LIVER FUNCTION IN EXPERIMENTAL DIABETES MELLITUS AND WAYS OF ITS CORRECTION

Jahangir K. Tursunov[1], Saodat Sh. Abdurasulova[2]
[1]*PhD, Senior Lecturer, Department of Medical and Biological Chemistry, Tashkent Medical Academy, Tashkent, Uzbekistan*
Email: johongirtursunov@gmail.com
ORCID: https://orcid.org/0000-0002-8774-1180,
[2]*Master's student of the Department of Medical and Biological Chemistry of Tashkent Medical Academy, Tashkent, Uzbekistan.*
Email: johongirtursunov@gmail.com

ABSTRACT

In diabetes mellitus, the provision of cells with the main substrates of plastic and energy metabolism and the activity of hepatocytes' intracellular enzyme systems are significantly disrupted. In this regard, the liver's functional capacity to maintain an adequate level of metabolites in the blood decreases, which affects the plastic and energy metabolism of other tissues, including the myocardium. Alcohol intake causes severe metabolic stress, so alcohol intoxication leads to an intensification of catabolic processes and can increase the metabolic disorders observed in diabetes mellitus. In the early period of alcohol intoxication caused in animals with experimental alloxan diabetes, signs of activation of the catabolism processes of nitrogen-containing compounds were found[3].

Keywords: alloxan, rat, ecdysterone, diabetes mellitus, enzymes, liver.

I. INTRODUCTION

As a result of many years of research, the Institute of Plant Chemistry of the Academy of Sciences of the Republic of Uzbekistan developed the drug Ecdysterone to correct metabolic processes. Ecdysterone (synonyms: Ecdysteroneum, ecdysterone, ectysterone, 20 Beta-Hydroxyecdysterone, ponasterone, ecdysone, ecdystene) is a natural compound of a steroid structure isolated from the roots and rhizomes of leucea safflower (raponticum safflower). The drug was registered in the Main Department for Quality Control of Medicines and Medical Equipment of the Ministry of Health of the Republic of Uzbekistan in 1998, under the number 87/848/2.

Experimental studies show that Ecdysterone is low-toxic, has a wide range of biological effects. When it is introduced into the body of animals, there is a pronounced tonic and strenghtening effect. It increases the animal body's adaptive capabilities concerning the stressful factors of the external environment and improves their dynamic performance. An essential point in the mechanism of Ecdysterone's action is its ability to activate the processes of protein biosynthesis in various organs and tissues, similar to the known steroid anabolic drugs (nerobol, retabolil).

However, having a fundamentally different anabolic action mechanism, unlike anabolic androgenic steroids, this drug does not have its inherent hormonal effects (androgenic, thymolytic, antigonadotropic, etc.), which often complicate the use of these drugs, especially in women and children. In addition to protein metabolism, Ecdysteronee also has a positive effect on carbohydrate-phosphorus and lipid metabolism. Under its influence, the accumulation of glycogen and macroergic phosphoric compounds (Adenosine triphosphate (ATP) and creatine phosphate) in organs and tissues is observed, and a clear hypocholesterolemic, hypotriacyl-glycerolemic effect is noted [5,6]. Long-term use of Ecdysterone, even in high doses (8-10 tablets per day for 1-2 months), does not cause disturbances in the content of the main hormones of the body (cortisol, somatotropin, testosterone, insulin, thyroid-stimulating hormone) in the blood, and does not have any side effects on the liver.

The effectiveness of its use in pathologies of the thyroid gland, skeletal muscles, and anabolic processes has been experimentally proven, it has immuno-modulating, stress-protective, hemostatic, and protein synthesis-enhancing properties, and it acts on intestinal absorption. Studies on its antioxidant properties are few, and there is no evidence of its use in experimental diabetes [7,8].

The study aims to examine the pharmacological and biochemical properties of the drug Ecdysterone in developing experimental alloxan diabetes.

Research objectives:

1. To study the indicators of carbohydrate and lipid metabolism disorders in the dynamics of the development of experimental diabetes mellitus and its correction with the drug "Ecdysterone" in comparison with the drug "DIABETON® MR" – tablets produced by Les Laboratoires Servier, France in an experiment on white rats.

2. To study the indicators of liver enzyme disorders in the dynamics of the development of experimental diabetes mellitus and its correction with the drug "Ecdysterone" in comparison with the drug "Hepa - Merz" - granules for the preparation of a solution for oral administration, produced by Merz Pharma GmbH & Co KGaA, Germany.

3. Statistical processing of the obtained research results

II.   MATERIALS AND METHODS

The experimental study was carried out on sexually mature mongrel rats of both sexes with a bodyweight of 180 – 200g in the autumn season, kept in standard Vivarium conditions. After a preliminary 24-hour fast (with preserved access to water), alloxan diabetes was modelled in rats by a single intraperitoneal alloxan administration at a dose of 135 mg/kg [3].

Alloxan is an unstable pyrimidine (2,4,5,6-tetraoxohexahydropyrimidine), which has a diabetogenic effect. After administration, alloxan binds to the membranes of pancreatic beta cells and leads to a rapid decrease in insulin secretion. Approximately two hours after the injection, hyperglycemia is replaced by severe hypoglycemia and significant insulin release due to beta-cell death. After 1-2 days, persistent hyperglycemia develops. The mechanism of the beta-cytotoxic action of insulin is most likely due to the destructive action of hydroxyl and superoxide radicals. The toxic effect of alloxan manifests itself within the first minutes after administration, severe insulin insufficiency-after a few days [1,4]

Alloxan diabetes was modelled for two weeks, with total rat mortality of 24%. For the experiment, the rats were divided into four groups of 15 heads each:

1. Group-intact-rats that received purified water in the amount of 2 ml per os;

2. Control group-rats with alloxan diabetes (intraperitoneally at a dose of 135 mg/kg) + purified water 2 ml per os;

3. Group-experimental-rats with alloxan diabetes + the drug "Ecdysterone" - tablets at a dose of 10 mg/kg per os;

4. Group-experimental-rats with alloxan diabetes + the drug "DIABETON® MR" – tablets, manufactured by Les Laboratoires Servier, France at a dose of 10 mg/kg per os;

On the 7th, 14th, and 21st days of the experiment, the animals were slaughtered by simultaneous beheading, which was previously administered a lethal dose of urethane at a dose of 1200 mg/kg intraperitoneally. The glucose level in the blood serum of animals of all groups was determined on an empty stomach. The serum content of total cholesterol, triglycerides, total protein, and albumins was determined using a semi-automatic analyzer. In the blood serum, the content of 3,4-Methylenedeoxyamphetamine (MDA) was studied by the method of Konyukhova et al.; catalase by the method of Korolyuk et al. The blood glucose level was determined using standard reagent kits: GLUCOSE liquicolor (Human GmbH, 12021 Germany) on a MINDREY BA-88 biochemical analyzer, no.BH - 86100323.

According to the Student's paired criterion, the obtained data were statistically processed using the STATISTICA program [6].

III.   RESULTS AND DISCUSSION

Administration of alloxan to white rats at a dose of 135 mg/kg showed an increase in serum glucose levels by 56.6%, 90%, and 163% on day 7, day 14, and day 21, respectively, compared with the intact group of rats, indicating hyperglycemia (Table 2).

Table 1

Antidiabetic effect of drugs "Ecdysterone" – tablets and "DIABETON® MR",
Les Laboratoires Servier, France (M ± m)

Weight, g	PD, mg / kg	Glucose level, mmol/l		
		Day 7	Day 14	Day 21
Intact				
189,8 ± 6,8	Purified water	5,3 ± 0,6	5,5 ± 0,5	5,4 ± 0,5
Control				
189,5 ± 7,3	Purified water	8,3 ± 0,23 P < 0,05	10,5 ± 0,34	14,2 ± 0,47
"Ecdysterone" – tablets				
191 ± 6,5	10	6,1 ± 0,25 P < 0,05	6,2 ± 0,3	6,5 ± 0,5
"DIABETON® MR", Les Laboratoires Servier, France				
192 ± 8,8	10	6,2 ± 0,24 P < 0,05	6,3 ± 0,4	6,5 ± 0,5

In rats treated with the drug "Ecdysterone" – tablets, there was a significant decrease in serum glucose levels on day 7, day 14 and day 21 by 26.5%, 41% and 54.3%, respectively, compared with the control group of rats.

In rats treated with the drug "DIABETON® MR" – tablets manufactured by Les Laboratoires Servier, France, there was a significant decrease in blood glucose levels by 25.4%, 40% and 54.3% compared to the control group of rats.

The compared drugs significantly reduced the glucose level in the blood serum, and the difference in values between the drugs was unreliable (P>0.5).

Table 2

Dynamics of lipid oxidation products (LOP) parameters in blood serum in experimental diabetes in rats on the background of therapy

Animal group	MDA, mmol/l	Catalase, mcat/sec/l
Intact	11,9 ± 0,66	0,06 ± 0,01
Control	42,1 ± 0,61	0,32 ± 0,01
Alloxan + Ecdysterone	8,13 ± 0,3	0,2 ± 0,01
Alloxan + "DIABETON® MR"	8,15 ± 1,34	0,26 ± 0,02

According to the study results, against the background of diabetes correction with the compared drugs, there is a decrease in the secondary product of LPO and catalase, an enzyme of antioxidant protection (Table 2).

The state of lipid metabolism in experimental rats was characterized by determining the content of total cholesterol (CH), α-cholesterol(α-CH), and triglycerides (TG) in the blood serum.

According to the study results, the level of all parameters of the lipid spectrum significantly increases in rats with alloxan diabetes (Table 3).

Table 3

Dynamics of lipid metabolism in the blood serum of white rats against the background of alloxan diabetes

Indicators	Cholesterol mmol/l	α - Cholesterol mmol/l	Triglycerides mmol/l
Intact	1,74 ± 0,17	0,83 ± 0,014	0,6 ± 0,05
Control (alloxan)	4,31 ± 0,34	2,93 ± 0,13	1,77 ± 0,14
Alloxan + Ectadisten	3,06 ± 0,29	1,47 ± 0,12	0,83 ± 0,02
Alloxan + "DIABETON® MR"	3,24 ± 0,29	1,89 ± 0,19	1,76 ± 0,07

Thus, the cholesterol level increases from 1.74 ± 0.17 mmol/l to 4.31± 0.34 mmol/l ($p < 0.001$), which is 247.7% concerning intact animals. Similarly, the serum Triglycerides (TG) level increases from 0.6 ± 0.05 mmol/l to 1.77 ± 0.14 mmol/l, which is 287.8% compared to the intact group.

Administration of the drug Ecdysterone to rats with alloxan diabetes resulted in a decrease in serum levels of total cholesterol and TG, the content of which was 74% and 46.8% compared to the control, the amount of α – cholesterol decreased by 49.9%. Similar data were obtained with the introduction of the drug "DIABETON® MR" – tablets manufactured by Les Laboratoires Servier, France.

IV. CONCLUSION

An experimental study of the pharmacological properties of the drug "Ecdysterone" showed that the drug:

- reduces the severity of hyperglycemia, normalizes the lipid spectrum of blood serum, reduces the rate of free radical oxidation;

- normalizes the level of ALT, AST and alkaline phosphatase, thereby expressing the hepatoprotective effect.

REFERENCES

1. Экспериментальные модели для изучения сахарного диабета. Часть 1. Аллоксановый диабет. Можейко Л.А. Журнал Гродненского государственного медицинского университета №3, 2013г. С. 26-29.
2. Методические указания по изучению гепатозащитной активности фармакологических веществ. /В Руководстве по экспериментальному (доклиническому) изучению новых фармакологических веществ. Под общей редакцией члена-корреспондента РАМН, профессора Р. У. ХАБРИЕВА. Издание второе, переработанное и дополненное/. М.: - 2005. - М.: ОАО «Издательство «Медицина», 2005.— С. 683-691.
3. Основные методы статистической обработки результатов фармакологических экспериментов. /В Руководстве по экспериментальному (доклиническому) изучению новых фармакологических веществ Под общей редакцией члена-корреспондента РАМН, профессора Р. У. ХАБРИЕВА. Издание второе, переработанное и дополненное/. М.: - 2005. - М: ОАО «Издательство «Медицина», 2005.— С. 763-774.
4. Стефанов А.В. Доклинические исследования лекарственных средств., Киев 2002. – с. 91.
5. Каттайл В.М., Арки Р.А. Патофизиология эндокринной системы. М.: Издательство БИНОМ, 2019. 336 с
6. Лелевич В.В., Леднева И.О., Лелевич С.В. Метаболические эффекты хронической алкогольной интоксикации // Журнал Гродненского государственного медицинского университета. 2017. т. 15. № 3. С. 314.
7. Kim J.Y., Lee D. Y., Lee Y.J., Park K.J., Kim K.H., Kim J.W., Kim W. Chronic alcohol consumption potentiates the development of diabetes through pancreatic β-cell dysfunction. World Journal of Biological Chemistry. 2015. Vol. 6. Iss. 1. P. 1-15
8. Blaine S.K., Milivojevic V., Fox H., Sinha R. Alcohol effects on stress pathways: impact on craving and relapse risk. The Canadian Journal of Psychiatry. 2016. Vol. 61. no. 3. P.145-153.