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UDC 577.175.6:577.115:547.93

THE EFFECT OF TESTOSTERONE ON THE BILE ACID AND BILE LIPID COMPOSITION IN RATS

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https://doi.org/10.31548/dopovidi2021.05.003

Abstract. *The study of sexual differences in the regulation of exocrine liver function is one of the topical areas in hepatology. After all, the liver serves as a mediator in a number of systemic effects of sex hormones on the body and is a key organ of their metabolism. In particular, the correlation between the concentration of steroid hormones can determine the direction of physiological processes and their possible distortions.*

Methods: physiological, biochemical, methods of mathematical statistics.

Cholesecretion increased in female rats under the influence of testosterone. Testosterone raised the concentration of taurocholic acid and at the end of the acute experiment the level of taurohenodeoxycholic and taurodeoxycholic acids significantly increased. By comparison, the content of glycocholates decreased significantly immediately after the administration of the hormone but at the end of the experiment, the content of glycocholic acid increased significantly. The level of free bile acids increased under the testosterone. Testosterone affected the bile lipid composition, in particular, it raised the concentrations of phospholipids, cholesterol and its ethers, while the content of free fatty acids decreased under the studied hormone.

Testosterone when administered intraperitoneally to female rats significantly affects the concentration of conjugated and free cholate, which may indicate its involvement in metabolic transformations and transport of bile acids to the primary bile ducts. The studied hormone raised the concentration of phospholipids, cholesterol and its ethers, but reduced the content of free fatty acids in the liver secretion of the studied animals.

Key words: *testosterone, bile, bile acids, lipids, liver*

Introduction. Over the past 20 years, there has been a growing tendency of liver diseases in all the world (Feysa S. V., 2016). If chronic cholecystitis was previously considered to be a common disease of the biliary tract, then in recent decades there has been a steady increase of gallbladder damage, especially in economically developed countries in America and

Europe. This happens due to metabolic disorders such as cholesterol cholelithiasis and gallbladder cholesterol (Stinton L. M., Shaffer E. A., 2012; Burmak Y. H., Kharchenko V. V., Yakubovskaya I. A., 2013; Chernukha I. S., Reshetnik E. M., Nuryshchenko N. E. et al., 2017).

It is currently known that there is a correlation between the reproductive and hepatobiliary systems (Kaminskyi V. V., Sumenko V. V., Kolomiichenko T. V. et al., 2016). The liver is involved in the metabolism of a number of hormones, so its chronic diseases may be accompanied by hormonal disorders (Parkhomenko L. K., Budreiko O. A., Strashok L. A. et al., 2018). Hormonal disorders are not only associated with reproductive pathology, but also affect the functions of many organs and organ systems (Kaminskyi V. V., Sumenko V. V., Kolomiichenko T. V. et al., 2016). Thus, the imbalance of sex hormones is associated with the development of insulin resistance and an increased risk of atherosclerosis, diabetes and other metabolic and functional disorders. It has been studied that low testosterone levels are cumulative and independent premonitory symptom of type 2 diabetes in middle-aged men, and deficiency of total and free testosterone is common in diabetics, especially with obesity (Chernukha I. S., Reshetnik E. M., Nuryshchenko N. E. et al., 2017; Boyer J. L, 2013; Kelly D. M, Jones T. H. 2013; Korpachev V. V., Melnychenko S. V., Lukashova R. G., 2015). In addition, testosterone may increase the mitogenic activity of hepatocytes (Nucci R. A. B., Teodoro A. C. S., Krause N. W. et al., 2017).

It is well known that non-alcoholic fatty liver disease is more common in men than in women. Presumably sex steroids play a role in its development, as it is common in men with hypogonadism and in postmenopausal women (Mintziori G., Poulakos P., Tsametis C. et al., 2017). It should be noted that according to clinical studies, cholelithiasis is more common in women than in men. This is due to a physiological increase in estrogen levels, as well as the use of hormonal contraceptives, which lead to increased cholesterol excretion by hepatocytes, bile oversaturation and thus increase the risk of cholesterol gallstones in women (Borovets O., Bened' V., Reshetnik E. et al., 2016).

The correlation of sex hormones and receptors to them differs significantly in the bodies of male and female rats. This specifies the course of physiological and biochemical processes in their bodies, including the reproduction of the digestive system functions. Hence, it is necessary to experimentally study the effect of changes in testosterone levels on one of the leading liver functions in the digestive system, in particular, exocrine, under different ways to increase the level of the studied hormone in experimental animals by means of its exogenous

administration. Thus, the aim of the work is to study the effects of testosterone on the bile acid and lipid composition of rat bile.

Materials and methods. The article deals with the effect of testosterone on the biliary secretory function of the liver of female (0.18-0.23 kg, n = 10) and male rats (0.18-0.23 kg, n = 9). Male and female rats of the same age were used for the experiments. Before surgical intervention, the animals were deprived of food, but they had free access to water. Thiopental sodium (OJSC Kyivmedpreparat, Ukraine) was used to anaesthetise rats during an acute experiment at a dose of 60 mg/kg of animal weight intraperitoneally. Experiments on animals were performed in compliance with the requirements of the European Convention for the Protection of Vertebrate Animals and the Law of Ukraine № 3447 IV "On the Protection of Animals from Cruelty".

The laparotomy was performed in layers by cutting the skin along the white line, subcutaneous tissue and peritoneum. Then, when the hepatoduodenal ligament was found, three ligatures were placed under the bile duct, and then a thin metal probe was inserted into the prepared duct through a small insection in its wall. Using a probe, a hollow plastic cannula was inserted into the bile duct cavity, which was connected to a glass micropipette. This allowed to measure the amount of liver secretion and collect bile over a definite period of time. To maintain a constant temperature in rats' bodies and to prevent the dissected peritoneum from drying out, the walls of opposite peritoneum were ligated, and a gauze pad, soaked in saline, was applied to the wound surface. It took the animal 20 minutes to stabilize its condition after the operation and only 30 minutes for the bile duct to registration the bile volume after the cannulation. Eighteen 10-minute samples were taken in 3 hours of acute experiment. The first three 10-minute bile samples were taken to determine the individual level of cholesecretion for each animal. Subsequently, the experimental group of animals was administered testosterone propionate (firm "Farmak", Ukraine) intraperitoneally at a dose of 700 μg per kg body weight of rats (with regard to the drug volume – 1 ml / kg), and the control group – saline (1 ml / kg), then the next 5 half-hour bile samples were collected.

The concentrations of bile acids and lipids in half-hour bile samples were determined using thin-layer chromatographic techniques improved in our laboratory (Veselsky SP, Lyashchenko PS, Luk'janenko YA, 1991; Veselsky SP, Lyashchenko PS, Kostenko SI, Horenko ZA, Kurovska LF, 2001). The experimental data were statistically processed using the software package STATISTICA 5.0 with the use of t-Student's criteria in the normal distribution, which was evaluated using the Shapiro-Wilk test. Differences at $P \leq 0.05$ were considered statistically significant.

Results and discussion. Under intraperitoneal administration of testosterone propionate (700 μg / kg) to female rats, a statistically significant increase in the mean volumetric rate of bile secretion was observed throughout the experiment compared with the control group of animals (Fig. 1).

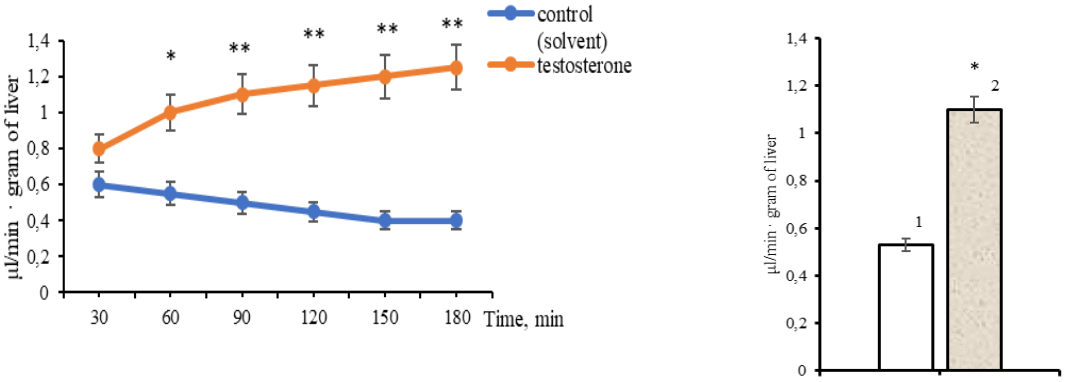

Fig. 1. The rate of bile secretion in female rats at half-hour intervals and the average volume of bile produced under the conditions of the experiment in the control group (1) and after intraperitoneal administration of testosterone propionate (2) (700 μg / kg), (M ± m)

Note: * P <0.05; ** P <0.01; 1 - control (solvent) n = 8; 2 - testosterone n = 10

In the second and third half-hour periods of the experiment, the volumetric rate of cholesecretion increased by 57 % (P <0.05) and 91 % (P <0.01) compared with the control group. And already in the fourth, fifth and sixth half-hour intervals of the experiment, the average volumetric rate of bile secretion was 14 % (P <0.01), 30 % (P <0.01) and 56 % (P <0.01) greater than in the control group (Fig. 1).

It should be noted that with intraperitoneal administration of testosterone propionate (700 μg / kg) to male rats, a statistically significant increase in the mean volumetric rate of bile secretion was observed after 1.5 h of acute experiment, namely by 8 % (P <0.05) compared with the control group. At the end of the experiment, the choleresis of the studied animals was significantly reduced by 7 % (P <0.05) compared with the control group of animals (Fig. 2).

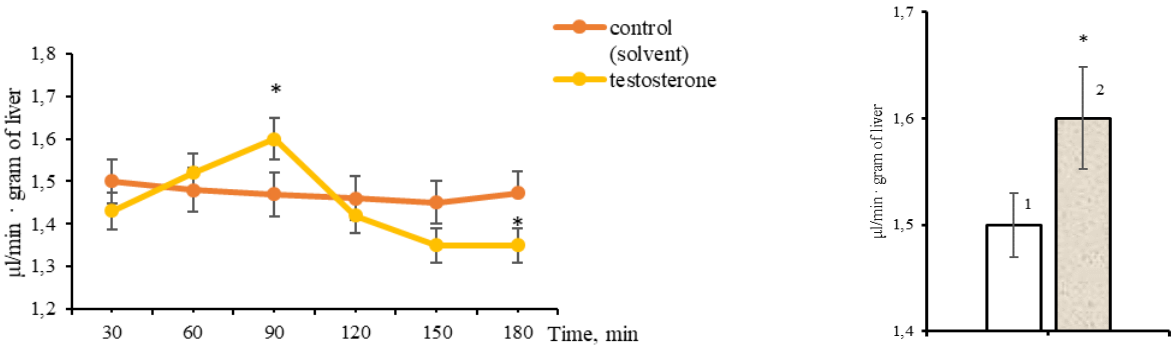

Fig. 2. The rate of bile secretion in male rats at half-hour intervals and the average volume of bile produced under experimental conditions in the control group (1) and after intraperitoneal administration of testosterone propionate (2) (700 µg / kg), (M ± m)

Note: * P <0.05; 1 - control (solvent) n = 11; 2 - testosterone n = 9

Thus, intraperitoneal administration of exogenous testosterone at a dose of 700 µg / kg body weight of the experimental animal in an acute experiment caused different cholesecretion in male and female rats. During the whole experiment, the amount of bile produced by the rats' liver was 7 % (P <0.05) in male rats, greater than in the control group (Fig. 2). In female rats, the same dose of exogenous testosterone raised the level of produced bile by 11 % (P <0.05) compared with the control group (Fig. 1).

Bile secretion is the result of metabolic reactions that take place in liver cells. The leading metabolic processes that provide bile formation are the synthesis and biotransformation of organic components of bile, among which bile acids and lipids have a special place. To maintain the physiological correlation of the main bile components, metabolic and exocrine processes in the liver are subject to complex neurohumoral regulation with the involvement of a wide range of hormones as regulatory factors (Korpachev V. V., Lukashova R. G., Melnytchenko S. V. et al., 2013; Cai Z., Xi H., Pan Y. et al., 2015).

The correlation of different bile components, in particular different bile acids is extremely important in the pathogenesis of many diseases of the hepatobiliary system. Given the significant gender differences in bile production and bile secretion, it was decided to experimentally reproduce the effect of exogenous testosterone on the bile acid composition of rats' bile. Determination of the content of bile acids and lipids in the bile obtained from animals that were under the influence of testosterone, allows us to establish the metabolic links on which the hormone has its regulatory effect.

It should be noted that a series of experiments were conducted where the same dose of testosterone by different

routes of administration was tested and its effect directly on liver cells and its effect at the systemic level were studied (Chernukha I. S., Reshetnik E. M., Nuryshchenko N. E. et al., 2017; Chernuha I. S., Reshetnik Y. M., Liashevych A. M. et al., 20180).

Intraperitoneal administration of testosterone to female rats on the background of its low endogenous level led to a statistically significant increase in the concentration of taurocholic acid in the third, fourth and fifth samples of bile by 12.1 % (P <0.05), 15.7 % (P <0, 05), 22.8 % (P <0.01) compared with the control indicators (Table 1).

The tested hormone, at the end of the acute experiment, significantly increased the level of taurohenodeoxycholic and taurodeoxycholic acids by 35.4 % (P <0,01). In contrast, the concentration of glycocholic, glycochenodeoxycholic and glycodeoxycholic acids decreased statistically significantly immediately after administration of the hormone. Glycocholic decreased by 21.8 % (P <0.01) and glycochenodeoxycholic and glycodeoxycholic – by 44.3 % (P <0.01) compared to control group. But, at the end of the experiment, i.e. in the last 30-minute sample of bile, the content of glycocholic acid significantly increased to 28.4 % (P <0,01) compared with the control group of animals (Table 1).

1. Concentration of conjugated bile acids (mg%) in the bile of female rats in the control group (n = 8) and after intraperitoneal administration of testosterone propionate (n = 10) (700 μg / kg), M ± m

Samples of bile	Series of experiments	Fractions of conjugated bile acids			
		taurocholic acid	taurochenodeoxycholic + taurodeoxycholic acid	glycocholic acid	glycochenodeoxycholic + glycodeoxycholic acid
1	control	177.0±17.6	97.7±19.5	91.3±20.2	36.4±5.3
	testosterone	178.0±9.1	86.8±4.3	80.8±12.5	29.8±3.7
Intraperitoneal administration of solvent or testosterone propionate					
2	control	176.6±13.9	98.6±16.3	91.4±17.8	36.1±5.2
	testosterone	191.5±10.6	92.1±8.1	71.5±7.0*	20.1±2.1**
3	control	171.0±13.8	96.1±15.9	89.1±16.9	34.1±5.0
	testosterone	191.7±3.5*	88.8±2.0	72.3±6.7	23.2±6.6*
4	control	167.2±14.0	95.2±14.1	84.6±17.8	32.3±4.5
	testosterone	193.5±12.4*	99.2±4.3	79.2±6.4	27.0±3.3
5	control	162.1±14.1	93.9±15.2	80.1±15.3	29.7±4.4
	testosterone	199.1±18.0**	108.6±3.6	87.5±5.8	28.8±0.4
6	control	158.3±13.6	90.2±14.4	77.7±14.0	27.1±4.2
	testosterone	173.3±13.1	122.2±5.1**	99.9±4.7**	31.0±0.4

Notes: * – P < 0.05; ** – P < 0.01 – statistically significant differences compared with the control group

It is to be noted that conjugation ensures the dissolution of cholates, makes them resistant to the formation of calcium salts and reduces the possibility of their penetration through cell membranes. The formation of conjugates is one of the ways of biological transformation and elimination of aggressiveness of endogenous and exogenous substances (Scott KA, Melhorn SJ, Sakai RR, 2012).

Under the influence of testosterone, which was administered intraperitoneally to female rats, the level of free bile acids increased, namely the concentration of cholic acid increased by 40.7% (P <0.01) in the third half-hour bile sample, in the fourth – 71.3% 0.001), the fifth – 41.8% (P <0.01) and the sixth by 32.5% (P <0.01) compared with the control group of animals (Table 2).

The concentration of the following unconjugated bile acids also increased: chenodeoxycholic and deoxycholic. Their level increased at the beginning of the acute experiment by 40.2% (P <0.01), and at the end – 74.7% (P <0.001) compared with the control group of animals (Table 2). Changes in the concentration of the above-mentioned bile acids in the bile may indicate the process of their synthesis from cholesterol.

2. The concentration of free bile acids (mg%) in the bile of female rats in the control group (n = 8) and after intraperitoneal administration of testosterone propionate (n = 10) (700 μg / kg), M ± m

Samples of bile	Series of experiments	Fractions of free bile acids	
		cholic acid	chenodeoxycholic + deoxycholic acid
1	control	16.8±3.7	8.2±1.9
	testosterone	19.3±3.0	9.0±1.0
Intraperitoneal administration of solvent or testosterone propionate			
2	control	16.2±3.1	7.7±1.0
	testosterone	17.5±2.7	10.8±1.8**
3	control	15.2±3.0	7.8±1.1
	testosterone	21.3±2.9**	10.0±1.7*
4	control	14.3±2.6	7.6±0.9
	testosterone	24.5±3.7***	11.2±2.0**
5	control	15.2±2.7	7.5±1.0
	testosterone	21.6±1.7**	13.1±2.5**
6	control	15.3±2.7	7.9±1.3
	testosterone	20.3±1.8**	12.9±2.7**

Notes: * – P < 0.05; ** – P < 0.01; *** – P <0.001 – statistically significant differences compared with the control group

The effect of testosterone on the bile acid composition of the bile of female rats is of great importance, because our research has shown that

exogenous testosterone alters the composition of hepatic secretion with minimal levels of endogenous testosterone. It is known that bile acids are highly active biological compounds that play a role in the functioning of the digestive system and the body as a whole.

Since the use of testosterone, significant changes in the concentrations of different physicochemical properties of bile acids in the bile of female rats were found, significant effects of this hormone on the secretion of bile lipids by the rats' liver should be expected. Such lipid compounds as phospholipids, triglycerides, cholesterol, free fatty acids are released from hepatocytes into the primary bile ducts together with bile acids, which is one of the important links in lipid metabolism (Chernukha I. S., Reshetnik E. M., Nuryshchenko N. E. et al., 2017).

In female rats injected with testosterone propionate (700 μg/kg) intraperitoneally, the most significant increase in phospholipids was observed in the fourth (13.7 % (P <0.05)), fifth (22.4 % (P <0, 01) and the sixth samples (30.5 % (P <0,001)) of bile compared with the control group, i.e. after 2-2.5 hours after tested hormone was injected (Table 3).

3. The concentration of lipids (mg%) in the bile of female rats in the control group (n = 8) and after intraperitoneal administration of testosterone propionate (n = 10) (700 μg / kg), M ± m

Samples of bile	Series of experiments	Fractions bile lipids				
		Phospholipids	Cholesterol	Free fatty acids,	Triglycerides	Ethers cholesterol
1	control	70.62 ± 7.66	24.34 ± 3.85	16.73 ± 1.92	3.38 ± 0.66	3.92 ± 0.37
	testosterone	74.08 ± 8.44	28.22 ± 4.74	15.25 ± 0.64	2.42 ± 0.30	4.81 ± 0.98
Intraperitoneal administration of solvent or testosterone propionate						
2	control	71.16 ± 5.47	23.48 ± 3.56	17.42 ± 2.84	3.36 ± 0.91	3.06 ± 0.43
	testosterone	76.12 ± 8.08	28.07 ± 4.75	17.93 ± 2.00	2.50 ± 0.52	6.41 ± 0.84***
3	control	71.54 ± 2.65	23.74 ± 2.31	18.12 ± 2.38	3.08 ± 0.77	3.12 ± 0.15
	testosterone	79.26 ± 9.15	25.34 ± 2.02	19.49 ± 2.10	2.67 ± 0.56	6.75 ± 0.80***
4	control	72.70 ± 1.58	23.70 ± 1.78	18.42 ± 1.85	2.98 ± 0.63	3.04 ± 0.21
	testosterone	82.83 ± 8.96*	26.00 ± 1.97	15.70 ± 1.56*	2.55 ± 0.37	6.72 ± 0.33***
5	control	74.32 ± 3.44	24.02 ±1.69	17.86 ± 1.42	2.84 ± 0.71	2.90 ± 0.19
	testosterone	91.01 ± 8.31**	27.40 ± 1.82**	15.01 ± 1.58**	2.29 ± 0.33	6.38 ± 0.19***
6	control	73.86 ± 4.80	23.92 ± 1.41	18.26 ± 1.80	2.80 ± 0.81	2.58 ± 0.18
	testosterone	96.38 ± 9.10***	28.63 ± 2.65**	13.22 ± 0.86***	2.11 ± 0.37	6.15 ± 0.16***

Notes: * – P < 0.05; ** – P < 0.01; *** – P <0.001 – statistically significant differences compared with the control group

As a result, our studies show that testosterone in female rats increases the concentration of free bile acids and phospholipids, and from this it can be

assumed that the studied hormone reduces the possibility of cholesterol precipitation.

Cholesterol concentration increased significantly at the end of the acute experiment, namely in the fifth sample of bile by 12.5 % (P <0.01), in the sixth by 20.8 % (P <0.01) compared with the control group of animals. Under the action of testosterone in females the content of free fatty acids statistically significantly decreased in the fourth bile sample by 14.8 % (P <0,05), in the fifth – 15.9 % (P <0,01) and the sixth – 27.6 % (P <0.001) compared with the control group of animals. And the esterified form of cholesterol increased statistically significantly under the action of testosterone throughout the acute experiment, compared with control values. Immediately after administration of the hormone, the concentration of cholesterol ethers increased by 9.5 % (P <0.001), in the next half hour by 16 % (P <0.001), an hour later by 21 % (P <0.001), in the penultimate sample of bile by 20 % (P <0,001), and in the latter by 38 % (P <0,001) compared with the control group of animals (Table 3). In human bile, cholesterol is in a solubilized state, which is facilitated by bile acids (cholic, deoxycholic and chenodeoxycholic acids), as well as phospholipids, which form special complexes with cholesterol, called micelles. In the case of a decrease in the concentration of these components in the bile, conditions are created for the precipitation of cholesterol and its crystallization (Moroz O. F., Veselsky S. P., Lyashchenko T. P. et al., 2009).

Thus, from the obtained results it follows that testosterone intraperitoneally acts in different ways on lipid synthesis in female rats. This, in turn, is mostly due to the peculiarities of the biotransformation of the hormone in tissues and in the liver as a whole and the density of testosterone receptors in the body of the studied animals.

Conclusions

Testosterone propionate when administered intraperitoneally to female rats significantly affects the concentration of conjugated and free cholates, which may indicate its involvement in metabolic transformations and transport of bile acids to the primary bile ducts. The tested hormone increased the concentration of phospholipids, cholesterol and its ethers, but reduced the content of free fatty acids in the liver secretion of the experimental animals. Due to the widespread use of testosterone propionate and its effects on the bile acid and lipid composition of bile in female rats, it is advisable to study its effect under intraperitoneal administration on exocrine function of male rats.

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ВПЛИВ ТЕСТОСТЕРОНУ НА ЖОВЧНОКИСЛОТНИЙ І ЛІПІДНИЙ СКЛАД ЖОВЧІ ЩУРІВ

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Анотація. *Дослідження статевих відмінностей у регуляції зовнішньосекреторної функції печінки розглядається як один із актуальних напрямків у гепатології. Адже печінка відіграє роль посередника в ряді системних впливів статевих гормонів на організм і є ключовим органом їх метаболізму. Зокрема, співвідношення між концентрацією стероїдних гормонів може визначати направленість фізіологічних процесів та можливі їх порушення.*

Методи: фізіологічні, біохімічні, методи математичної статистики.

Під впливом тестостерону підвищувалася холесекреція у самиць щурів. Тестостерон збільшував концентрацію таурохолевої кислоти і наприкінці гострого досліду, істотно підвищив рівень таурохенодезоксихолевої і тауродезоксихолевої кислот. Натомість, вміст глікохолатів відразу після введення гормону суттєво зменшувалася, але, наприкінці експерименту, вміст глікохолевої кислоти істотно підвищувався. При дії тестостерону збільшувався рівень вільних жовчних кислот. Тестостерон вплинув на ліпідний склад жовчі, зокрема підвищував концентрації фосфоліпідів, холестеролу та його етерів, а вміст вільних жирних кислот зменшувався під впливом досліджуваного гормону.

Тестостерон за внутрішньоочеревного введенняі самицям щурів істотно впливає на концентрацію кон'югованих і вільних холатів, що може свідчити про його участь у метаболічних перетвореннях і транспорті жовчних кислот до первинних жовчних канальців. Досліджуваний гормон зумовив підвищення концентрації фосфоліпідів, холестеролу та його етерів, але знижував вміст вільних жирних кислот у печінковому секреті досліджуваних тварин.

Ключові слова: *тестостерон, жовч, жовчні кислоти, ліпіди, печінка*