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V.G. Banzaraksheev, Ya.G. Razuvaeva

PATHOMORPHOLOGICAL AND PATHOPHYSIOLOGICAL EVALUATION OF LIVER CHANGES IN WHITE RATS WITH EXPERIMENTAL DYSLIPIDEMIA AND ITS CORRECTION

ABSTRACT

In the experiment, a morphofunctional assessment of liver changes in rats with dyslipidemia and its phytotherapeutic correction was performed. It was found that the appointment of an atherogenic diet is accompanied by an increase in the total blood cholesterol, triglycerides, low density lipoproteins cholesterol and a decrease in the level of high density lipoproteins cholesterol. Against this background, the liver develops pathomorphological changes in the form of fatty hepatosis, necrobiosis and circulatory disorders. In addition, an increase in malonic dialdehyde concentration and inhibition of catalase activity are observed in rats liver homogenates. At the same time, the course introduction of phytoremedy normalizes the lipid metabolism, raises the activity of catalase in liver homogenates and reduces the content of malonic dialdehyde, and also reduces the severity of pathomorphological changes in the liver. Apparently, the polyvalent effect of phytoremedy is due to the content in its components of a complex of biologically active substances that exert lipid-lowering, antioxidant and hepatoprotective effects.

Keywords: dyslipidemia, hepar, lipid peroxidation, phythoremedy.

INTRODUCTION

In the 21st century the steady growth of atherosclerosis-associated cardiovascular pathology continues to be the main problem of Healthcare all over the world including Russia [2]. Besides, in many regions dyslipidemia is a common and significantly modified risk factor of atherosclerosis [6]. It is well known that the pathophysiological role of dyslipidemia, regardless of its etiology and pathogenesis, lies in its injuring

influence on the vascular endothelium via activation of oxidative mechanisms of atherogenesis [8]. Another important target of dyslipidemia is the liver – a key organ of the lipid homeostasis where the proatherogenic effect of dyslipidemia results in the early impairments of its morpho-functional state [9]. Undoubtedly, a complex rational pharmacotherapy directed at the anti- dyslipidemic, antioxidant and hepato-protective correction is one of the ways to interrupt such a "vicious circle" of disturbances. In this context, the use of multicomponent remedies of plant origin is of interest; they have polyvalent effect due to their rich content of biologically active substances and render a complex effect on the body [7].

The aim of the study is to estimate patho-morphological and pathophysiological alterations in the liver of the rats with experimental dyslipidemia and its correction by plant remedies.

MATERIALS AND METHODS

The experiments were carried out on male and female Wistar rats weighing 180-190 g. The animals were kept in the standard vivarium conditions observing a similar care, nutrition, and light and temperature regimen according to the GLP rules (Order N. 708H dated 23.08.2010) and the "European Convention for the protection of vertebrate animals used for experimental and other scientific purposes" (Strasburg, 1986). The test report was approved by the ethics committee of the Institute of General and Experimental Biology SB RAS (Report N. 6 dated 12.10.2016).

The animals were distributed into 3 groups: intact, control and experimental ones. Dyslipidemia was simulated in rats by atherogenic diet for 12 weeks [10]. Pharmacotherapy of dyslipidemia was carried out by introduction of the plant multicomponent remedy to the animals of the experimental group. The remedy was developed on the base of formulae described in the *rGyud bzhi* – the main source of Tibetan medicine [12]; it contains the rhizomes of *Zingiber officinalis* L., fruits of *Rosa cinnamomea* L., beet-roots (*Beta vulgaris* L.), fruits of *Malus baccata* (L) Borkh., fruits of *Crataegus sanguinea* Pall., rhizomes of *Glycyrrhiza glabra* L., bark of *Cinnamomum cassia* Blume and other components. The plant remedy was intragastrically administered to rats in the form of decoction at a dose of 1 ml/100 g daily during the whole period of the experiment. The animals of the control group received the same volume of the purified water according to the analogous scheme.

The state of the lipid metabolism was estimated by determination of the total cholesterol content (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) with the use of fermentative method [3]. To estimate the intensity of lipid peroxidation (LPO) processes in the homogenates of the liver the concentration of the malonic dialdehyde (MDA) was determined [11]. The state of the antioxidant protection (AOP) was estimated by the catalase activity in the liver homogenate [5].

To carry out patho-morphological studies the paraffin liver sections were stained by hematoxylin-eosin [4]. To reveal neutral fats in the liver parenchyma, the quick-frozen sections, prepared on the cryostat, were stained by cerasine red and the degree of the fat dystrophy of the liver was determined by semiquantitative method using the five-grade scale for the lipid content estimation [10].

The statistical data processing was made with the use of the Excel programs package; the significance of the differences was determined with the use of the Student's t-criterion.

RESULTS AND DISCUSSION

The disturbances of the absorption and transport of nutritional lipids form the basis of exogene-induced postprandial dyslipidemia [3]. In this case the mechanism of its development comes to the increased formation of triglyceride-rich chylomicrons in the intestines and the following accumulation of remnants formed in the blood after their lipolysis. It is known, that the pathophysiology of circulating remnants involves their penetration into the arterial wall, macrophagal phagocytosis and their transformation into "foam cells" – a morphological basis of atherosclerosis [6, 8]. The experimental studies showed that the 12-week administration of the atherogenic diet including high caloric fatty nutrition resulted in significant disturbances of the lipid metabolism (Table 1). The lipidogram of the control animals has shown the increase in the TC content by 38%, TG – by 2.2 times, LDL-C – by 5 times and the 22% decrease in the level of anti-atherogenic HDL-C. At the same time, in the experimental group of animals, the course treatment with the plant remedy was followed by the decrease of TC, TG and LDL-C contents by 23%, 42% and 36% respectively and the 18% increase of HDL-C as compared to the control.

It is known that any disturbances in the lipid metabolism are followed by the impairment in the functional state of the liver – a key organ of the lipid homeostasis; moreover, the occurrence of pathological processes in it is likely not only to cause dyslipidemia, but to give a boost to the development of the lipid dysmetabolism [3, 9].

The findings of the pathomorphological studies of the animals' liver have shown that the atherogenic diet results in the development of the fatty hepatosis in rats; the average level of the liver fat in the control was 4.6±0.22 (Fig. 1). In all animals of the control group there were noted significant morphological signs of the diffuse liver fat in the form of lipid drops of different sizes; they invade the whole cytoplasm of hepatocytes. Particularly, in 5 animals the steatosis spread all over the whole liver acinus and in 38% of rats it invaded 2/3 of the hepatic tubule, mostly in the periportal area. Besides, the hepatocytes with necrobiotic and necrotic alterations and local spot necrosis were revealed all over the whole liver parenchyma in animals of the control group. Against the background of the focal-diffuse liver steatosis and necrotic alterations in hepatocytes, the tubular-radial structure of the acini appeared erased in some animals.

Along with the above patho-morphological alterations, there were noticed the signs of circulation disturbances in the liver. Particularly, in individual central veins there was revealed the blood filling and hemorrhagic suffusion of the parenchyma, mild dilation of perisinusoid space in most cases and erythrocyte stasis in capillaries. Besides, some portal tracts were slightly dilated; in their stroma there was noted moderate focal lympho-macrophagal infiltration with individual polymorphonuclear cells (Fig. 2). Also, there was noticed the margination and leukopedesis in the vessels; in the stroma of the acinus there was revealed the mild cellular, mostly, lymphohysteocytic infiltration along the sinusoidal capillaries.

The given findings of the experimental studies conform to the information in the literature; the atherogenic diet reportedly results in the marked deformation of the segmental structure of the liver, focal and diffuse inflammatory infiltration, apoptosis of hepatocytes along the portal tracts and micro- and macro-dripping liver steatosis [9].

Table 1

Influence of the plant remedy on the indices of lipid metabolism in induced dyslipidemia in rats

Indices	Intact (n=8)	Control (n=8)	Experimental (n=8)
TC, mmol/l	2,76±0,40	3,81±0,42	2,94±0,04*
TG, mmol/l	3,97±0,35	8,87±1,07	5,15±0,12*
HDL-C, mmol/l	1,82±0,05	1,42±0,21	1,68±0,15
LDL-C, mmol/l	0,15±0,01	0,81±0,02	0,52±0,02

Note: * – hereinafter the difference is significant in comparison with the control when p≤0.05.

However, the course administration of the complex remedy to animals significantly restrained the development of the liver steatosis. For example, in 2 animals from the experimental group, there was noted no fatty hepatocyte infiltration; the cytoplasm of cells had the granular form. A zonal fatty hepatocyte dystrophy was noticed in 6 animals, but in most cases the infiltration had a dust like and micro-drop character, therefore, it was revealed only by histochemical method and on specimens with high resolution of the microscope (Fig. 2). It is worthy to note, that hepatocytes containing lipids, were located in the zone of the portal tract and in individual cases they spread till the centrolobular zone. The level of the liver steatosis in the experimental group of rats averaged 2.6±0.30 (p≤0.001) being 43% less than the same index in the control. On the background of the tested plant remedy use, only individual liver cells underwent necrotic alterations and the tubular structure of hepatocytes remained intact.

It is known that the chronic dyslipidemia as an endogenic prooxidant inhibits antioxidant potential of the body and activates the oxidative stress [8]. In the previous studies we have established that, along with the changes in the ratio of atherogenic and antiatherogenic lipoprotein fractions, the induced dyslipidemia is characterized by hypoantioxidantemia and hyperlipoperoxidemia and, particularly, by the increase in the level of modified forms of LDL [1].

The findings of the studies demonstrated the signs of the AOP depression and acceleration of the peroxidation processes in the animals of the control group. Against the background of the induced dyslipidemia, the MDA content increased by 39%, the catalase activity decreased by 25% as compared to the data in the intact group (Table 2).

However, the administration of the plant remedy to the animals of the experimental group was characterized by less marked alterations in the indices of peroxidation and parameters of the antioxidant potential. Particularly, the MDA concentration in the liver homogenates of the control animals was 38% lower and the catalase activity was 16% higher as compared to the same indices in the control.

Conclusion

Thus, the experimental studies have shown that the atherogenic diet administered to rats significantly disturbs the lipid metabolism; as a result, it suppresses the antioxidant system of the body and leads to the excessive accumulation of peroxidation products. The given pathophysiological processes in laboratory animals are followed by patho-morphological alterations in the form of fatty hepatosis, necrobiosis and circulation failure in the liver. However, the course preventive phytotherapy favorably influences the lipid imbalance, diminishes peroxidation processes and decreases the manifestation of injuries in the liver architectonics. Obviously, such polyvalent effect of the plant remedy is due to the content of the spectrum of biologically active compounds having the complex hypolipidemic, antioxidant and hepatoprotective effects [7]. It is assumed that the tested plant remedy will break new ground for a rational and effective etiopathogenetic therapy of lipid metabolism disturbances.

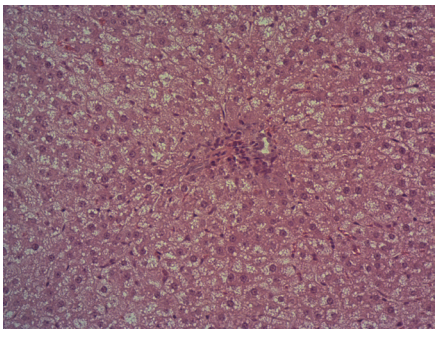

Fig.1. The liver of the control group animal. Hematoxylin-eosin staining. Optical zoom 10x20.

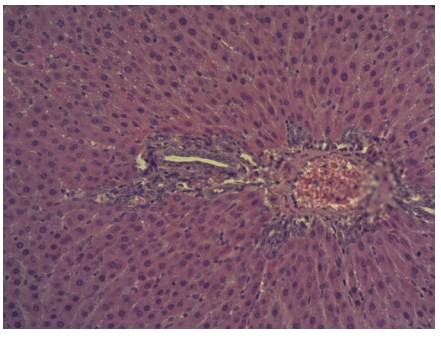

Fig.2. The liver of the animal treated with the complex remedy. Hematoxylin-eosin staining. Optical zoom 10x20.

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Table 2

Influence of the plant remedy on LPO and AOP indices in the liver of the rats with induced dyslipidemia

Indices	Intact (n=8)	Control (n=8)	Experimental (n=8)
MDA, nM/g	0,051±0,50	0,071±1,20	0,044±0,85*
Catalase, mkat/g	3,88±0,28	2,94±0,16	3,43±0,15

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ORGANIZATION OF HEALTH, MEDICAL SCIENCE AND EDUCATION

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ASSESSMENT OF POPULATION, AGE AND SEX STRUCTURE CHANGE IN TERRITORIAL SUBJECTS OF THE RUSSIAN FEDERATION IN THE TERRITORY OF THE FEFD

ABSTRACT

Successful functioning of territorial programs of the preferential provision of medicines (PM) is possible at the correct assessment of population, changes of age and sex structure as bases of formation of requirement and objective justification of the application medical institutions taking into account medico-demographic indicators and structure of incidence of the population in territorial subjects of the Russian Federation in the territory of the FEFD.

The analysis of age and sex composition in territorial subjects of the Russian Federation in the territory of the FEFD reveals detailed features at a negative gain of male population, and is result of evolution of reproduction of the population. The main reason of the Russian «female overpoise», including territorial subjects of the Russian Federation in the territory of the FEFD – a consequence of the Great Patriotic War of the 20th century, participation of the Russian Federation in the local and international conflicts. Also male «supermortality» at able-bodied age and on diseases for the studied period (2010-2014) remains very high.

Keywords: subjects, economics, evaluation, Far, Eastern, Federal, District, FED, coefficient of demographic loading, indicators, reproduction, working, population, Russia, Russian Federation.

INTRODUCTION

The important direction in work on implementation of programs of supply of medicines of socially unprotected segments of the population is formation of requirement and justification of the application of medical institutions. Formation of requirement has to begin from the physician of primary link or narrow experts on acquisition of medicines and has to be made taking into account data of the personified account, a medico-demographic situation and structure of a case rate of the population in territorial subjects of the Russian Federation in the territory of the FEFD for successful functioning of regional programs of supply of medicines. Certainly, at the same time the rest of medicinal preparations in drugstores and in warehouses, the consumption of drugs for the previous period, and also history of their sales and appointment has to be considered.

MATERIALS AND METHODS OF A RESEARCH

Comparative systems analysis; information and analytical; assessment of dynamic rows; statistical data handling by means of the plate Microsoft Excel