

There was a decrease in the level of total serum protein in all experiments to 71.6 - 76.9%.

The content of cholesterol, total and free bilirubin in the blood serum increased significantly during all days of the study. At the same time, cholesterol levels increased and were 9.02 ± 0.46; 11.43 ± 1.06; 9.67 ± 0.55 and 10.7 ± 0.65 μmol/l on days 15, 30, 60 and 90 respectively. The cholesterol level in the control group was 6.14 ± 0.28 μmol/l.

Particularly sharp changes were observed in pigment metabolism. The concentration of total protein increased to 137.6 - 205.6%. Similar phenomena were observed in the content of direct bilirubin, which changed to 137 - 130%.

To clarify the mechanism of action of chemical (dichloroethane) and physical factors (noise, vibration) under the chronic influence, we studied the content of lactic, pyruvic acids and glycogen, as well as the activity of enzymes dehydrogenases and alkaline phosphatase in the liver tissue (Table 4).

Table 3.

Effect of dichloroethane, noise and vibration on some blood biochemical parameters

№	Indicators	Statistic indicators	Control	Day 15	Day 30	Day 60	Day 90
1.	Total protein (g/l)	Mcp ± m %	72,7 ± 3,13	55,9 ± 3,67** 76,9%	52,07 ± 3,34*** 71,6%	53,6 ± 2,88*** 73,7%	54,9 ± 3,69** 75,5%
2.	Cholesterol (µmol/l.h.)	Mcp ± m %	6,14 ± 0,28	9,02 ± 0,46*** 146,9%	11,43 ± 1,06*** 186,6%	9,67 ± 0,55*** 156,6%	10,7 ± 0,65*** 174,2%
3.	AST (µmol/l.ch.)	Mcp ± m %	0,36 ± 0,05	0,82 ± 0,05*** 227,7%	1,51 ± 0,13*** 419,4%	0,82 ± 0,03*** 227,7%	0,91 ± 0,05*** 252,7%
4.	ALT (µmol/l.ch.)	Mcp ± m %	0,53 ± 0,62	1,00 ± 0,07** 188,6%	1,27 ± 0,12*** 239,6%	1,12 ± 0,08 211,3%	1,02 ± 0,05* 192,4%
5.	Total bilirubin (µmol/l)	Mcp ± m %	5,31 ± 0,22	7,31 ± 0,29*** 137,6%	10,92 ± 0,96** 205,6%	7,5 ± 0,24*** 141%	10,35 ± 0,60*** 194,9%
6.	Direct bilirubin (µmol/l)	Mcp ± m %	2,48 ± 0,17	3,4 ± 0,24*** 137%	3,74 ± 0,28*** 150,8%	2,61 ± 0,21 105,2%	

*Note: Reliability: * - P<0,05; ** - P<0,01; *** - P<0,001 in relation to the control group*

As a result of studies of metabolites of carbohydrate metabolism under chronic exposure to dichloroethane, noise and vibration the content of lactic acid in the liver on the 15, 30, 60 and 90 days of the experiment increased to 3.19 ± 0.11; 2.87 ± 0.14; 2.83 ± 0.16; 3.92 ± 0.14 mmol/g.

The content of pyruvic acid in liver tissue under the influence of dichloroethane, noise and vibration during the whole experiment increased and made up accordingly: 176.0 ± 8.84; 188.0 ± 11.14; 191.4 ± 10.45; 159.7 ± 8.73 μmole/g (122.0 ± 4.18 μmole/g in control).

In the control group the level of glycogen was 20.0 ± 0.68 mg/g, and in experimental animals under the influence of complex factors (dichloroethane, noise and vibration) on the organism of animals after 15, 30, 60 and 90 days its level decreased to 15.1 ± 0.69; 14.18 ± 0.94; 14.3 ± 0.53; 14.4 ± 0.48 mg/g. And so under the chronic influence of dichloroethane, noise and vibration, there is the accumulation of underoxidized products of metabolites of carbohydrate metabolites and reduction of glycogen content.

It is evident from the above mentioned that under the influence of chemical and physical factors the increase of glycogen in liver tissue, as well as the rise in anaerobic glycolysis intensity and decrease of oxidizing processes are revealed. As a result, the accumulation of lactic and pyruvic acids concentration in experimental animals is observed.

Under prolonged exposure to hepatotropic chemical and physical factors, at levels that do not cause an external effect, hidden changes in the body of experimental animals revealed by several physiological reactions, biochemical indicators of the function of individual organs and systems.

The activity of some enzymes can change quite early and deeply, therefore, the indicators can be used as early diagnostic tests in the evaluation of biological action of harmful factors.

Multiple exposures to dichloroethane, noise and vibration in laboratory animals has led to changes in enzyme activity in liver tissue. In the liver, the activity of dehydrogenases at all times (15, 30, 60 and 90 days) of the study was reduced to GDG - 6.95 ± 0.75; 7.64 ± 0.71; 6.61 ± 0.76; 4.84 ± 0.59 μmol/g.h. (control 11.0 ± 0.89 μmol/g.h.).

Table 4.

Influence of dichloroethane, noise and vibration on metabolites of carbohydrate energy exchange in the liver

№	Indicators	Statistic indicators	Control	Day 15	Day 30	Day 60	Day 90
1.	Lactic acid (mmole/g)	Mcp ± m %	1,93 ± 0,077	3,19 ± 0,11*** 165,3%	2,88 ± 0,14*** 149%	2,83 ± 0,16*** 146%	3,92 ± 0,14 203% t-12,44
2.	Pyruvic acid (µmol/g)	Mcp ± m %	122,0 ± 4,18	176,0 ± 8,84*** 144,3%	188,0 ± 11,14*** 154%	191,4 ± 10,45*** 156,5%	159,7 ± 8,73** 130,9%
3.	Glycogen (mg/g)	Mcp ± m %	20,0 ± 0,68	15,1 ± 0,69*** 75,5%	14,18 ± 0,94*** 70,9%	14,3 ± 0,53*** 71,5%	14,4 ± 0,48*** 72%
4.	GDG (µmol/g.h.)	Mcp ± m %	11,0 ± 0,89	6,95 ± 0,75* 63,2%	7,64 ± 0,711* 69,4%	6,61 ± 0,76** 60,1%	4,84 ± 0,59*** 44%
5.	SDG (µmol/g.h.)	Mcp ± m %	35,0 ± 2,70	29,1 ± 2,93* 83,1%	20,83 ± 1,79*** 59,5%	21,2 ± 2,70** 63,1%	18,8 ± 2,73*** 53,7%
6.	MDG (µmol/g.h.) MDG (µmol/g.h.)	Mcp ± m %	24,0 ± 2,18	16,05 ± 1,1** 66,9%	11,9 ± 1,23*** 49,6%	12,6 ± 1,17*** 52,5%	9,60 ± 1,39*** 40%
7.	Alkaline phosphatase (µmol/g.h.)	Mcp ± m %	51,0 ± 3,18	39,90 ± 3,89* 78,2%	31,62 ± 2,68*** 62%	34,1 ± 2,25*** 66,8%	

*Note: Reliability: * - P<0,05; ** - P<0,01; *** - P<0,001 in relation to the control group*

The study of SDG activity in liver tissue under the influence of dichloroethane, noise and vibration showed that in all the periods (15, 30, 60, 90 days) of the experiments, the activity decreased by 53.7 - 83.1% respectively.

The activity of MDH in the liver was reduced in all terms of the study. In liver on 15, 30, 60 and 90 days the level was 16.05 ± 1.1; 11.9 ± 1.23; 12.6 ± 1.17; 9.60 ± 1.39 μmol/g.h.

Similar changes were observed in the decrease of activity of alkaline phosphatase in the liver. Inhibition of enzyme activity (dehydrogenase) in all studied biospheres can be explained by the influence of dichloroethane, noise and vibration on enzyme functional activity. Inhibition of enzymes GDG, MDG, SDG and alkaline phosphatase in the liver is observed at multiple effects of dichloroethane, noise and vibration. As a result of the reduction of redox enzymes, under-oxidized products of anaerobic glycolysis of lactic, pyruvic acid are accumulated and the level of glycogen is reduced.

Conclusions:

1. Chronic exposure to dichloroethane, noise and vibration disrupts serum biochemical processes, which indicates a change in the functional state of the liver.

2. change of metabolic disorders at 3-month exposure to dichloroethane, noise and vibration is manifested by an increase in the activity of enzymes AST, ALT, cholesterol, bilirubin content of the total and direct, a decrease in the total protein in the blood serum and liver tissue, which indicates the development of destructive processes in liver tissue with violation of cell membrane permeability. The increase in serum activity of alkaline phosphatase against the background of a decrease in the activity of enzymes in the liver indicates a lesion of the hepatobiliary system.

3. Prolonged exposure of various chemical and physical factors in concentrations causing external effects in experimental animals is manifested by latent changes in some physiological reactions, biochemical indicators of the function of individual organs and systems. We are confirming the influence of xenobiotics on cellular structures, mainly in the discoordination of functional activity of organs and specific enzyme systems.

4. The activity of some enzymes can change quite early and profoundly, and the indicators can be used, obviously, as early diagnostic tests in the evaluation of biological action of chemical hepatotropic substances.

Conflict of interest. All authors state that there is no potential conflict of interest that should be disclosed in this article.

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