



"STATE OF CARBOHYDRATE-ENERGY, PIGMENT, PROTEIN METABOLISM IN THE LIVER IN CHRONIC TOXIC DAMAGE"

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Article history:	Abstract:
Received: January 4 th 2022 Accepted: February 4 th 2022 Published: March 12 th 2022	In recent years, the use of organophosphorus pesticides - Fozalon and Baton EU - has significantly expanded in agriculture. This circumstance puts forward as one of the priorities the elucidation of the mechanism of action and the development of specific prevention and treatment for chronic pesticide poisoning.

Keywords: phosphorylation, pyruvate substrates, oxaloacetic acid and liver succinate, protein, glyeogen, pyruvate, activity of ALT, AST, total and conjugated bilirubin, lipid, metabolism, carbohydrate-energy, protein, laboratory, biologically, experimental;

THE PURPOSE OF THE STUDY: to identify pathogenetic mechanisms and assess the functional state of the liver in toxic damage

MATERIAL AND RESEARCH METHODS

The experiments were carried out on white male rats weighing 150-220 g. 1/20 LD50 (7.25 mg/kg, LD50 = 158 (111.3±224.4) mg/kg) for 90 days. In the studies, the state of carbohydrate-energy, protein metabolism, tissue respiration and oxidative phosphorylation, pyruvate substrates, oxaloacetic acid and liver succinate were determined, as well as the content of total protein, glycogen, pyruvate, the activity of ALT, AST, total and conjugated bilirubin in the blood.

RESULTS AND DISCUSSION

The state of biochemical parameters in the blood serum - we studied the levels of glycogen, pyruvate, the content of total and conjugated bilirubin and the activity of alanine-, asparagine aminotransferases with repeated intragastric administration of Fosalone at a dose of 7.3 mg/kg for 90 days (determination of indicators was carried out at 30, 60 and 90 days of experiments) (table 1).

Table № 1
Biochemical indicators of blood
in chronic poisoning with the pesticide Fozalon

Research days	Stat.Indicators	Glycogen g/l	Pyruvate μmol/l	ALT μmol/l	ACT μmol/l	General bilirubin mmol/l	Related-ny bilirubin
Control	Mcp±m %	8,27±0,28	94,5±3,96	0,29±0,02	0,24±0,02	18,83±0,85	1,96±0,12
Experience 30 days	Mcp±m %	7,17±0,21* 86,7%	130,43±6,17** 138%	0,33±0,03 113,8%	0,37±0,03*** 154,2%	37,57±1,91*** 199,5%	3,73±0,19*** 190,3%
Experience 30 days+LP	Mcp±m %	8,33±0,18 100,7%	97,0±5,54 102,6%	0,27±0,02 93,1%	0,28±0,02 116,7%	26,64±1,68* 141,5%	2,16±0,21 110,2%
Experience	Mcp±m	7,41±0,20	121,14±6,59*	0,36±0,0	0,36±0,0	36,07±1,04	3,77±0,21



e 60 days	%	89,6%	128,2%	2 124,3%	2* 150%	** 191,6%	*** 192,3%
Experienc e 90 days	Mcp±m %	7,33±0,25* 88,6%	118,5±9,29 125,4	0,35±0,0 3* 120,9%	0,34±0,0 3* 141,7%	36,19±1,71 *** 192,2%	3,67±0,21 *** 187,2%

Note: reliability relative to control: * - p<0.05; ** - p<0.01; *** - p<0.001.

The table shows that the content of glycogen and pyruvate, total and free bilirubin in the blood of the control group was 8.21±0.28 g/l, respectively; 94.5±3.96 µmol/l; 18.83±0.85; 1.96±0.12 mmol/l.

The content of glycogen in the blood for 30-90 days with chronic poisoning with Fozalon decreased to 86.7-88.6%. Upon receipt of drugs consisting of lipoic, orate, ascorbic acids and St. John's wort, corn column and stigmas, the level of glycogen was restored to the values of the control group. The concentration of pyruvic acid in all periods of the experiment increased, respectively, on days 30, 60, 90 to 180; 128.2; 125.4%. When using therapeutic synthetic and herbal preparations, the content of pyruvate reached the level of control indicators and amounted to 102.3%.

The activity of alanine and aminotransferases in the blood serum of animals increased in relation to the indicators of the control group. At the same time,

the intensity of transamination between alanine and α-ketoglutaric acid in all periods of the experiment was 113.8-114.3% and aspartic acid transaminases 154.2-141.7%.

Particularly sharp changes in the blood serum during Fozalon poisoning were observed in the metabolites of the pigment index. At the same time, on days 30, 60 and 90, the content of total bilirubin increased to 191.6-199.5%, and bound bilirubin to 190.3-192.3 and 187.2%. So, there was a significant increase in total and conjugated bilirubin in the blood serum of laboratory animals, which indicates a violation of the excretory function of hepatocytes.

The effect of the pesticide Fozalon on some indicators of metabolites of carbohydrate and protein metabolism in the liver and medicinal plant and synthetic preparations is presented in Table 2.

Table № 2
The content of biochemical parameters of the liver
with repeated intragastric administration of the pesticide Fosalona

Research days	Stat.Indicators	Glycogen (mg/g)	Pyruvate µmol/l	AST (mmol/g.h)	ALT (mmol/g.h)	Total protein (mg/g)
Control	Mcp±m %	9,26±0,37	142,29±5,59	52,43±2,59	34,81±2,20	5,86±0,24
Experience 30 days	Mcp±m %	8,06±0,31* 87,0%	157,14±8,08 100,4%	67,66±3,44** 129,0%	43,44±2,18 124,8%	3,67±0,26*** 62,6%
Experience 30 days+LP	Mcp±m %	8,33±0,39 89,9%	146,14±5,13 102,7%	51,87±2,19 98,8%	41,16±2,69 118,2%	4,11±0,29* 70,1%
Experience 60 days	Mcp±m %	7,51±0,33** 81,1%	155,14±9,01 109,0%	66,90±2,50** 127,6%	51,87±3,36** 149,0%	3,55±0,18*** 60,6%
Experience 90 days	Mcp±m %	7,54±0,18** 81,4%	156,43±6,35 109,9%	71,66±3,01*** 136,7%	49,89±3,16*** 143,3%	3,61±0,22*** 61,6%

Note: reliability in relation to control: * - p<0.05; ** - p<0.01; *** - p<0.001

The table shows that the biochemical parameters in the liver tissue of the control group are: glycogen level 9.26±0.37 mg/g, pyruvic acid 142.3±5.59 µmol/g and total protein 5.86±0, 24 mg / 100, activity of alanine

aminotransferase 34.81 ± 2.20 and asparagine aminotransaminase - 52.43 ± 2.59 mmol / g.h.

The content of glycogen in chronic poisoning of animals decreased on the 30th day to 87.0%, on the 60th and 90th days 81.1 and 81.4%, respectively.



When using drugs, the level of glycogen increased by 2.9-8.8%. So, with chronic poisoning with the pesticide Fozalon, a decrease in the glycogen-forming function of the liver is observed, and with the use of drugs, an approach to the indicators of the control group was observed.

The concentration of pyruvic acid in the liver at all times of the experiment, compared with the control group, was within physiological fluctuations (by 1.3%). When using medicinal preparations, its content decreased to 102.7%. The level of total protein in the liver with repeated administration of the pesticide significantly decreased and amounted to 62.6-60.6%, in treated animals, the protein concentration increased by 8-10%.

The activity of AST and ALT in chronic pesticide poisoning significantly increased in all periods of the study. At the same time, AST activity on days 30, 60, and 90 increased, respectively, to 129.0; 127.6 and 136.7%. The activity of alanine aminotransaminases increased to 124.8; 149.0 and 143.3%, and with the introduction of drugs, the activity of AST and ALT transaminases decreased to 98.8 and 118.2%, respectively. These changes in the activity of transaminases indicate a violation of the permeability of cell membranes and a decrease in the

protein-synthesizing function of the liver. When using drugs, the activity of transaminases (AST, ALT) and the protein level approached those of the control group.

The study of the effect of the pesticide Fozalon on the intensity of respiration and oxidative phosphorylation in the liver showed that the function of a living cell is its ability to supply energy. Because, for this, the cell uses external energy resources. The generally accepted criterion for assessing the ability of cells to produce macroergic compounds is the state of oxidative phosphorylation in the process of their regulation.

The redox process in cells accelerates metabolic processes, participates in the formation of metabolites necessary for the cell, in the formation of toxic substances and the burning of underoxidized products. Currently, there is some information about the change in the activity of the reaction of tissue respiration and oxidative phosphorylation in the liver tissue during intoxication with toxic chemicals.

The aim of the work was to study the state of tissue respiration and oxidative phosphorylation of substrates of keto acids of the tricarboxylic acid cycle in liver mitochondria during chronic poisoning with the pesticide Fozalon (at a dose of 7.3 mg/kg) (table 3).

Table № 3
The content of the activity of liver dehydrogenases
in chronic poisoning with the pesticide Fozalon

Research days	Stat.Indicators	MDH (mmol/g.h)	GDG (mmol/g.h)	LDH (mmol/g.h)	SDG (mmol/g.h)
Control	Mcp±m %	32,54±1,81	12,18±0,42	29,8±1,85	34,93±1,76
Experience 30 days	Mcp±m %	25,39±1,15* 78,0%	9,23±0,42*** 75,8%	48,5±2,12*** 162,7%	27,21±1,58* 77,9%
Experience 30 days+LP	Mcp±m %	25,06±1,02 77,0%	11,21±0,34 92,0%	28,8±1,48 96,6	32,36±1,46 92,6%
Experience 60 days	Mcp±m %	21,53±1,16*** 66,2%	9,64±0,38* 79,1%	45,5±2,29*** 152,7%	26,25±1,90** 75,1%
Experience 90 days	Mcp±m %	21,99±1,00*** 67,6%	8,93±0,57** 73,3%	46,57±1,58*** 166,3%	27,64±1,82* 79,1%

In animals after slaughter, by decapitation every 30 days for 90 days, the liver was recorded on an LP-9 polarograph by implanting a platinum electrode. When determining the functional activity in liver mitochondria, oxaloacetic and liponic acids, succinate,

pyruvate, and malate dehydrogenases per mmol were used as substrates.

When studying the intensity of respiration and oxidative phosphorylation of substrates, the rate of oxidation (V₂), the rate of oxidation with the addition



of ADP (V3), the rate of respiration after (Table 4)
 phosphorylation of added ADP (V4) were determined

Table № 4
The state of the rate of oxidative phosphorylation of pyruvate (PVK) in the liver tissue in chronic pesticide poisoning

Research days	Stat.Indicators	V ₂ → (mkAO ₂)	V ₃ → (mkAO ₂)	V ₄ → (mkAO ₂)	DK→	ADP/O
Control	Mcp±m %	24,92±0,70	36,43±1,02	27,73±1,28	1,34±0,04	1,81±0,05
Experience 30 days	Mcp±m %	18,30±1,02** 73,4%	28,23±1,08** 77,5%	20,10±1,67** 72,5%	1,45±0,06 108,2%	1,58±0,08* 87,3%
Experience 30 days + LP	Mcp±m %	22,78±0,77 91,4%	30,68±2,00* 84,2%	24,28±1,41 87,5%	1,31±0,02 97,8%	1,79±0,09 98,8%
Experience 60 days	Mcp±m %	18,33±1,22* 73,6%	27,68±1,26** 75,9%	18,98±0,75** 68,4	1,39±0,09 103,7%	1,46±0,07** 80,7%
Experience 90 days	Mcp±m %	17,40±0,83** 69,8%	26,20±1,29*** 71,9%	20,80±1,53* 75,1%	1,52±0,07 113,4%	1,51±0,06 83,4%

Note: reliability in relation to control: *-p<0.05; **-p<0.01;***-p<0.001

Phosphorylation efficiency (ADP/O ratio) was calculated according to Chaks-Vilgis: the rate of tissue respiration was expressed in micromoles of oxygen per minute (μAO₂/min).

In chronic poisoning with the pesticide Fozalon, the intensity of respiration and oxidative phosphorylation decreased in all leads and terms of poisoning with the use of the liver pyruvate substrate. At the same time, the rate of oxidation in the medium with the substrate of oxidation on the 30th, 60th, and 90th days of poisoning decreased, respectively, to 73.4; 73.6 and 69.8%, the rate of oxidation with the addition of ADP - decreased to 77.5-71.9% and the rate of respiration after phosphorylation in the V4 position and amounted to 20.1 ± 0.75 μA / 0 on days

30-80 at the control level of 27.73±1.29 μmolO₂, the respiratory rate with the addition of DNP (inhibitor) decreased in all periods of the study (DNP), the changes were 103.2-113.4%. The state of the ADP/O ratio decreased to 83.7; 80.7; 83.4% at 30, 60 and 90 days of seeding. Thus, the intensity of respiration and oxidative phosphorylation is inhibited by the addition of the substrate pyruvate in liver mitochondria during chronic Fosalone poisoning.

Table 5 shows the effect of the pesticide Fozalon at a dose of 1/20 LD₅₀ on the rate of respiration and oxidative phosphorylation of the succinic acid substrate (succinate) in liver mitochondria.

Table № 5
The state of oxidative phosphorylation of the succinic acid substrate in chronic poisoning with the pesticide Fozalon

Research days	Stat.Indicators	V ₂ → (mkAO ₂)	V ₃ → (mkAO ₂)	V ₄ → (mkAO ₂)	DK	ADP/O
Control	Mcp±m %	20,18±0,55	30,62±1,09	23,97±1,09	1,34±0,10	2,07±0,07
Experience 30 days	Mcp±m %	17,28±0,79* 85,6%	26,58±1,19** 86,9%	20,17±0,95 84,1%	1,33±0,09 99,2%	1,82±0,08* 87,9%
Experience30	Mcp±m	18,8±0,77	29,97±1,03	21,08±1,07	1,43±0,10	1,92±0,08



days+LP	%	93,2%	97,9%	87,9%	106,7%	92,7%
Experience 60 days	Mcp±m %	17,42±0,80 86,3%	27,27±1,12* 89,1%	19,83±1,23* 82,7%	1,47±0,14 109,7%	1,74±0,08* 84%
Experience 90 days	Mcp±m %	17,13±0,83* 84,9%	26,18±0,98* 85,5%	18,02±0,73** 75,2%	1,47±0,11 109,7%	1,20±0,10** 57,9%

Note: reliability in relation to control: *-p<0.05; **-p<0.01; ***-p<0.001

At the same time, in the animals of the control groups in positions V2 it was 20.18±0.55 μAO₂, V3 - 30.62±1.39, V4 - 23.97±1.09 μAO₂, and the respiratory control, respectively, ADP/O was at the level 1.34±0.10 and 2.07±0.07. When using succinic acid in poisoned animals in the V2 position in all periods of the experiments, it decreased to 85.6; 86.3 and 89.9%. In positions V3 and V4 it also decreased to 85.5-86.9% and 75.2-84.1%, DC changes were disproportionate. ADP/O indicators decreased by 57.9-

87.8% in all terms. Therefore, the use of the succinate substrate, the intensity of respiration and redox processes in the liver, is taken into account in Fozalon poisoning. The use of a citric acid substrate in the liver homogenate reduces the intensity of oxidative phosphorylation of respiration, as with the use of substrates. At the same time, in animals of the control group, the indicators of respiration and phosphorylation in positions V₂, V₃ and V₄ decrease at all times (Table 6).

Table № 6

The state of respiration and oxidative phosphorylation of the citric acid substrate in chronic poisoning with the pesticide Fozalon

Research days	Stat. Indicators	V ₂ (mkAO ₂)	V ₃ (mkAO ₂)	V ₄ (mkAO ₂)	DK	ADP/O
Control	Mcp±m %	22,7±0,74	33,33±0,92	26,50±1,35	1,24±0,09	1,89±0,06
Experience 30 days	Mcp±m %	18,18±0,74** 80,1%	28,95±0,69** 86,9%	22,13±0,96* 83,5%	1,31±0,05 105,6%	1,49±0,10 78,8%
Experience 30 days +LP	Mcp±m %	19,53±1,03 86%	31,68±1,05 95%	23,30±1,29* 87,9%	1,34±0,11 108,1%	1,94±0,15 102,6%
Experience 60 days	Mcp±m %	18,02±0,89*** 79,4%	27,38±0,90*** 82,1%	19,07±0,72** 71,9%	1,43±0,09 115,3%	1,52±0,08 80,4%
Experience 90 days	Mcp±m %	18,33±0,95** 80,7%	27,73±0,88** 83,2%	18,70±0,89** 70,6%	1,51±0,09 121,8%	1,48±0,08 78,3%

The rate of oxidation with the oxidation substrate of the control group was 22.7±0.74 mCAO₂, V₃ - 33.3±0.92

In experimental groups with chronic poisoning with the pesticide Fozalon, in terms of citric acid oxidation in the liver, the intensity in positions V₂, V₃ and V₄ at all times (30, 60, 90 days) decreased in relation to the control from 80.1 to 86.9 and 70, 6%. With the use of drugs, the rate of respiration and oxidative phosphorylation in all leads (V₂, V₃, V₄) increased up to 86-95% and approached those in the

control group. The indicator of respiratory control increased to 105.6 and 121.8%, and the state of the ADP/O ratio decreased from 68.8-80.4%. So, the use of a substrate of citric acid, the intensity of respiration and oxidative phosphorylation in the mitochondria of the liver is inhibited. When using drugs, the intensity of respiration and oxidative phosphorylation in Fosalone poisoning has a positive effect.

Similar changes were observed in the rate of respiration and oxidative phosphorylation of the



substrate oxaloacetic acid (OAA) in the liver during chronic Fosalone poisoning (Table 7).

Table № 7

The state of oxidative phosphorylation of the oxaloacetic acid substrate in chronic poisoning with the pesticide Fozalon

Research days	Stat.Indicators	V ₂ → (mkAO ₂)	V ₃ → (mkAO ₂)	V ₄ → (mkAO ₂)	DK	ADP/O
Control	Mcp±m %	19,5±0,74	26,9±0,89	20,82±1,06	1,29±0,06	1,74±0,04
Experience 30 days	Mcp±m %	14,0±1,23* 71,7%	20,28±0,90** 75,4%	17,48±0,82 83,9%	1,16±0,05 89,9%	1,44±0,08* 82,8%
Experience 30 days+LP	Mcp±m %	19,63±0,56 100,7%	24,37±1,28 90,6%	17,72±0,93 85,1%	1,33±0,07 103,1%	1,64±0,05 94,2%
Experience 60 days	Mcp±m %	15,95±1,06* 81,8%	21,23±1,31* 78,9%	15,72±0,69* 75,5%	1,36±0,09 105,4%	1,44±0,05 82,8%
Experience 90 days	Mcp±m %	14,73±1,04* 75,5%	19,72±0,81 73,0%	16,6±0,83* 79,7%	1,19±0,04 92,2%	1,34±0,04** 77,0%

At the same time, in position V₂ at all times (30, 60 and 90 days), the indicators decreased in relation to the control to 71.7-81.8%. In leads V₃ - up to 75.4-78.9%, and V₄ - also decreased in all periods of the study. With the addition of the homogenate, the termination of the process of dinitrophenolhydrozine respiratory control changes were within the limits of physiological fluctuations. The ratio of adenosine phosphate (ADP) and oxygen decreased to 77.0-82.8%.

Thus, the data obtained indicate that the intensity of tissue respiration and oxidative phosphorylation of the substrates of succinate, pyruvate, citric and oxaloacetic acids metabolized through the cycle of tricarboxylic acids in liver mitochondria under the influence of the pesticide Fozalon was observed inhibition of processes. The pathogenetic mechanism of the development of the pathological process in the liver is the inhibition of tissue respiration due to a decrease in oxidative phosphorylation in the mitochondria of hepatocytes.

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