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Research Article

Treatment of hepatitis induced by anti-tuberculosis drugs (experimental research)

Vladimir N. Fedorov[1], Nikolai A. Smirnov[1], Vladimir P. Vdovichenko[2], Tatyana B. Fedorova[1], Edgar E. Kerbenev[1], Aleksei K. Petrovsky[1]

1 *Yaroslavl State Medical University, 5 Revolyutsionnaya St., Yaroslavl 150000, Russian Federation*

2 *Grodno State Medical University, 80 Gorky St., Grodno 230009, Republic of Belarus*

Corresponding author: Aleksei K. Petrovskii (gcvl2013@mail.ru)

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Abstract

Introduction: Tuberculosis is a widely spread infection. While treating patients for it, they are given simultaneously and for a long period 5-6 antibacterial drugs, which are, as a rule, bad for the liver. It quite often (up to 20%) causes drug-induced hepatitis. As experimental means of protecting the liver, the following peptides are suggested: chorionic gonadotropin, a recombinant drug of luteinizing hormone – luveris, and oligopeptide drugs: semax and selank.

Materials and Methods: The research was conducted on 104 outbred white male rats weighing 170-220 g. Each group included at least 10 animals. Drug-induced hepatitis was simulated through the combined 21-day administration of isoniazid, rifamycin, and ethanol. Chorionic gonadotropin, luveris, semax and selank, as well as a comparison drug mexidol, were administered once a day during the experiment. Healthy control animals and rats with drug-induced hepatitis were used as comparison groups. For evaluation of the efficiency of administered drugs, the obtained biochemical and histomorphological research data was used.

Results and Discussion: During the experiment, chorionic gonadotropin (ChG), semax and selank showed a greater therapeutic activity than mexidol and luveris. Only in the case of administering ChG, selank and semax, there was parallelism between the restoration of biochemical parameters of blood and histomorphological parameters of the liver. Administering both selank and ChG was also characterized by more active regenerative processes.

Conclusion: Administering ChG, selank and semax to patients with tuberculosis would significantly reduce the number and severity of hepatotoxic reactions.

Keywords

tuberculosis, hepatoprotection, hepatoprotector, drug-induced liver lesions, chorionic gonadotropin, luteinizing hormone of hypophysis, semax, selank.

Introduction

Tuberculosis is one of the undefeated infections and one of the main causes of death among people, holding the 9th position in the death cause ranking (Zakharov et al 2018). The rate of tuberculosis contamination (positive Mantoux test) around the globe is estimated to be at 32%, while 5-20% out of this group are at risk of the disease activation (Noaham and Clarke 2008). In the Russian Federation, as of 01.01.2019, the general tuberculosis morbidity was about 101.6 cases for every 100 thousand people (Health Care in Russia 2019).

Considerable growth of acutely progressing and widespread forms of tuberculosis, as well as the growing number of polyresistant forms of tuberculosis mycobacteria (TMB) call for the combined use of 5-6 drugs in chemotherapy, which provokes drug-induced hepatitis (Cai et al. 2012; Tang et al. 2012; Ivanova and Borisov 2017). The minimal combination is at least 3 drugs, and the minimal course of treatment is at least 6 months (Mishin et al. 2007; Madasova and Aksenova 2008; Ministry of Health of the Russian Federation (2014).

The main anti-tuberculosis drugs (isoniazid, ethambutol, ethionamide, pyrazinamide and rifampicin) have a hepatoxic effect and cause toxic hepatitis, whereas their combined use increases the toxic effect (Madasova and Aksenova 2008; Kazakov et al. 2018). The rate of drug-induced liver lesions (DILLs) during the anti-tuberculosis polychemotherapy is between 15 and 20% (Sukhanov et al. 2009; Drobin 2014; Mordyk et al. 2014; Testov et al. 2014; Ivanova and Borisov 2017; Yakovleva et al. 2017), which is a peril to administering a complete chemotherapy treatment.

The most widely used drug in treatment of tuberculosis is isoniazid, which after acetylation turns into hydrazine, from which a powerful acetylating substance causing liver necrosis is formed under the influence of enzymes (Bueverov 2009; Mozhokina and Elistratova 2016). The toxic effect of isoniazid increases if it is administered simultaneously with cytochromes enzyme system inducers, like rifampicin, as well as with alcohol, anaesthetics, and paracetamol. A combination of isoniazid and pyrazinamide increases the death rate dramatically (Cai et al. 2012; Kazakov et al. 2018). Isoniazid, in turn, increases a hepatoxic effect of rifampicin and pyrazinamide. With the combined administration of isoniazid and rifampicin, hepatitis is noted in 5-8% of cases, while with the isoniazid monotherapy – in 1.2% cases, and with the rifampicin monotherapy – in 0.3% cases (Polunina and Maev 2007).

In the treatment of DILLs, hepaprotectors are used for pathogenetic therapy; the choice of them depends on the leading disease mechanism (Minushkin et al. 2016). The effect of hepatoprotectors is aimed at restoring liver homeostasis, increasing the organ's resistance to pathogenic factors, normalization of its functional activity and stimulation of reparative regeneration processes in the liver (Kovtun et al. 2011; Kucheryavy and Morozov 2012; Vyalov 2013). The biochemical mechanism of the protective effect of most hepatoprotector groups includes the membrane-stabilizing (increasing membrane activity and fluidity, decreasing density in the mosaic membrane model of phospholipid elements and normalizing their permeability, activating phospholipid-dependent enzymes), antioxidant (inhibiting lipid peroxidation, decreasing the free-radical synthesis rate), antifibrotic, regenerational (increasing ribonucleic acid and protein synthesis by means of hepatocytes) and hypolipidemic effects (Yakovenko et al. 2017).

Yet, the hepatoprotector therapy as of today has certain drawbacks: undesirable side effects, drug-drug interaction, variability of the clinical effect of drugs produced by different manufacturers, as well as (nota bene!) a rather narrow spectrum of a therapeutic effect mechanism, which forces one to combine drugs of different groups (Crocenzi and Roma 2006; Matveev et al. 2011; Babayan and Havkin 2013).

One of the promising hepaprotectors lacking the drawbacks of the 'classical' drugs is chorionic gonadotropin (ChG), which participates in regulating the reproduction of mammals' cells and bodies, their development, regeneration and homeostasis at different levels of the hierarchic organization. ChG and its beta-subunit are produced not only in trophoblast and placenta chorion, but also in phoetus tissue, as well as in multiple tissues of both children and adults of both sexes. An increase in ChG synthesis leads to stimulating and normalizing the reproduction of mammals' cells and bodies and their development in embryogenesis and early postnatal ontogenesis, as well as in the processes of physiological, reparative and intracellular regeneration in the early and late postnatal ontogenesis.

According to experimental and clinical data given in literature (Solopaeva 2003), with liver pathologies of various etiologies, ChG stimulates regeneration processes and promotes normalization of the structure and function of the organ. In particular, with administering ChG, there is an increase in the mitotic activity of hepatocites, a decrease in the number of degenerating cells and an increase in the number of normal ones. What is more, resorption of proliferated connective tissue; activation of synthesis of RNA, soluble and insoluble proteins; stimulation and normalization of enzyme and lipid metabolisms, manifested in a considerable decrease of fatty infiltration. As a result, ChG stimulates reparative regeneration in the liver, naturally leading to reversibility of pathologic changes and normalization of the structure and functioning of the organ. Administering ChG as part of a complex therapy for children with chronic hepatitis proved that 1-1.5 years after the end of hormonotherapy 90% of the total number of patients showed stable clinical performance, which is 10 times higher than in the comparison group.

According to its biological characteristics in mammals' bodies, ChG is the closest to luteinizing hormone one of hypophysis, which contains the same alpha-subunit as ChG, differing only by a beta-subunit. In view of this, until recently, ChG produced from pregnant women urine has been the only medicine used when the patient's

body had to receive a substance with a luteinizing activity. Thanks to the advance of pharmaceutical technologies, clinicians got the recombinant drug of a luteinizing human hormone – luveris, used together with ChG solely for treating infertility, while its possible use as a hepatoprotector is yet to be checked experimentally.

Another trend in solving the problem of counteracting drug-induced hepatoxicity is introducing into clinical practice the drugs of the glyproline group, possessing the properties of regulatory peptides (RPs). RPs activate processes of self-regulation and self-healing of disrupted functions of organs and systems affected in various diseases (Myasoedov 2016). The typical representatives of the RP class are semax and selank, belonging to the glyproline family. Semax is a synthetic peptide based on a fragment of adrenocorticotropic hormone $ACTH_{4-7}$ (Met-Glu-His-Phe), whereas the structure of selank is based on a peripheral immunomodulator taftsin (H-Thr-Lys-Pro-Arg-OH). To protect from the hydrolysed action of peptidases, tripeptide Pro-Gly-Pro, which has a cytoprotective activity, was added to them in the C-position (Myasoedov 2016). The introduction of semax and selank to the body promotes activation of the peptidergic system and secondary synthesis of a wide range of regulatory peptides (Solovyev et al. 2011). They prevent the liver damage in stress situations (Ivanov et al. 2017). It is worth noting that they contribute to regulation of inflammatory processes due to reducing the level of cytokine imbalance and normalizing the activity of the kinin-bradykinin system, and also reduce the activity of apoptosis in the damaged tissues. The drugs are characterised with a high level of safety (Myasoedov 2016).

The purpose of this research was to study the hepatoprotective effect of chorionic gonadotropin, a recombinant drug of luteinizing human hormone, selank and semax in liver damage caused by anti-tuberculous drugs.

Materials and methods

The research was conducted on 104 outbred white male rats, each weighing 170-220 g. The experimental group included at least 10 animals. The laboratory animals were treated according to the Rules of Laboratory Practice (Ministry of Health of the Russian Federation 2016). All the animals were kept in the identical standard conditions of care.

Drug-induced hepatitis was simulated through a combined administration of isoniazid (100 mg/kg, intragastrically), rifamycin (130 mg/kg, intragastrically) and a 25% ethanol solution (3gr/kg, intragastrically) for 21 days. A number of biochemical parameters were studied in the blood of the animals on the 22nd day after the start of administering liver toxicants. These biochemical parameters were combined into functional groups: cytolysis markers [activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT)], lactate dehydrogenase (LDG); indicators of the protein-synthetic activity of hepatocytes (total protein, albumins, globulins), carbohydrate metabolism (activity of total and pancreatic alpha-amylase, content of glucose), lipid metabolism [activity of lipase, content of triglycerides (TG), total cholesterol (ChT), cholesterol of high-density lipoproteins (HDL) and low-density lipoproteins (LDL)], and detoxification function of liver (contents of direct bilirubin). The osmotic resistance of erythrocytes (ORE) was studied with a standardized method.

During a histomorphological study, the general evaluation of the preparations was carried out by hematoxilin and eosin staining; collagen fibres were shown by Masson staining; elastic fibres were stained by fuchselin (Hart's staining), and reticuline fibres – by Foot's silver impregnation. A stereometrical study of the liver was done to define the correlation between different tissue compounds.

Chorionic gonadotropin (ChG) and a recombinant drug of luteinizing human hormone (rLH-luveris) were administered hypodermically at a dose of 500 IU/kg and 50 IU/kg, respectively. Semax (methionine-glutamine-histidine-phenylalanine-proline-glycine-proline) and selank (threonine-lysine-proline-arginine-propline-glycine-proline) were administered intranasally, 0.04 ml in each nasal passage; the dosage was 0.2 mg/kg. For comparison, a synthetic antioxidantive drug mexidol (ethylmethylhydroxipyridine succinate) was used as a hepatoprotector patented for toxic liver lesions caused by chronic administering of tuberculostatic drugs (Smirnov et al. 2002). Mexidol was administered hypodermically at a dose of 30 mg/kg. All the drugs under study were administered once a day during the whole experiment. Comparison was made between the healthy control groups and the animals with simulated hepatitis, administered saline solution of sodium chlorides of the equivalent volume hypodermically.

All the calculations were made using Biostatistics software. Each parameter in different experiments was measured 10-18 times. For intergroup comparison, there was used Student's t-criterion (in case of normal distribution) and a non-parametric Wilcoxon criterion (with no-normal distribution); for multiple comparisons, Student's criterion with a Bonferroni's adjustment was used. The significance of intragroup differences was defined by paired Student's t-criterion. The difference was considered significant at $p<0.05$.

Results and discussion

The analysis of dynamics in activities of cytolytic enzymes in blood showed (Table1) that in the case of toxic hepatitis there was a statistical increase in AST and ALT by 46% and 21%, respectively, and a tendency towards a 15% increase in total LDH activity, but, at the same time, the activity of GGT remained unchanged. All this points at moderate hepatocytes cytolysis. Administering rLH and mexidol for hepatitis treatment did not prevent the destruction of hepatocytes, but the level of cytolysis somewhat decreased by use of mexidol, which prevented an increase in ALT (with AST increasing by 36%, $p<0.05$).

On the contrary, ChG, selank and semax prevented an increase in the activity of blood transaminases. ChG statistically decreased ALT and AST activities by 41% and 28%, respectively, while semax decreased AST activity

Table 1. The Influence of Tested Drugs on Hepatocytes Cytolysis Activity.

Groups	ALT un/L	AST un/L	GGT un/L
intact	103.3±11.5	136.5±6.7	5.46±0.76
control	150.6±14.5*	164.5±11.1*	5.98±0.74
hepatitis + ChG	107.0±13.2**	128.2±9.7**	5.82±0.72
hepatitis + rLH	150.8±14.1*	178.6±10.6*	7.08±0.76
hepatitis + semax	102.2±21.1	114.5±9.8**	5.78±0.46
hepatitis + selank	132.7±15.6	149.7±6.5	5.44±0.74
hepatitis + mexidol	129.5±11.8	185.2±19.1*	6.72±0.86

Note: * – statistical difference with intact animals ($p < 0.05$); ** – statistical difference with control animals ($p < 0.05$)

by 30% as compared to that in the control group.

Protein metabolism imbalance is typical in liver damage. The 21-day administration of hepatotoxic drugs (Table 2) to the control rats caused a statistical decrease in the total protein level in blood by 16% due to a drop in albumin concentration (-23%, $p<0.05$); no statistical changes in the globulin concentration in blood were registered. Administering selank and ChG normalized all the disrupted indices. Semax and ChG had almost no influence on the total protein content in blood, but rLH statistically increased the albumin level as compared to the control group. Together they decreased globulin concentration in blood by 20-21%. Mexidol administering was not effective.

Table 2. The Influence of Tested Drugs on Synthesis of Protein in Liver Against the Background of Simulated Hepatitis.

Groups	Total protein g/L	Albumins g/L	Globulins g/L
intact	64.3±1.2	33.7±0.6	30.6±0.5
control	54.2±2.7*	26.0±1.1*	28.2±1.2
hepatitis + ChG	58.7±2.8	31.3±0.4**	27.4±1.3
hepatitis + rLH	55.7±1.8*	31.3±0.6**	24.4±1.0*
hepatitis + semax	56.9±2.5	29.8±1.5	24.1±0.8*/**
hepatitis + selank	59.6±2.1	31.6±1.1**	28.0±1.2
hepatitis + mexidol	51.4±4.2*	29.0±1.0*	22.4±1.0*/**

Note: * – statistical difference with intact animals ($p<0.05$); ** – statistical difference with control animals ($p<0.05$)

During hepatitis simulation, there was a statistical reduction in amylase activity by 17%, with glucose content in blood remaining at the normal level (Table 3). Out of the tested drugs, only administering selank caused the normalisation of amylase activity.

The liver is the key organ in lipid metabolism: cholesterol and lipoproteins, its transporters, are synthesized in hepatocytes; it is also the place of most synthesis of phospholipids and endogenic triglycerides, as well as of their .degradation. When simulating toxic hepatitis in rats (Table 4), there was a decrease in blood lipase activity (-57% at $p<0.05$) against the background of a statistical increase in the TG concentration (+43%) in blood and a tendency towards an increase in the total ChS level (+20% at $p<0.05$).

Table 3. The Influence of Tested Drugs on the Carbohydrate Metabolism Rate in Case of Simulated Hepatitis.

Groups	Alpha amylase of blood un/L	Alpha-amylase pancreatic un/L	Glucose mmol/L
intact	2173±94	1218±53	8.6±0.4
control	1796±60*	1012±41*	8.7±0.4
hepatitis + ChG	1558±128*	874±73*	7.7±0.9
hepatitis + rLH	1499±77*/**	843±63*/**	7.7±0.5
hepatitis + semax	1776±92*	991±51*	8.5±0.9
hepatitis + selank	2024±104**	1135±61	8.1±0.3
hepatitis + mexidol	1493±67*/**	796±63*/**	8.6±0.6

Note: * – statistical difference with intact animals ($p < 0.05$); ** – statistical difference with control animals ($p < 0.05$)

Administering ChG, rLH, semax and selank prevented the disruption of lipid metabolism in simulated hepatitis; mexidol only normalized the lipase activity, but did not prevent a 78% growth in TG concentration in blood (at $p<0.05$) and, above all, its administration statistically decreased the level of HDLP ChS by 28%. The lipid metabolism parameters were mostly effected by rLH: not only did it normalize the content of general ChS in blood, but also statistically decreased the level of HDLP ChS both in the control group rats, and in those from the intact group. ChG also statistically decreased the level of HDLP.

Table 4. The Influence of Tested Drugs on the Lipid Metabolism in Simulated Hepatitis.

Groups	Triglyceride mmol/L	Total ChS mmol/L	ChS LDL mmol/L	ChS HDL mmol/L
intact	0.54±0.03	1.60±0.13	0.87±0.07	0.43±0.05
control	0.77±0.10*	1.93±0.11	0.90±0.07	0.46±0.03
hepatitis + ChG	0.56±0.06	1.49±0.53	0.32±0.10*/**	0.52±0.07
hepatitis + rLH	0.78±0.13	1.51±0.06**	0.36±0.02*/**	0.64±0.05*/**
hepatitis + semax	0.71±0.15	1.70±0.22	0.74±0.17	0.37±0.08
hepatitis + selank	0.56±0.06**	1.71±0.14	0.89±0.06	0.50±0.04
hepatitis + mexidol	0.96±0.18*	1.66±0.16	0.63±0.08*/**	0.38±0.09

Note: * – statistical difference with intact animals ($p < 0.05$); ** – statistical difference with control animals ($p < 0.05$)

One of main functions of the liver is detoxification: the organ detoxicates both exogenous and endogenous toxic products. The latter include direct bilirubin, the level of which significantly increased by 27% (Table 5) in the sick rats. The use of rLH was not effective, and the administration of mexidol decreased the detoxification properties of the liver: concentration of direct bilirubin in blood statistically increased by further 41% compared to the control and by 79% as compared to the intact animals. The administration of semax and selank restored the detoxification function of hepatocytes. Semax was the most active, as it statistically decreased the level of direct bilirubin in blood by 1.5 times as compared to the control group.

The osmotic resistance of erythrocytes (ORE) is an integral indicator of the body's resistance to lipid peroxi-

Table 5. Influence of Tested Drugs on the Detoxification Functions of Liver Indices in Simulated Hepatitis.

Groups	Direct bilirubin mkmol/L
intact	0.52±0.02
control	0.66±0.05*
hepatitis + ChG	0.50±0.05**
hepatitis + rLH	0.73±0.04*
hepatitis + semax	0.44±0.06**
hepatitis + selank	0.56±0.09
hepatitis + mexidol	0.93±0.11*/**

Note: * – statistical difference with intact animals ($p < 0.05$); ** – statistical difference with control animals ($p < 0.05$)

dation; there is also a close connection between changes in the permeability of erythrocyte membranes and of the membranes of cells affected by a pathological process (Zakharova et al. 1991).

When simulating toxic hepatitis, there was a statistical decrease in ORE by 30% in the animals. ChG, semax, selank, and mexidol prevented an increase in the level of erythrocytes hemolysis under hypo-osmotic conditions; administering rLH was ineffective. The obtained results made it possible to suppose that in cases of toxic hepatitis the above mentioned drugs limited the activity of free-radical oxidation of lipids and protected cytoplasmic membrane functions, thus preventing cytolysis and disturbance of metabolic processes in the liver.

The simulation of drug-induced hepatitis revealed significant histomorphological changes in the liver structure. In the liver, there developed acute hyperaemia of the arterial and venous networks; there was expansion of sinusoids and the lymphatic bed. At the same time, extralobular stroma was infiltrated by mononuclear cells, neutrophils, and eosinophils; besides, proliferation of fibrous connective tissue was also observed, including that in vessels (arteries and branches of the portal vein) and bile ducts. Hepatocytes underwent hydropic protein degeneration, sometimes turning into focal necrosis, which caused a decrease in the specific area of parenchyma. The specific area of hepatocytes decreased 1.3 ($p<0.001$) times as compared to the control group. And vice versa, the specific area of sinusoids increased 1.3 ($p<0.001$) times, and the specific area of the stroma increased 1.2 ($p<0.05$) times (Table 6). On the whole, the morphological picture could be characterized as chronic active hepatitis with fibrosis of stroma, and hepatitis in the experiment in its structural manifestations fully complied with that observed in clinical practice.

Table 6. Influence of Tested Drugs on Osmotic Resistance of Erythrocytes (ORE) in Simulated Hepatitis.

Groups	ORE (% of hemolysis)
intact	55.1±3.2
control	78.1±4.6*
hepatitis + ChG	65.8±3.5**
hepatitis + rLH	70.7±4.1*
hepatitis + semax	59.2±4.7**
hepatitis + selank	62.3±4.2**
hepatitis + mexidol	60.7 ± 4.1**

Note: * – statistical difference with intact animals ($p < 0.05$); ** – statistical difference with control animals ($p < 0.05$)

After administering selank, semax and ChG, a regress of pathological changes in the liver tissue was observed: inflammatory hyperaemia of inflow and outflow blood vessels of the liver, as well as of sinusoids, decreased sharply; sclerotic changes in both the arterial walls and in portal vein branches decreased equally well, and their tonus returned to normal. Besides, the usual lobular structure of the liver was preserved, and there were no signs of liver cell damage, such as degeneration and necrosis. A considerable difference of the selank effect from that of semax was the reinforcement of regeneration processes in liver parenchyma, which showed in an increase in and hyperchromatosis of cellular nuclei and the emergence of binuclear forms, as well as considerably less expressed inflammatory infiltration of portal tracts and a noticeable decrease in the sclerosis level and the area of the portal stroma. The level of the ChG regenerating activity was somewhere between those of selank and semax: there appeared binuclear hepatocytes, though inflammatory infiltration was more pronounced than in the case of selank.

After administering rLH, minor positive dynamics was observed in the rats. The differences mostly concerned the liver parenchyma, in which there were no signs of necrosis; at the same time, dystrophic changes in liver cells were well expressed (though less so than in the control group). When administering mexidol, no considerable morphological differences were observed.

A stereometrical study showed that (Table 7) all the tested drugs prevented a statistical decrease in the specific area of hepatocytes as compared to the sick animals. However, normalization of this indicator could be proved only after administering selank and semax, which statistically increased it as compared to the control group by 22 and 20% ($p<0.01$), respectively. An increase in the specific area of sinusoids by 21-31% occurred when administering all the tested drugs, but it was observed to a lesser extent when using ChG and selank (-9%; $p>0.05$). ChG, selank, and semax prevented an increase in the area of the stroma with selank, statistically decreasing it by 14% as compared to the control group. The obtained data proved the anti-fibrotic activity of the drugs in question.

Table 7. Stereometrical Research of Liver Tissue in Intact and Control Group of Rats (%).

Groups	Hepatocytes	Sinusoids	Stroma
intact	58.2±2.3	29.6±1.2	8.5±0.3
control	46.7±2.1*	38.8±2.0*	10.3±0.4*
hepatitis + ChG	54.2±2.6	35.6±1.9*	9.3±0.5
hepatitis + rLH	51.2±2.4*	37.1±2.0*	10.0±0.6*
hepatitis + semax	55.1±2.4**	37.6±1.8*	9.1±0.5
hepatitis + selank	56.9±2.2**	35.7±1.7*	8.9±0.3**
hepatitis + mexidol	52.0±2.2	38.6±2.1*	10.3±0.5*

Note: * – statistical difference with intact animals ($p < 0.05$); ** – statistical difference with control animals ($p < 0.05$)

Lethality of the animals is the most important integral indicator of the effect of toxic agents on the organism. While

simulating toxic hepatitis, there was a 20% lethality of animals. Administering semax, selank, and ChG completely prevented it, whereas mexidol and rLH were ineffective.

On the whole, the research showed that when simulating drug-induced hepatitis in white rats by means of hepatotoxic agents (isoniazid, rifampicin and ethanol), lipid peroxidation was activated, which resulted in the disruption of the integrity of liver cell membrane structures, a cytolytic syndrome, necrotic death of some hepatocytes and subsequent fibrosis. This subsequently led to protein, carbohydrate and lipid metabolic imbalance, as well as to an impaired detoxification function of the liver. At the same time, negative changes in biochemical blood indices of the experimental rats strictly correlated with obvious morphological changes in the liver.

Conclusion

During the experimental pharmacotherapy of drug-induced hepatitis, ChG, semax and, especially, selank showed a greater therapeutic activity than rLH or mexidol. All the five tested drugs promoted the normalization of biochemical indicators in blood of the sick animals to a greater (ChG, selank and semax) or smaller (rLH and mexidol) degree. However, only in the case of administering ChG, selank and semax, the restoration of biochemical indicators of blood was observed along with the restoration of hystomorphological parameters of the liver. And only selank and ChG showed the proven increase in the activity of regenerative processes.

The research proved that, after more clinical studies, administering ChG, selank, and semax will be possible to patients with pulmonary tuberculosis who already receive a massive antibacterial therapy. It would enable to decrease the number and intensity of hepatotoxical reactions, to optimize the duration and scheme of polychemotherapy, and also to prevent the development of polyresistance of tuberculosis mycobacteria.

Conflict of interests

The authors declare no conflict of interests.

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Author Contributors

- **Vladimir N. Fedorov,** Doctor Habil. of Medical Sciences, Professor, Department of Pharmacology; e-mail: fedorov.vladimir@hotmail.com The author planned the experiment, processed the results and carried out their analysis.
- **Nikolay A. Smirnov,** Candidate of Medical Sciences, Associate Professor, Department of Pharmacology; e-mail: smirnovvv.n@mail.ru The author planned the experiment, proces sed the results and carried out their analysis.
- **Vladimir P. Vdovichenko,** Candidate of Medical Sciences, Associate Professor, Department of Pharmacology; e-mail: vmariposa60@yahoo.com The author wrote the introduction and provided the theoretical grounding for the paper.
- **Tatiana B. Fedorova,** Assistant Professor, Department of Pharmacology; e-mail: adm@odkb76.ru The author conducted the experiments.
- **Edgar E. Kerbenev,** post-graduate student, Department of Pharmacology; e-mail: Spawn1318@gmail.com The author worked out the ways of modelling the pathology in question and conducted the experiments.
- **Alexey K. Petrovsky,** post-graduate student, Department of Pharmacology; e-mail: gcvl2013@mail.ru The author planned and conducted the experiments.